Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-102248- -00000-0000
Fecha: 2011-08-11 14:43:02 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTES II Eve: 378 FASENACIONALI-
Act: 411 PRESENTACION Folios: 654

SOLICITUD DE

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 11-102248

54. TITULO: **INHIBIDORES DE POLI (ADP-RIBOSA) POLIMERASA (PARP)**

52. CLASIFICACION INTERNACIONAL: **C07D 471/04, C07D 471/14, C07D 498/14, C07D 513/14, A61K 31/4985, A61K 31/5365, A61K 31/542, A61P 25/00, A61P 35/00, A61P 9/00, A61P 29/00**

71. SOLICITANTE: **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

DOMICILIO: **1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045, JAPON**

74. APODERADO: **Dra. MARGARITA CASTELLANOS A.**

22. BOGOTA, D.C., _____

23-08-2011

Industria y Comercio
SUPERINTENDENCIA

PETITO[illegible] No. 11-102248- -00000-0000
Fecha: 2011-08-11 14:43:02 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTES II Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 654

UI

cación

FORMULARIO UNICO DE SOLICITUD DE PATENTES
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

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

[X] Capítulo I [ ] Capítulo II

(2) **SOLICITANTE (71)**	Nombre: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** Dirección: **1-1, Doshomachi 4-chome Chuo-ku, Osaka-shi Osaka 541-0045 JAPON** Nacionalidad o Domicilio: **Osaka - JAPON** Lugar de Constitución: **JAPON** Teléfono: Fax: E-mail:	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
(3) **REPRESENTANTE O APODERADO**	Nombre: **MARGARITA CASTELLANOS A.** Dirección: **CALLE 94A No. 7A-09** Teléfono: **756 0770** Fax: **755 0158** E-mail: info@castellanosyco.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual Número **39'779.654** TPA **70.819**
(4) **INVENTOR (ES) (72)**	**VER ANEXO # 1**	

(5) **PCT (86)**

Solicitud Internacional No. **PCT/US2010/021669** Fecha **21/01/2010**

Publicación Internacional No. **WO 2010/085570 A1** Fecha **29/07/2010**

(6) **Título (54)** **INHIBIDORES DE POLI (ADP-RIBOSA) POLIMERASA (PARP)**

(7) **Clasificación Internacional (51)** C07D 471/04, C07D 471/14, C07D 498/14, C07D 513/14, A61K 31/4985, A61K 31/5365, A61K 31/542, A61P 25/00, A61P 35/00, A61P 9/00, A61P 29/00

(8) **Prioridad** SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	23/01/2009	61/146,740
US	27/07/2009	61/228,879

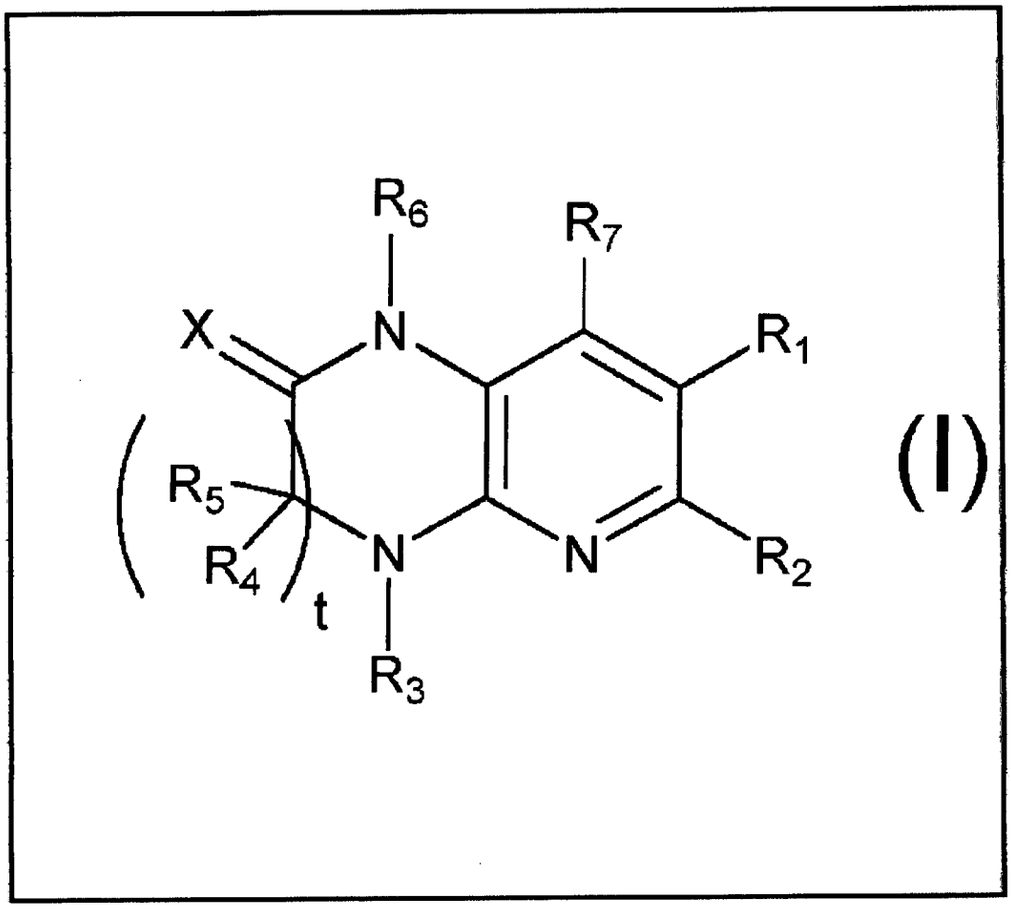
(9) **Comprobante de pago No.** **11-0069209 y 11-0069211** **Fecha** **Julio 18 de 2011**

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

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros: **Tarjeta Propietario y Extracto para la publicación**

(11) FIGURA CARACTERISTICA:



(12) Solicito la concesión de la patente,

NOMBRE: **MARGARITA CASTELLANOS ABONDANO**

FIRMA:

C.C. No. 39'779.654 Usaquén - TPA-70.819 C.S.J.

11 AGO. 2011

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página. - MCA/gcb - P 22 48

CASTELLANOS & CO LTDA
ABOGADOS
Calle 94 A No. 7 A-09
Bogotá, D.C. – COLOMBIA

ANEXO # 1
INVENTORES

1. **ANTHONY R. GANGLOFF**
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   San Diego, CA 92121
   ESTADOS UNIDOS DE AMERICA

3. **BENJAMIN JONES**
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   San Diego, CA 92121
   ESTADOS UNIDOS DE AMERICA

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

000004

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0069209

Bogotá D.C., Julio 18 de 2011 - 14:19:10

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387634645	18/07/2011	13.833.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-102248- -00000-0000
Fecha: 2011-08-11 14:43:02 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 654

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0069211

Bogotá D.C., Julio 18 de 2011 - 14:19:10

RECIBIDO DE : CASTELLANOS Y Y CO NI 800.174.641

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	387634645	18/07/2011	13.833.000.00

*** Conceptos Pagados ***

CANT	RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
30	50005-01-01 SOLICITUDES	1607 REIVINDICACION UNITARIA ADICIONAL A LAS 10 INICIALES	27.000.00	810.000.00
				$810.000.00

SON: **OCHOCIENTOSDIEZ MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-102248- -00000-0000
Fecha: 2011-08-11 14:43:02 Dep: 3020 DIR NUEVASCR
Tra: 11 PATENTEVII Eve: 378 PASENACIONALI
Act: 411 PRESENTACION Folios: 654

P2 U5 000006 PP195
3698 COOP
TCB

COLOMBIA

PODER

El (los)

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Domiciliados en **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japón**

Nombran por el presente a **YIMENA CASTELLANOS A. y/o MARGARITA CASTELLANOS A.** abogadas con oficinas en la Calle 94A No. 7A-09, Bogotá-Colombia para
y para obtener la protección de mi.(nuestra) propiedad Industrial e intelectual y con este fin autorizamos a dichos apoderados para que nos representen ante cualesquiera autoridades o personas de los órdenes administrativo, contencioso –administrativo y judicial en todo lo relacionado con los siguientes actos y gestiones:

a) Obtención de patentes de invención, modelos y dibujos industriales; registro de marcas de fabrica, de servicio, colectivas o defensivas y de denominaciones de origen, depósito de nombres y enseñas comerciales; su renovación, prórroga, inscripción de traspaso y cambio de nombre o domicilio, cancelación voluntaria y el registro de licencias de uso de esos derechos;
b) Para la obtención de registros sanitarios;
c) Para la obtención de registros de derechos de autor.
d) Acciones de oposición, observación, cancelación, nulidad, medidas cautelares y en general los juicios civiles, penales, administrativos o contencioso - administrativos que promovamos o se nos promuevan.

Pudiendo en todos los actos y gestiones arriba mencionados sustituir éste mandato entre los apoderados, transigir, desistir, recibir, cancelar, renunciar, aceptar notificaciones y nombrar apoderados judiciales y extra-judiciales. .

Finalmente, este poder ratifica la validez de todos los actos y solicitudes que, a nombre de la poderdante hubieren realizado los apoderados en relación con las facultades anteriormente enumeradas, antes de la suscripción del presente poder

Dado y firmado hoy 01/06/2011

en Kanagawa, Japón

por Takeda Pharmaceutical Company Limited.

(El notario debe suscribir el documento en la pagina siguiente)
(Se requiere legalización consular o mediante apostilla)

POWER OF ATTORNEY

I (we) the undersigned

TAKEDA PHARMACEUTICAL COMPANY LIMITED

Of **1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, 541-0045, Japan**

hereby grant(s) Power of Attorney to **YIMENA CASTELLANOS A. and /or MARGARITA CASTELLANOS** a. attorneys residing at Calle 94A No. 7A-09, Bogotá- Colombia, to
and to obtain the protection of my (our) Intellectual Property, for which purpose we authorize the said attorneys to represent us before any authorities, or persons, specially those, administrative, contentious and judicial, in all matters concerning the following:

a) Obtainment of patents, models and designs, registration of trademarks, service, collective and defensive marks, and of designations of origin; the deposit of trade names and ensigns; its renewal, extension, recordal of assignments, change of name or domicile, voluntary cancellation, and the registration of licenses of use of the above rights;
b) For the obtainment of Sanitary registrations;
c) For the obtainment of copyright registrations
d) Actions of opposition, cancellation, nullity, infringement, granting of licenses; and in general the civil, criminal and administrative suits related to those rights; actions and suits instituted by us or against us;

In all the above matters they may substitute this power of attorney within the appointed attorneys, compromise, cancel, receive, withdraw, renounce, accept notifications and appoint attorneys in fact in or out of court.

Finally, this power of attorney ratifies the validity of all acts and applications made by the representatives in the name of the signatory of this power of attorney, with regard to the faculties above given, before the execution of the present power of attorney.

Given and signed this 01/06/2011

in Kanagawa, Japan

by Yoichi Okumura

Yoichi Okumura
General Manager, Intellectual Property Department.
Takeda Pharmaceutical Company Limited

(Notary shall execute on the other side)
(Consular legalization or apostille is required)

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia coincide con original que se he presentado
Bogotá D.C. - Colombia.
14 JUL 2011
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

CASTELLANOS & CO.
INTELLECTUAL PROPERTY LAW FIRM
CALLE 94 A No. 7 A – 09 / P.O. BOX 6349
PHONE (57 1) 756 07 70 / FAX (57 1) 755 01 58
BOGOTÁ D.C. COLOMBIA
info@castellanosyco.com

平成２３年登簿第　79　号　　000007

認　証

日本国政府大阪法務局の平成２３年４月１８日発行にかかる履歴事項全部証明書により明らかなところであるが、日本国法律により設立され本店が大阪府大阪市中央区道修町４丁目１番１号に所在する武田薬品工業株式会社の知的財産部長與村洋一は別紙委任状に署名する権限を付与されており、別紙委任状の証書の署名が自己のものに相違ない旨代理人LEVESQUE SON HYUN REGINAを通じ本公証人に対し自認した。　以上

よって、これを認証する。

平成２３年　６月　１　日、本公証人役場において

藤沢市鵠沼石上2丁目11番2号
横浜地方法務局所属
公証人
Notary

曾我大三郎

DAISABURO SOGA

証　明

上記署名は、横浜地方法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成２３年　６月　１　日

横浜地方法務局長　神尾　徹

APOSTILLE
(Convention de La Haye du 5 octobre 1961)

1. Country : JAPAN
   This public document
2. has been signed by DAISABURO SOGA
3. acting in the capacity of Notary of the Yokohama District Legal Affairs Bureau
4. bears the seal/stamp of DAISABURO SOGA , Notary

Certified

5. at Tokyo　　6. JUN. 1.2011
7. by the Ministry of Foreign Affairs
8. 11- № 301579
9. Seal/stamp :　　10.Signature :

Kazutoyo OYABE
For the Minister for Foreign Affairs

Como Notario Veintiséis del Circulo de Bogotá, hago constar que esta copia coincide con original que se he presentado
Bogotá D.C., Colombia.
14 JUL 2011
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

000003

Registered No. 7 9

NOTARIAL CERTIFICATE

This is to certify that LEVESQUE SON HYUN REGINA, an agent of Yoichi OKUMURA, General Manager, Intellectual Property Department of Takeda Pharmaceutical Company Limited , who has been authorized to grant Power of Attorney on behalf of said company organized and existing according to the law of Japan, located at 1-1 , Dochomachi 4-chome, Chuo-ku Osaka-shi Osaka Japan, has stated in my very presence that said Yoichi OKUMURA has acknowledged himself that the signature on the attached document is his own.

The foregoing was duly evidenced by the certified Register of said company issued by the Certificate of All Registered Items dated 18 April, 2011 from Osaka Legal Affairs Bureau for Corporate Number KU250214 and Title Certificate dated April 14, 2011.

Dated this 1st day of June, 2011.

Daisaburo Soga

YOKOHAMA DISTRICT
LEGAL AFFAIRS BUREAU
NOTARY
2-11-2, KUGENUMAISHIGAMI
FUJISAWA-SHI, KANAGAWA-KEN
JAPAN

Daisaburo Soga

Notary

attached to Yokohama District Legal Affairs Bureau

2-11-2, Kugenuma Ishigami Fujisawa-shi

Kanagawa-ken Japan

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Bogotá D.C., Colombia.
14 JUL 2011
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

000003

----------TRADUCCION OFICIAL No. 11-0607----------

De un documento escrito en INGLES, el cual para su identificación lleva el sello y firma de la Traductora e Intérprete Oficial, Res. 2755/68 y 01144/97 de Minjusticia.----------

(Anexos a un documento de Poder de TAKEDA PHARMACEUTICAL COMPANY LIMITED)

Registro No. 79

CERTIFICADO NOTARIAL

La presente es para certificar que LEVESQUE SOH HYUH PEGINA, agente de Yoichi OKUMURA, Gerente General, Departamento de Propiedad Intelectual de Takeda Pharmaceutical Company Limited, quien ha sido autorizado para otorgar Poder en nombre de dicha compañía, constituida y existente de acuerdo con la ley de Japón, domiciliada en 1-1, Doshomachi 4-chome, Chuo-ku Osaka-shi, Osaka Japòn ha manifestado en mi propia presencia que la firma en el documento adjunto es de éste.

Lo anterior fue debidamente evidenciado por el Certificado de Registro de dicha compañía expedido por el Certificado de Todos los Items Registrados de fecha abril 18 de 2011 de la Oficina de Asuntos Legales de Osaka para Sociedades No. KU250214 y el Certificado de Título de fecha Abril 14, 2011.

Dado hoy dìa primero de Junio de 2011.

(fdo) ilegible

Daisaburo Soga

Como Notario Veintiséis del Circuito de Bogotá, hago constar que esta copia coincide con original que se ha presentado. Bogotá D.C. Colombia.

14 JUL 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

000010

Notario

Adjunto a la Oficina de Asuntos Legales del Distrito de Yokohama – 2-11-2, Kugenuma Ishigami Fujisawa-shi Kanagawa-ken, Japón

(Sello Notarial): OFICINA DE ASUNTOS LEGALES
DISTRITO DE YOKOHAMA
NOTARIO
2-11-2, Kugenumaishigami
Fujisawa-shi, Kanagawa-ken – Japón

APOSTILLA

(Convención de La Haya de Octubre 5, 1961)

1. País: JAPON

Este documento público

2. ha sido firmado por: DAISAEUPO SOGA

3. actuando en su carácter de: Notario Público de la Oficina de Asuntos Legales deL Distrito de Yokohama

4. lleva el sello de DAISUPO SOGA - Notario

CERTIFICADO:

5. en Tokyo 6. el día 1° de Junio de 2011

7. por el Ministerio de Relaciones Exteriores

8. 11 No. 301579

9. Sello 10. Firma: (fdo) ilegible

Como Notaria Veintiseis del Circulo de Bogotá, hago constar que esta copia coincide con original que se ha presentado Bogotá D.C., Colombia.

14 JUL 2011

GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

MARIA DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
R.S. 02755/78 Y 01144/97 - MINJUSTICIA
RE. DE COLOMBIA

000011

Kazutoyo OYABE

Por el Ministerio de Relaciones Exteriores (Sello)

ES TRADUCCION FIEL Y COMPLETA, a la cual me remito,

Bogotá, D. C., Junio 13, 2011

MARIA DORA DUQUE DE BERNAL
TRADUCTORA E INTERPRETE OFICIAL
R.S. 02755/68 Y 01144/97 - MINJUSTICIA
RE. DE COLOMBIA

Como Notario Veintiséis del Círculo de Bogotá, hago constar que esta copia coincide con original que se ha presentado
Bogotá D.C. - Colombia.
14 JUL 2011
GUSTAVO SAMPER RODRIGUEZ
NOTARIO VEINTISEIS

EN BLANCO
NOTARIA VEINTISEIS

000012

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 July 2010 (29.07.2010)

PCT

(10) International Publication Number
WO 2010/085570 A1

(51) International Patent Classification:
C07D 471/04 (2006.01) *A61K 31/542* (2006.01)
C07D 471/14 (2006.01) *A61P 25/00* (2006.01)
C07D 498/14 (2006.01) *A61P 35/00* (2006.01)
C07D 513/14 (2006.01) *A61P 9/00* (2006.01)
A61K 31/4985 (2006.01) *A61P 29/00* (2006.01)
A61K 31/5365 (2006.01)

(21) International Application Number:
PCT/US2010/021669

(22) International Filing Date:
21 January 2010 (21.01.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/146,740 23 January 2009 (23.01.2009) US
61/228,879 27 July 2009 (27.07.2009) US

(71) Applicant *(for all designated States except US)*: **TAKEDA PHARMACEUTICAL COMPANY LIMITED** [JP/JP]; 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi, Osaka 541-0045 (JP).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **GANGLOFF, Anthony R.** [US/US]; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California 92121 (US). **JENNINGS, Andrew John** [GB/US]; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California 92121 (US). **JONES, Benjamin** [US/US]; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California 92121 (US). **KIRYANOV, Andre A.** [US/US]; c/o Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California 92121 (US).

(74) Agents: **RUSSO, Matthew** et al.; Takeda San Diego, Inc., 10410 Science Center Drive, San Diego, California 92121 (US).

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

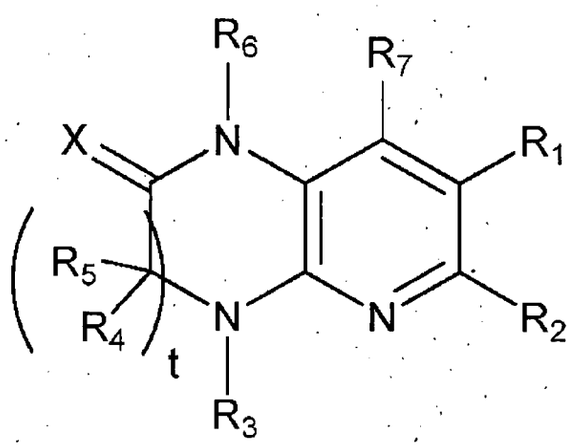
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS,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

Published:

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

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

(54) **Title**: Poly (ADP-Ribose) Polymerase (PARP) Inhibitors



(I)

(57) **Abstract**: Disclosed are compounds of the following formula: (I) in which R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, and t are defined in the specification. Also disclosed are pharmaceutical compositions, kits, and articles of manufacture, which contain the compounds, methods and intermediates useful for making the compounds, and methods of using the compounds to treat diseases, disorders, and conditions related to PARP activity.

WO 2010/085570 A1

Poly (ADP-Ribose) Polymerase (PARP) INHIBITORS

FIELD OF THE INVENTION

[0001] The present invention relates to compounds that may be used to inhibit Poly (ADP-ribose) Polymerase (PARP), as well as compositions of matter, kits and articles of manufacture comprising these compounds. The invention also relates to methods for inhibiting PARP and treatment methods using compounds according to the present invention. In addition, the invention relates to methods of making the compounds of the present invention, as well as intermediates useful in such methods.

BACKGROUND OF THE INVENTION

[0002] The present invention relates to inhibitors of the enzyme poly(ADP-ribose)polymerase (PARP), previously known as poly(ADP- ribose)synthase and poly(ADP-ribosyl)transferase. PARP constitutes a super family of proteins containing PARP catalytic domains. These proteins include PARP-1, PARP-2, PARP-3, vaultPARP and TiPARP. PARP-I consists of an amino (N)-terminal DNA-binding domain (DBD) containing two zinc fingers; an automodification domain; and a carboxy (C)-terminal catalytic domain.

[0003] PARP is a nuclear and cytoplasmic enzyme that cleaves NAD+ to nicotinamide and ADP- ribose to form long and branched ADP-ribose polymers on target proteins, including topoisomerases, histones and PARP itself. PARP has been implicated in several biological processes, including DNA repair, gene transcription, cell cycle progression (including proliferation and differentiation), cell death, chromatin functions, genomic (*e.g.*, chromosomal) stability and telomere length.

[0004] Activation of PARP and the resultant formation of poly(ADP-ribose) can be induced by DNA strand breaks after exposure to chemotherapy, ionizing radiation, oxygen free radicals, or nitric oxide (NO). Because this cellular ADP-ribose transfer process is associated with the repair of DNA strand breakage in response to DNA damage caused by radiotherapy or chemotherapy, it can contribute to the resistance that often develops to various types of cancer therapies. Consequently, inhibition of PARP is expected to retard intracellular DNA repair and enhance the antitumor effects of cancer therapies.

[0005] In addition, tankyrases (*e.g.*, tankyrase-1 and tankyrase-2) which bind to the telomeric protein TRF-1, a negative regulator of telomere length maintenance, have a catalytic domain that is homologous to PARP. It has been proposed that telomere function in human cells is regulated by poly(ADP-ribosyl)ation. As a consequence of regulation of telomerase

activity by tankyrase. PARP inhibitors are expected to have utility as agents for use in cancer therapy (*e.g.*, to shorten the life-span of immortal tumor cells) or as anti-aging therapeutics, since telomere length is believed to be associated with cell senescence.

[0006] In addition, PARP modulation has been implicated in vascular and cardiovascular diseases, metabolic diseases, inflammatory diseases, reperfusion injuries, ischemic conditions, neurodegenerative diseases and more.

[0007] There is a continued need to find new therapeutic agents to treat human diseases. PARP is an especially attractive target for the discovery of new therapeutics due to its important role in cancers, vascular and cardiovascular diseases, metabolic diseases, inflammatory diseases, reperfusion injuries, ischemic conditions, neurodegenerative diseases and other diseases.

SUMMARY OF THE INVENTION

[0008] The present invention relates to compounds that have activity for inhibiting PARP. The present invention also provides compositions, articles of manufacture and kits comprising these compounds. In addition, the invention relates to methods of making the compounds of the present invention, as well as intermediates useful in such methods. The compounds of the present invention show *in vivo* efficacy in animal models, increased cellular potentiation, strong and sustained pharmacodynamic effects in tumours, and longer time-to-tumour progression (TTP).

[0009] In one embodiment, a pharmaceutical composition is provided that comprises a PARP inhibitor according to the present invention as an active ingredient. Pharmaceutical compositions according to the invention may optionally comprise 0.001%-100% of one or more inhibitors of this invention. These pharmaceutical compositions may be administered or co-administered by a wide variety of routes, including for example, orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadipocally, intraarticularly, or intrathecally. The compositions may also be administered or co-administered in slow release dosage forms.

[0010] The invention is also directed to kits and other articles of manufacture for treating disease states associated with PARP.

[0011] In one embodiment, a kit is provided that comprises a composition comprising at least one PARP inhibitor of the present invention in combination with instructions. The

instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0012] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one PARP inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0013] Also provided are methods for preparing compounds, compositions and kits according to the present invention. For example, several synthetic schemes are provided herein for synthesizing compounds according to the present invention.

[0014] Also provided are methods for using compounds, compositions, kits and articles of manufacture according to the present invention.

[0015] In one embodiment, the compounds, compositions, kits and articles of manufacture are used to inhibit PARP.

[0016] In another embodiment, the compounds, compositions, kits and articles of manufacture are used to treat a disease state for which PARP possess activity that contributes to the pathology and/or symptomology of the disease state.

[0017] In another embodiment, a compound according to the present invention is administered to a subject wherein PARP activity within the subject is altered, preferably reduced.

[0018] In another embodiment, a prodrug of a compound according to the present invention is administered to a subject that is converted to the compound *in vivo* where it inhibits PARP.

[0019] In another embodiment, a method of inhibiting PARP is provided that comprises contacting a PARP with a compound according to the present invention.

[0020] In another embodiment, a method of inhibiting PARP is provided that comprises causing a compound according to the present invention to be present in a subject in order to inhibit PARP *in vivo*.

[0021] In another embodiment, a method of inhibiting a PARP is provided that comprises administering a first compound to a subject that is converted *in vivo* to a second compound wherein the second compound inhibits PARP *in vivo*. It is noted that the compounds of the present invention may be the first or second compounds.

[0022] In another embodiment, a therapeutic method is provided that comprises administering a compound according to the present invention.

[0023] In another embodiment, a method is provided for treating a condition in a patient that is known to be mediated by PARP, or which is known to be treated by PARP inhibitors, the method comprising administering to the patient a therapeutically effective amount of a compound according to the present invention.

[0024] In another embodiment, a method is provided for treating a disease state for which PARP possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: causing a compound according to the present invention to be present in a subject in a therapeutically effective amount for the disease state.

[0025] In another embodiment, a method is provided for treating a disease state for which PARP possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a first compound to a subject that is converted *in vivo* to a second compound such that the second compound is present in the subject in a therapeutically effective amount for the disease state. It is noted that the compounds of the present invention may be the first or second compounds.

[0026] In another embodiment, a method is provided for treating a disease state for which PARP possess activity that contributes to the pathology and/or symptomology of the disease state, the method comprising: administering a compound according to the present invention to a subject such that the compound is present in the subject in a therapeutically effective amount for the disease state.

[0027] In another embodiment, a method is provided for using a compound according to the present invention in order to manufacture a medicament for use in the treatment of a disease state that is known to be mediated by PARP, or that is known to be treated by PARP inhibitors.

[0028] It is noted in regard to all of the above embodiments that the present invention is intended to encompass all pharmaceutically acceptable ionized forms (*e.g.*, salts) and solvates (*e.g.*, hydrates) of the compounds, regardless of whether such ionized forms and solvates are specified since it is well known in the art to administer pharmaceutical agents in an ionized or solvated form. It is also noted that unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all possible stereoisomers (*e.g.*, enantiomers or

diastereomers depending on the number of chiral centers), independent of whether the compound is present as an individual isomer or a mixture of isomers. Further, unless otherwise specified, recitation of a compound is intended to encompass all possible resonance forms and tautomers. With regard to the claims, the language "compound comprising the formula," "compound having the formula" and "compound of the formula" is intended to encompass the compound and all pharmaceutically acceptable ionized forms and solvates, all possible stereoisomers, and all possible resonance forms and tautomers unless otherwise specifically specified in the particular claim.

[0029] It is further noted that prodrugs may also be administered which are altered *in vivo* and become a compound according to the present invention. The various methods of using the compounds of the present invention are intended, regardless of whether prodrug delivery is specified, to encompass the administration of a prodrug that is converted *in vivo* to a compound according to the present invention. It is also noted that certain compounds of the present invention may be altered *in vivo* prior to inhibiting PARP and thus may themselves be prodrugs for another compound. Such prodrugs of another compound may or may not themselves independently have PARP inhibitory activity.

DEFINITIONS

[0030] Unless otherwise stated, the following terms used in the specification and claims shall have the following meanings for the purposes of this Application.

[0031] It is noted that, as used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise. Further, definitions of standard chemistry terms may be found in reference works, including Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. Also, unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology, within the skill of the art are employed.

[0032] "Alicyclic" means a moiety comprising a non-aromatic ring structure. Alicyclic moieties may be saturated or partially unsaturated with one, two or more double or triple bonds. Alicyclic moieties may also optionally comprise heteroatoms such as nitrogen, oxygen and sulfur. The nitrogen atoms can be optionally quaternerized or oxidized and the sulfur atoms can be optionally oxidized. Examples of alicyclic moieties include, but are not limited to moieties with (C_{3-8}) rings such as cyclopropyl, cyclohexane, cyclopentane, cyclopentene,

cyclopentadiene, cyclohexane, cyclohexene, cyclohexadiene, cycloheptane, cycloheptene, cycloheptadiene, cyclooctane, cyclooctene, and cyclooctadiene.

[0033] "Aliphatic" means a moiety characterized by a straight or branched chain arrangement of constituent carbon atoms and may be saturated or partially unsaturated with one, two or more double or triple bonds.

[0034] "Alkenyl" means a straight or branched, carbon chain that contains at least one carbon-carbon double bond (-CR=CR'- or –CR=CR'R", wherein R, R' and R" are each independently hydrogen or further substituents). Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like. In particular embodiments, "alkenyl," either alone or represented along with another radical, can be a (C_{2-20})alkenyl, a (C_{2-15})alkenyl, a (C_{2-10})alkenyl, a (C_{2-5})alkenyl or a (C_{2-3})alkenyl. Alternatively, "alkenyl," either alone or represented along with another radical, can be a (C_2)alkenyl, a (C_3)alkenyl or a (C_4)alkenyl.

[0035] "Alkenylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon double bonds (-CR=CR'-, wherein R and R' are each independently hydrogen or further substituents). Examples of alkenylene include ethene-1,2-diyl, propene-1,3-diyl, methylene-1,1-diyl, and the like. In particular embodiments, "alkenylene," either alone or represented along with another radical, can be a (C_{2-20}) alkenylene, a (C_{2-15}) alkenylene, a (C_{2-10}) alkenylene, a (C_{2-5}) alkenylene or a (C_{2-3}) alkenylene. Alternatively, "alkenylene," either alone or represented along with another radical, can be a (C_2) alkenylene, a (C_3) alkenylene or a (C_4) alkenylene.

[0036] "Alkoxy" means an oxygen moiety having a further alkyl substituent. The alkoxy groups of the present invention can be optionally substituted.

[0037] "Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having a chain of carbon atoms, optionally with one or more of the carbon atoms being replaced with oxygen (See "oxaalkyl"), a carbonyl group (See "oxoalkyl"), sulfur (See "thioalkyl"), and/or nitrogen (See "azaalkyl"). (C_X)alkyl and (C_{X-Y})alkyl are typically used where X and Y indicate the number of carbon atoms in the chain. For example, (C_{1-6})alkyl includes alkyls that have a chain of between 1 and 6 carbons (*e.g.*, methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (*e.g.*, as in arylalkyl, heteroarylalkyl and the like) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (*e.g.*,

(C_{6-10})aryl(C_{1-3})alkyl includes, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, 2-thienylmethyl, 2-pyridinylmethyl and the like). In particular embodiments, "alkyl," either alone or represented along with another radical, can be a (C_{1-20})alkyl, a (C_{1-15})alkyl, a (C_{1-10})alkyl, a (C_{1-5})alkyl or a (C_{1-3})alkyl. Alternatively, "alkyl," either alone or represented along with another radical, can be a (C_1)alkyl, a (C_2)alkyl or a (C_3)alkyl.

[0038] "Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical. (C_X)alkylene and (C_{X-Y})alkylene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, (C_{1-6})alkylene includes methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), trimethylene ($-CH_2CH_2CH_2-$), tetramethylene ($-CH_2CH_2CH_2CH_2-$) 2-butenylene ($-CH_2CH=CHCH_2-$), 2-methyltetramethylene ($-CH_2CH(CH_3)CH_2CH_2-$), pentamethylene ($-CH_2CH_2CH_2CH_2CH_2-$) and the like. In particular embodiments, "alkylene," either alone or represented along with another radical, can be a (C_{1-20})alkylene, a (C_{1-15})alkylene, a (C_{1-10})alkylene, a (C_{1-5})alkylene or a (C_{1-3})alkylene. Alternatively, "alkylene," either alone or represented along with another radical, can be a (C_1)alkylene, a (C_2)alkylene or a (C_3)alkylene.

[0039] "Alkylidene" means a straight or branched, saturated or unsaturated, aliphatic radical connected to the parent molecule by a double bond. (C_X)alkylidene and (C_{X-Y})alkylidene are typically used where X and Y indicate the number of carbon atoms in the chain. For example, (C_{1-6})alkylidene includes methylene ($=CH_2$), ethylidene ($=CHCH_3$), isopropylidene ($=C(CH_3)_2$), propylidene ($=CHCH_2CH_3$), allylidene ($=CH-CH=CH_2$), and the like. In particular embodiments, "alkylidene," either alone or represented along with another radical, can be a (C_{1-20})alkylidene, a (C_{1-15})alkylidene, a (C_{1-10})alkylidene, a (C_{1-5})alkylidene or a (C_{1-3})alkylidene. Alternatively, "alkylidene," either alone or represented along with another radical, can be a (C_1)alkylidene, a (C_2)alkylidene or a (C_3)alkylidene.

[0040] "Alkynyl" means a straight or branched, carbon chain that contains at least one carbon-carbon triple bond ($-C\equiv C-$ or $-C\equiv CR$, wherein R is hydrogen or a further substituent). Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like. In particular embodiments, "alkynyl," either alone or represented along with another radical, can be a (C_{2-20})alkynyl, a (C_{2-15})alkynyl, a (C_{2-10})alkynyl, a (C_{2-5})alkynyl or a (C_{2-3})alkynyl. Alternatively, "alkynyl," either alone or represented along with another radical, can be a (C_2)alkynyl, a (C_3)alkynyl or a (C_4)alkynyl.

[0041] "Alkynylene" means a straight or branched, divalent carbon chain having one or more carbon-carbon triple bonds ($-CR\equiv CR'-$, wherein R and R' are each independently hydrogen or further substituents). Examples of alkynylene include ethyne-1,2-diyl, propyne-

1,3-diyl, and the like. In particular embodiments, "alkynylene," either alone or represented along with another radical, can be a (C_{2-20}) alkynylene, a (C_{2-15}) alkynylene, a (C_{2-10}) alkynylene, a (C_{2-5}) alkynylene or a (C_{2-3}) alkynylene. Alternatively, "alkynylene," either alone or represented along with another radical, can be a (C_2) alkynylene, a (C_3) alkynylene or a (C_4) alkynylene.

[0042] "Amido" means the radical –C(=O)-NR-, –C(=O)-NRR', -NR-C(=O)- and/or -NR-C(=O)R', wherein each R and R' are independently hydrogen or a further substituent.

[0043] "Amino" means a nitrogen moiety having two further substituents where, for example, a hydrogen or carbon atom is attached to the nitrogen. For example, representative amino groups include $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH((C_{1-10})alkyl), -N((C_{1-10})alkyl)$_2$, -NH(aryl), -NH(heteroaryl), -N(aryl)$_2$, -N(heteroaryl)$_2$, and the like. Optionally, the two substituents together with the nitrogen may also form a ring. Unless indicated otherwise, the compounds of the invention containing amino moieties may include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like.

[0044] "Animal" includes humans, non-human mammals (*e.g.*, dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (*e.g.*, birds, and the like).

[0045] "Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi electrons is equal to 4n+2. An aromatic ring may be such that the ring atoms are only carbon atoms or may include carbon and non-carbon atoms (See "heteroaryl").

[0046] "Aryl" means a monocyclic or polycyclic ring assembly wherein each ring is aromatic or when fused with one or more rings forms an aromatic ring assembly. If one or more ring atoms is not carbon (*e.g.*, N, S), the aryl is a heteroaryl. (C_X)aryl and (C_{X-Y})aryl are typically used where X and Y indicate the number of carbon atoms in the ring. In particular embodiments, "aryl," either alone or represented along with another radical, can be a (C_{3-14})aryl, a (C_{3-10})aryl, a (C_{3-7})aryl, a (C_{5-10})aryl or a (C_{5-7})aryl. Alternatively, "aryl," either alone or represented along with another radical, can be a (C_5)aryl, a (C_6)aryl, a (C_7)aryl, a (C_8)aryl., a (C_9)aryl or a (C_{10})aryl.

[0047] "Azaalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with substituted or unsubstituted nitrogen atoms (-NR- or -NRR', wherein R and R' are each independently hydrogen or further substituents). For example, a (C_{1-10})azaalkyl refers to a chain comprising between 1 and 10 carbons and one or more nitrogen atoms.

[0048] "Bicycloalkyl" means a saturated or partially unsaturated fused, spiro or bridged bicyclic ring assembly. In particular embodiments, "bicycloalkyl," either alone or represented along with another radical, can be a (C_{4-15})bicycloalkyl, a (C_{4-10})bicycloalkyl, a (C_{6-10})bicycloalkyl or a (C_{8-10})bicycloalkyl. Alternatively, "bicycloalkyl," either alone or represented along with another radical, can be a (C_8)bicycloalkyl, a (C_9)bicycloalkyl or a (C_{10})bicycloalkyl.

[0049] "Bicycloaryl" means a fused, spiro or bridged bicyclic ring assembly wherein at least one of the rings comprising the assembly is aromatic. (C_X)bicycloaryl and (C_{X-Y})bicycloaryl are typically used where X and Y indicate the number of carbon atoms in the bicyclic ring assembly and directly attached to the ring. In particular embodiments, "bicycloaryl," either alone or represented along with another radical, can be a (a (C_{4-15})bicycloaryl, a (C_{4-10})bicycloaryl, a (C_{6-10})bicycloaryl or a (C_{8-10})bicycloaryl. Alternatively, "bicycloalkyl," either alone or represented along with another radical, can be a (C_8)bicycloaryl, a (C_9)bicycloaryl or a (C_{10})bicycloaryl.

[0050] "Bridging ring" and "bridged ring" as used herein refer to a ring that is bonded to another ring to form a compound having a bicyclic or polycyclic structure where two ring atoms that are common to both rings are not directly bound to each other. Non-exclusive examples of common compounds having a bridging ring include borneol, norbornane, 7-oxabicyclo[2.2.1]heptane, and the like. One or both rings of the bicyclic system may also comprise heteroatoms.

[0051] "Carbamoyl" means the radical -OC(O)NRR', wherein R and R' are each independently hydrogen or further substituents.

[0052] "Carbocycle" means a ring consisting of carbon atoms.

[0053] "Carbonyl" means the radical –C(=O)- and/or –C(=O)R, wherein R is hydrogen or a further substituent. It is noted that the carbonyl radical may be further substituted with a variety of substituents to form different carbonyl groups including acids, acid halides, aldehydes, amides, esters, and ketones.

[0054] "Carboxy" means the radical –C(=O)-O- and/or –C(=O)-OR, wherein R is hydrogen or a further substituent. It is noted that compounds of the invention containing carboxy moieties may include protected derivatives thereof, *i.e.*, where the oxygen is substituted with a protecting group. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the like.

[0055] "Cyano" means the radical -CN.

[0056] "Cycloalkyl" means a non-aromatic, saturated or partially unsaturated, monocyclic, bicyclic or polycyclic ring assembly. (C_X)cycloalkyl and (C_{X-Y})cycloalkyl are typically used where X and Y indicate the number of carbon atoms in the ring assembly. For example, (C_{3-10})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like. In particular embodiments, "cycloalkyl," either alone or represented along with another radical, can be a (C_{3-14})cycloalkyl, a (C_{3-10})cycloalkyl, a (C_{3-7})cycloalkyl, a (C_{8-10})cycloalkyl or a (C_{5-7})cycloalkyl. Alternatively, "cycloalkyl," either alone or represented along with another radical, can be a (C_5)cycloalkyl, a (C_6)cycloalkyl, a (C_7)cycloalkyl, a (C_8)cycloalkyl., a (C_9)cycloalkyl or a (C_{10})cycloalkyl.

[0057] "Cycloalkylene" means a divalent, saturated or partially unsaturated, monocyclic, bicyclic or polycyclic ring assembly. (C_X)cycloalkylene and (C_{X-Y})cycloalkylene are typically used where X and Y indicate the number of carbon atoms in the ring assembly. In particular embodiments, "cycloalkylene," either alone or represented along with another radical, can be a (C_{3-14})cycloalkylene, a (C_{3-10})cycloalkylene, a (C_{3-7})cycloalkylene, a (C_{8-10})cycloalkylene or a (C_{5-7})cycloalkylene. Alternatively, "cycloalkylene," either alone or represented along with another radical, can be a (C_5)cycloalkylene, a (C_6)cycloalkylene, a (C_7)cycloalkylene, a (C_8)cycloalkylene., a (C_9)cycloalkylene or a (C_{10})cycloalkylene.

[0058] "Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, *i.e.*, the "side effects" of such therapy.

[0059] "Fused ring" as used herein refers to a ring that is bonded to another ring to form a compound having a bicyclic structure where the ring atoms that are common to both rings are directly bound to each other. Non-exclusive examples of common fused rings include decalin, naphthalene, anthracene, phenanthrene, indole, furan, benzofuran, quinoline, and the like. Compounds having fused ring systems may be saturated, partially saturated, carbocyclics, heterocyclics, aromatics, heteroaromatics, and the like.

[0060] "Halo" means fluoro, chloro, bromo or iodo.

[0061] "Heteroalkyl" means alkyl, as defined in this Application, provided that one or more of the atoms within the alkyl chain is a heteroatom. In particular embodiments, "heteroalkyl," either alone or represented along with another radical, can be a hetero(C_{1-20})alkyl, a hetero(C_{1-15})alkyl, a hetero(C_{1-10})alkyl, a hetero(C_{1-5})alkyl, a hetero(C_{1-3})alkyl or a

hetero(C_{1-2})alkyl. Alternatively, "heteroalkyl," either alone or represented along with another radical, can be a hetero(C_1)alkyl, a hetero(C_2)alkyl or a hetero(C_3)alkyl.

[0062] "Heteroaryl" means a monocyclic, bicyclic or polycyclic aromatic group wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. Monocyclic heteroaryl groups include, but are not limited to, cyclic aromatic groups having five or six ring atoms, wherein at least one ring atom is a heteroatom and the remaining ring atoms are carbon. The nitrogen atoms can be optionally quaternerized and the sulfur atoms can be optionally oxidized. Heteroaryl groups of this invention include, but are not limited to, those derived from furan, imidazole, isothiazole, isoxazole, oxadiazole, oxazole, 1,2,3-oxadiazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrroline, thiazole, 1,3,4-thiadiazole, triazole and tetrazole. "Heteroaryl" also includes, but is not limited to, bicyclic or tricyclic rings, wherein the heteroaryl ring is fused to one or two rings independently selected from the group consisting of an aryl ring, a cycloalkyl ring, a cycloalkenyl ring, and another monocyclic heteroaryl or heterocycloalkyl ring. These bicyclic or tricyclic heteroaryls include, but are not limited to, those derived from benzo[b]furan, benzo[b]thiophene, benzimidazole, imidazo[4,5-c]pyridine, quinazoline, thieno[2,3-c]pyridine, thieno[3,2-b]pyridine, thieno[2,3-b]pyridine, indolizine, imidazo[1,2a]pyridine, quinoline, isoquinoline, phthalazine, quinoxaline, naphthyridine, quinolizine, indole, isoindole, indazole, indoline, benzoxazole, benzopyrazole, benzothiazole, imidazo[1,5-a]pyridine, pyrazolo[1,5-a]pyridine, imidazo[1,2-a]pyrimidine, imidazo[1,2-c]pyrimidine, imidazo[1,5-a]pyrimidine, imidazo[1,5-c]pyrimidine, pyrrolo[2,3-b]pyridine, pyrrolo[2,3-c]pyridine, pyrrolo[3,2-c]pyridine, pyrrolo[3,2-b]pyridine, pyrrolo[2,3-d]pyrimidine, pyrrolo[3,2-d]pyrimidine, pyrrolo[2,3-b]pyrazine, pyrazolo[1,5-a]pyridine, pyrrolo[1,2-b]pyridazine, pyrrolo[1,2-c]pyrimidine, pyrrolo[1,2-a]pyrimidine, pyrrolo[1,2-a]pyrazine, triazo[1,5-a]pyridine, pteridine, purine, carbazole, acridine, phenazine, phenothiazene, phenoxazine, 1,2-dihydropyrrolo[3,2,1-*hi*]indole, indolizine, pyrido[1,2-a]indole and 2(1H)-pyridinone. The bicyclic or tricyclic heteroaryl rings can be attached to the parent molecule through either the heteroaryl group itself or the aryl, cycloalkyl, cycloalkenyl or heterocycloalkyl group to which it is fused. The heteroaryl groups of this invention can be substituted or unsubstituted. In particular embodiments, "heteroaryl," either alone or represented along with another radical, can be a hetero(C_{1-13})aryl, a hetero(C_{2-13})aryl, a hetero(C_{2-6})aryl, a hetero(C_{3-9})aryl or a hetero(C_{5-9})aryl. Alternatively, "heteroaryl," either alone or represented along with another radical, can be a hetero(C_3)aryl, a hetero(C_4)aryl, a hetero(C_5)aryl, a hetero(C_6)aryl., a hetero(C_7)aryl, a hetero(C_8)aryl or a hetero(C_9)aryl.

[0063] "Heteroatom" refers to an atom that is not a carbon atom. Particular examples of heteroatoms include, but are not limited to, nitrogen, oxygen, and sulfur.

[0064] "Heteroatom moiety" includes a moiety where the atom by which the moiety is attached is not a carbon. Examples of heteroatom moieties include -NR-, $-N^{+}(O^{-})=$, -O-, -S- or $-S(O)_2-$, wherein R is hydrogen or a further substituent.

[0065] "Heterobicycloalkyl" means bicycloalkyl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example hetero(C_{9-12})bicycloalkyl as used in this application includes, but is not limited to, 3-aza-bicyclo[4.1.0]hept-3-yl, 2-aza-bicyclo[3.1.0]hex-2-yl, 3-aza-bicyclo[3.1.0]hex-3-yl, and the like. In particular embodiments, "heterobicycloalkyl," either alone or represented along with another radical, can be a hetero(C_{1-14})bicycloalkyl, a hetero(C_{4-14})bicycloalkyl, a hetero(C_{4-9})bicycloalkyl or a hetero(C_{5-9})bicycloalkyl. Alternatively, "heterobicycloalkyl," either alone or represented along with another radical, can be a hetero(C_5)bicycloalkyl, hetero(C_6)bicycloalkyl, hetero(C_7)bicycloalkyl, hetero(C_8)bicycloalkyl or a hetero(C_9)bicycloalkyl.

[0066] "Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the atoms within the ring is a heteroatom. For example, hetero(C_{4-12})bicycloaryl as used in this Application includes, but is not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, tetrahydroisoquinolinyl, and the like. In particular embodiments, "heterobicycloaryl," either alone or represented along with another radical, can be a hetero(C_{1-14})bicycloaryl, a hetero(C_{4-14})bicycloaryl, a hetero(C_{4-9})bicycloarylor a hetero(C_{5-9})bicycloaryl Alternatively, "heterobicycloaryl," either alone or represented along with another radical, can be a hetero(C_5)bicycloaryl, hetero(C_6)bicycloaryl, hetero(C_7)bicycloaryl, hetero(C_8)bicycloaryl or a hetero(C_9)bicycloaryl.

[0067] "Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the atoms forming the ring is a heteroatom selected, independently from N, O, or S. Non-exclusive examples of heterocycloalkyl include piperidyl, 4-morpholyl, 4-piperazinyl, pyrrolidinyl, perhydropyrrolizinyl, 1,4-diazaperhydroepinyl, 1,3-dioxanyl, 1,4-dioxanyl and the like. In particular embodiments, "heterocycloalkyl," either alone or represented along with another radical, can be a hetero(C_{1-13})cycloalkyl, a hetero(C_{1-9})cycloalkyl, a hetero(C_{1-6})cycloalkyl, a hetero(C_{5-9})cycloalkyl or a hetero(C_{2-5})cycloalkyl. Alternatively, "heterocycloalkyl," either alone or represented along with another radical, can be a hetero(C_2)cycloalkyl, a hetero(C_3)cycloalkyl, a

hetero(C_4)cycloalkyl, a hetero(C_5)cycloalkyl, a hetero(C_6)cycloalkyl, hetero(C_7)cycloalkyl, hetero(C_8)cycloalkyl or a hetero(C_9)cycloalkyl.

[0068] "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms is replaced by a heteroatom. In particular embodiments, "heterocycloalkylene," either alone or represented along with another radical, can be a hetero(C_{1-12})cycloalkylene, a hetero(C_{1-9})cycloalkylene, a hetero(C_{1-6})cycloalkylene, a hetero(C_{5-9})cycloalkylene or a hetero(C_{2-6})cycloalkylene. Alternatively, "heterocycloalkylene," either alone or represented along with another radical, can be a hetero(C_2)cycloalkylene, a hetero(C_3)cycloalkylene, a hetero(C_4)cycloalkylene, a hetero(C_5)cycloalkylene, a hetero(C_6)cycloalkylene, hetero(C_7)cycloalkylene, hetero(C_8)cycloalkylene or a hetero(C_9)cycloalkylene.

[0069] "Hydroxy" means the radical -OH.

[0070] "IC_{50}" means the molar concentration of an inhibitor that produces 50% inhibition of the target enzyme.

[0071] "Imino" means the radical –CR(=NR') and/or –C(=NR')-, wherein R and R' are each independently hydrogen or a further substituent.

[0072] "Isomers" means compounds having identical molecular formulae but differing in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers." Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers." A carbon atom bonded to four nonidentical substituents is termed a "chiral center." A compound with one chiral center has two enantiomeric forms of opposite chirality. A mixture of the two enantiomeric forms is termed a "racemic mixture." A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomer or as a mixture of diastereomers, termed a "diastereomeric mixture." When one chiral center is present a stereoisomer may be characterized by the absolute configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art

(*e.g.*, see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

[0073] "Leaving group" means the group with the meaning conventionally associated with it in synthetic organic chemistry, *i.e.*, an atom or group displaceable under reaction (*e.g.*, alkylating) conditions. Examples of leaving groups include, but are not limited to, halo (*e.g.*, F, Cl, Br and I), alkyl (*e.g.*, methyl and ethyl) and sulfonyloxy (*e.g.*, mesyloxy, ethanesulfonyloxy, benzenesulfonyloxy and tosyloxy), thiomethyl, thienyloxy, dihalophosphinoyloxy, tetrahalophosphoxy, benzyloxy, isopropyloxy, acyloxy, and the like.

[0074] "Moiety providing X atom separation" and "linker providing X atom separation" between two other moieties mean that the chain of atoms directly linking the two other moieties is X atoms in length. When X is given as a range (*e.g.*, X_1-X_2), then the chain of atoms is at least X_1 and not more than X_2 atoms in length. It is understood that the chain of atoms can be formed from a combination of atoms including, for example, carbon, nitrogen, sulfur and oxygen atoms. Further, each atom can optionally be bound to one or more substituents, as valencies allow. In addition, the chain of atoms can form part of a ring. Accordingly, in one embodiment, a moiety providing X atom separation between two other moieties (R and R') can be represented by R-$(L)_x$-R' where each L is independently selected from the group consisting of CR"R'", NR"", O, S, CO, CS, C=NR"", SO, SO_2, and the like, where any two or more of R", R'", R"" and R"" can be taken together to form a substituted or unsubstituted ring.

[0075] "Nitro" means the radical -NO_2.

[0076] "Oxaalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with oxygen atoms (-O- or –OR, wherein R is hydrogen or a further substituent). For example, an oxa(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbons and one or more oxygen atoms.

[0077] "Oxoalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with carbonyl groups (-C(=O)- or –C(=O)-R, wherein R is hydrogen or a further substituent). The carbonyl group may be an aldehyde, ketone, ester, amide, acid, or acid halide. For example, an oxo(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbon atoms and one or more carbonyl groups.

[0078] "Oxy" means the radical –O- or –OR, wherein R is hydrogen or a further substituent. Accordingly, it is noted that the oxy radical may be further substituted with a variety of substituents to form different oxy groups including hydroxy, alkoxy, aryloxy, heteroaryloxy or carbonyloxy.

[0079] "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

[0080] "Pharmaceutically acceptable salts" means salts of compounds of the present invention which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

[0081] Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

[0082] "Polycyclic ring" includes bicyclic and multi-cyclic rings. The individual rings comprising the polycyclic ring can be fused, spiro or bridging rings.

[0083] "Prodrug" means a compound that is convertible *in vivo* metabolically into an inhibitor according to the present invention. The prodrug itself may or may not also have activity with respect to a given target protein. For example, a compound comprising a hydroxy group may be administered as an ester that is converted by hydrolysis *in vivo* to the hydroxy compound. Suitable esters that may be converted *in vivo* into hydroxy compounds include acetates, citrates, lactates, phosphates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulfonates, ethanesulfonates, benzenesulfonates,

p-toluenesulfonates, cyclohexylsulfamates, quinates, esters of amino acids, and the like. Similarly, a compound comprising an amine group may be administered as an amide that is converted by hydrolysis *in vivo* to the amine compound.

[0084] "Protected derivatives" means derivatives of inhibitors in which a reactive site or sites are blocked with protecting groups. Protected derivatives are useful in the preparation of inhibitors or in themselves may be active as inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

[0085] "Ring" and "ring assembly" means a carbocyclic or a heterocyclic system and includes aromatic and non-aromatic systems. The system can be monocyclic, bicyclic or polycyclic. In addition, for bicyclic and polycyclic systems, the individual rings comprising the polycyclic ring can be fused, spiro or bridging rings.

[0086] "Subject" and "patient" include humans, non-human mammals (*e.g.*, dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (*e.g.*, birds, and the like).

[0087] "Substituent convertible to hydrogen *in vivo*" means any group that is convertible to a hydrogen atom by enzymological or chemical means including, but not limited to, hydrolysis and hydrogenolysis. Examples include hydrolyzable groups, such as acyl groups, groups having an oxycarbonyl group, amino acid residues, peptide residues, o-nitrophenylsulfenyl, trimethylsilyl, tetrahydro-pyranyl, diphenylphosphinyl, and the like. Examples of acyl groups include formyl, acetyl, trifluoroacetyl, and the like. Examples of groups having an oxycarbonyl group include ethoxycarbonyl, t-butoxycarbonyl [$(CH_3)_3C$-OCO-], benzyloxycarbonyl, p-methoxybenzyloxycarbonyl, vinyloxycarbonyl, β-(p-toluenesulfonyl)ethoxycarbonyl, and the like. Examples of suitable amino acid residues include amino acid residues *per se* and amino acid residues that are protected with a protecting group. Suitable amino acid residues include, but are not limited to, residues of Gly (glycine), Ala (alanine; $CH_3CH(NH_2)CO$-), Arg (arginine), Asn (asparagine), Asp (aspartic acid), Cys (cysteine), Glu (glutamic acid), His (histidine), Ile (isoleucine), Leu (leucine; $(CH_3)_2CHCH_2CH(NH_2)CO$-), Lys (lysine), Met (methionine), Phe (phenylalanine), Pro (proline), Ser (serine), Thr (threonine), Trp (tryptophan), Tyr (tyrosine), Val (valine), Nva (norvaline), Hse (homoserine), 4-Hyp (4-hydroxyproline), 5-Hyl (5-hydroxylysine), Orn (ornithine) and β-Ala. Examples of suitable protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), t-

butoxycarbonyl groups [$(CH_3)_3C$-OCO-], and the like. Suitable peptide residues include peptide residues comprising two to five, and optionally two to three, of the aforesaid amino acid residues. Examples of such peptide residues include, but are not limited to, residues of such peptides as Ala-Ala [$CH_3CH(NH_2)CO$-$NHCH(CH_3)CO$-], Gly-Phe, Nva-Nva, Ala-Phe, Gly-Gly, Gly-Gly-Gly, Ala-Met, Met-Met, Leu-Met and Ala-Leu. The residues of these amino acids or peptides can be present in stereochemical configurations of the D-form, the L-form or mixtures thereof. In addition, the amino acid or peptide residue may have an asymmetric carbon atom. Examples of suitable amino acid residues having an asymmetric carbon atom include residues of Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr and Tyr. Peptide residues having an asymmetric carbon atom include peptide residues having one or more constituent amino acid residues having an asymmetric carbon atom. Examples of suitable amino acid protecting groups include those typically employed in peptide synthesis, including acyl groups (such as formyl and acetyl), arylmethyloxycarbonyl groups (such as benzyloxycarbonyl and p-nitrobenzyloxycarbonyl), t-butoxycarbonyl groups [$(CH_3)_3C$-OCO-], and the like. Other examples of substituents "convertible to hydrogen *in vivo*" include reductively eliminable hydrogenolyzable groups. Examples of suitable reductively eliminable hydrogenolyzable groups include, but are not limited to, arylsulfonyl groups (such as o-toluenesulfonyl); methyl groups substituted with phenyl or benzyloxy (such as benzyl, trityl and benzyloxymethyl); arylmethoxycarbonyl groups (such as benzyloxycarbonyl and o-methoxy-benzyloxycarbonyl); and halogenoethoxycarbonyl groups (such as β,β,β-trichloroethoxycarbonyl and β-iodoethoxycarbonyl).

[0088] "Substituted or unsubstituted" means that a given moiety may consist of only hydrogen substituents through available valencies (unsubstituted) or may further comprise one or more non-hydrogen substituents through available valencies (substituted) that are not otherwise specified by the name of the given moiety. For example, isopropyl is an example of an ethylene moiety that is substituted by $-CH_3$. In general, a non-hydrogen substituent may be any substituent that may be bound to an atom of the given moiety that is specified to be substituted. Examples of substituents include, but are not limited to, aldehyde, alicyclic, aliphatic, (C_{1-10})alkyl, alkylene, alkylidene, amide, amino, aminoalkyl, aromatic, aryl, bicycloalkyl, bicycloaryl, carbamoyl, carbocyclyl, carboxyl, carbonyl group, cycloalkyl, cycloalkylene, ester, halo, heterobicycloalkyl, heterocycloalkylene, heteroaryl, heterobicycloaryl, heterocycloalkyl, oxo, hydroxy, iminoketone, ketone, nitro, oxaalkyl, and oxoalkyl moieties, each of which may optionally also be substituted or unsubstituted. In one particular embodiment, examples of substituents include, but are not limited to, hydrogen, halo,

nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, (C_{1-10})azaalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl. In addition, the substituent is itself optionally substituted by a further substituent. In one particular embodiment, examples of the further substituent include, but are not limited to, hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, (C_{1-10})azaalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl.

[0089] "Sulfinyl" means the radical –SO- and/or –SO-R, wherein R is hydrogen or a further substituent. It is noted that the sulfinyl radical may be further substituted with a variety of substituents to form different sulfinyl groups including sulfinic acids, sulfinamides, sulfinyl esters, and sulfoxides.

[0090] "Sulfonyl" means the radical -SO_2- and/or –SO_2-R, wherein R is hydrogen or a further substituent. It is noted that the sulfonyl radical may be further substituted with a variety of substituents to form different sulfonyl groups including sulfonic acids, sulfonamides, sulfonate esters, and sulfones.

[0091] "Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

[0092] "Thio" denotes replacement of an oxygen by a sulfur and includes, but is not limited to, -SR, -S- and =S containing groups.

[0093] "Thioalkyl" means an alkyl, as defined above, except where one or more of the carbon atoms forming the alkyl chain are replaced with sulfur atoms (-S- or –S-R, wherein R is

hydrogen or a further substituent). For example, a thio(C_{1-10})alkyl refers to a chain comprising between 1 and 10 carbons and one or more sulfur atoms.

[0094] "Thiocarbonyl" means the radical –C(=S)- and/or –C(=S)-R, wherein R is hydrogen or a further substituent. It is noted that the thiocarbonyl radical may be further substituted with a variety of substituents to form different thiocarbonyl groups including thioacids, thioamides, thioesters, and thioketones.

[0095] "Treatment" or "treating" means any administration of a compound of the present invention and includes:

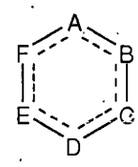
(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, arresting further development of the pathology and/or symptomatology), or

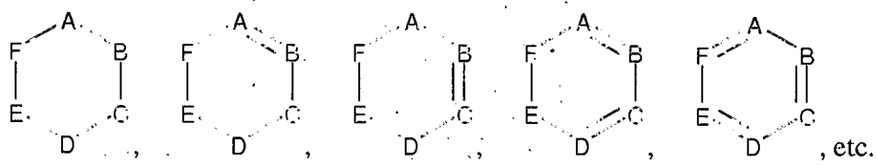
(3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (*i.e.*, reversing the pathology and/or symptomatology).

[0096] It is noted in regard to all of the definitions provided herein that the definitions should be interpreted as being open ended in the sense that further substituents beyond those specified may be included. Hence, a C_1 alkyl indicates that there is one carbon atom but does not indicate what the substituents on the carbon atom are. Hence, a (C_1)alkyl comprises methyl (*i.e.*, -CH_3) as well as -CR'R"R" where R, R', and R" may each independently be hydrogen or a further substituent where the atom attached to the carbon is a heteroatom or cyano. Hence, CF_3, CH_2OH and CH_2CN, for example, are all (C_1)alkyls. Similarly, terms such as alkylamino and the like comprise dialkylamino and the like.

[0097] A compound having a formula that is represented with a dashed bond is intended to include the formulae optionally having zero, one or more double bonds, as exemplified and shown below:



represents



, etc.

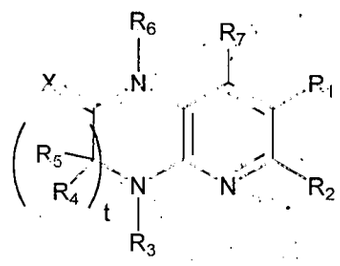
[0098] In addition, atoms making up the compounds of the present invention are intended to include all isotopic forms of such atoms. Isotopes, as used herein, include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include ^{13}C and ^{14}C.

DETAILED DESCRIPTION OF THE INVENTION

[0099] The present invention relates to compounds that may be used to inhibit PARP. The present invention also relates to pharmaceutical compositions, kits and articles of manufacture comprising such compounds. In addition, the present invention relates to methods and intermediates useful for making the compounds. Further, the present invention relates to methods of using said compounds. It is noted that the compounds of the present invention may also possess activity for other members of the same protein family and thus may be used to address disease states associated with these other family members.

PARP Inhibitors

[0100] In one of its aspects, the present invention relates to compounds that are useful as PARP inhibitors. In one embodiment, PARP inhibitors of the present invention comprise:



or a polymorph, solvate, ester, tautomer, enantiomer, pharmaceutically acceptable salt or prodrug thereof, wherein

t is selected from the group consisting of 1 or 2;

X is selected from the group consisting of O, S and NR_8;

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, amino(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_1 is $-L_1$-R_{13};

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{13} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_2 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_3 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_3 has the formula $-L_2-R_{18}$;

L_2 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{18} and the ring to which L_2 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_4 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_5 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

or any two of P_3, P_4 and P_5 are taken together to form a substituted or unsubstituted ring;

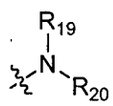
P_6 is selected from the group consisting of hydrogen, carbonyloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_8 is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl,

aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_{13} has the formula:



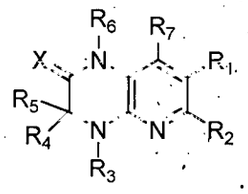
;

R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

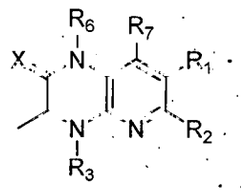
R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{19} and R_{20} are taken together to form a substituted or unsubstituted ring.

[0101] In one variation of the above embodiment, the compound is not: (i) 3-methylpyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one; (ii) 3-methoxypyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one; (iii) 2-(3-chloro-6-oxo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-N-o-tolylacetamide; (iv) 2-(3-chloro-6-oxo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-N-(3-(trifluoromethyl)phenyl)acetamide; (v) 5-Oxo-3-(2-trifluoromethyl-benzyl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid isopropylamide; (vi) 3-(5-Fluoro-2-trifluoromethyl-benzoyl)-5-oxo-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid phenylamide; (vii) 5-Oxo-3-(2-trifluoromethyl-benzoyl)-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid pentylamide; or (viii) 3-(5-Fluoro-2-trifluoromethyl-benzoyl)-5-oxo-2,3,4,4a,5,6-hexahydro-1H-pyrazino[1,2-a]quinoxaline-8-carboxylic acid butylamide.

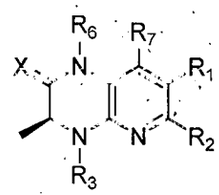
[0102] In a further embodiment, PARP inhibitors of the present invention comprise:



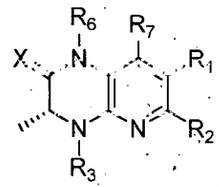
[0103] In another embodiment, PARP inhibitors of the present invention comprise:



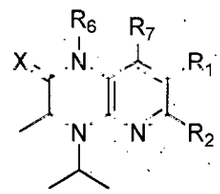
[0104] In still another embodiment, PARP inhibitors of the present invention comprise:



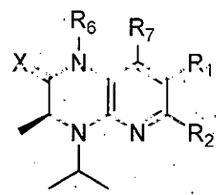
[0105] In yet another embodiment, PARP inhibitors of the present invention comprise:



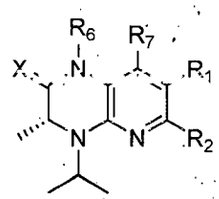
[0106] In a further embodiment, PARP inhibitors of the present invention comprise:



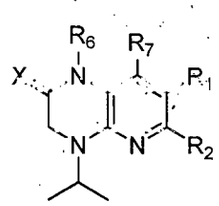
[0107] In still a further embodiment, PARP inhibitors of the present invention comprise:



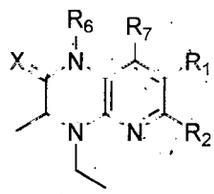
[0108] In yet a further embodiment, PARP inhibitors of the present invention comprise:



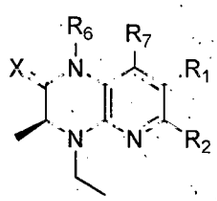
[0109] In another embodiment, PARP inhibitors of the present invention comprise:



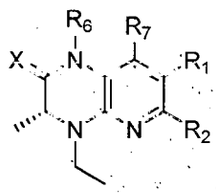
[0110] In still another embodiment, PARP inhibitors of the present invention comprise:



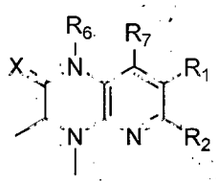
[0111] In yet another embodiment, PARP inhibitors of the present invention comprise:



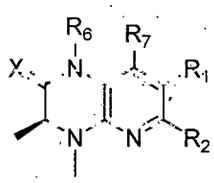
[0112] In a further embodiment, PARP inhibitors of the present invention comprise:



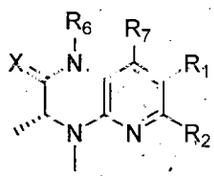
[0113] In still a further embodiment, PARP inhibitors of the present invention comprise:



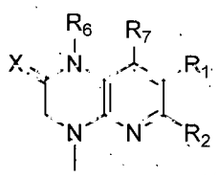
[0114] In yet a further embodiment, PARP inhibitors of the present invention comprise:



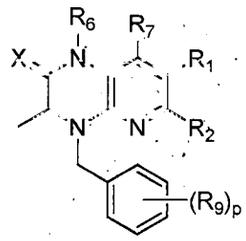
[0115] In another embodiment, PARP inhibitors of the present invention comprise:



[0116] In still another embodiment, PARP inhibitors of the present invention comprise:



[0117] In yet another embodiment, PARP inhibitors of the present invention comprise:

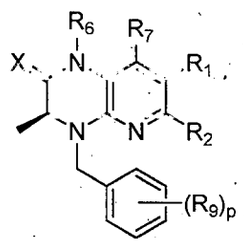


wherein

p is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0118] In a further embodiment, PARP inhibitors of the present invention comprise:



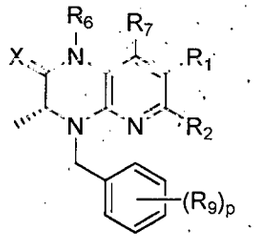
wherein

p is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0119] In still a further embodiment, PARP inhibitors of the present invention comprise:

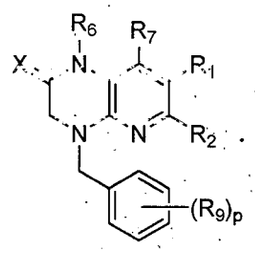


wherein

p is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0120] In yet a further embodiment, PARP inhibitors of the present invention comprise:

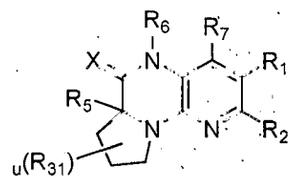


wherein

p is selected from the group consisting of 0, 1, 2, 3, 4 and 5; and

R_9 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0121] In a further embodiment, PARP inhibitors of the present invention comprise:



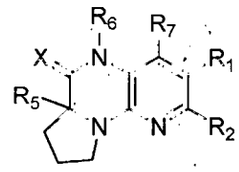
wherein

u is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

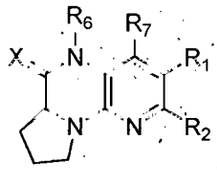
R_{31} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

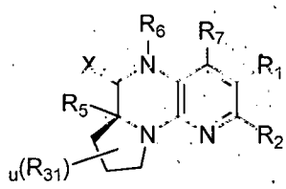
[0122] In another embodiment, PARP inhibitors of the present invention comprise:



[0123] In a further embodiment, PARP inhibitors of the present invention comprise:



[0124] In yet a further embodiment, PARP inhibitors of the present invention comprise:

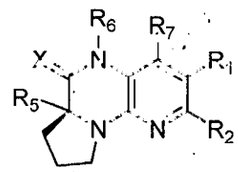


wherein

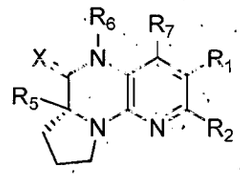
u is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

R_{31} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

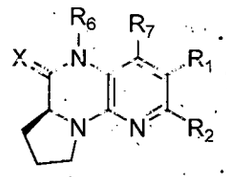
[0125] In still another embodiment, PARP inhibitors of the present invention comprise:



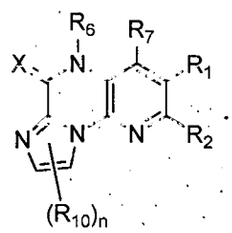
[0126] In yet another embodiment, PARP inhibitors of the present invention comprise:



[0127] In another embodiment, PARP inhibitors of the present invention comprise:



[0128] In a further embodiment, PARP inhibitors of the present invention comprise:



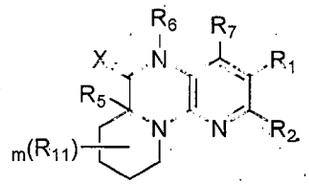
wherein

n is selected from the group consisting of 0, 1 and 2; and

R_{10} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0129] In still a further embodiment, PARP inhibitors of the present invention comprise:

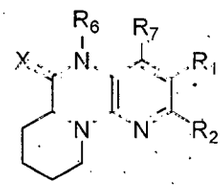


wherein

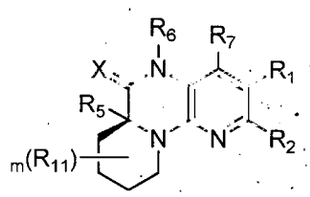
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{3-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0130] In another embodiment, PARP inhibitors of the present invention comprise:



[0131] In still another embodiment, PARP inhibitors of the present invention comprise:

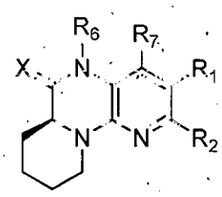


wherein

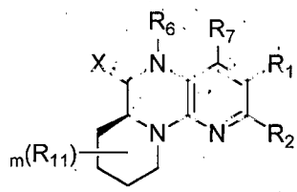
m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

P_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0132] In yet another embodiment, PARP inhibitors of the present invention comprise:



[0133] In yet a further embodiment, PARP inhibitors of the present invention comprise:



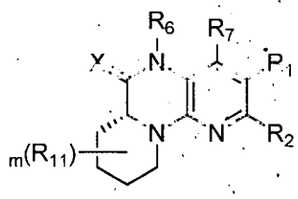
wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

R_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0134] In another embodiment, PARP inhibitors of the present invention comprise:

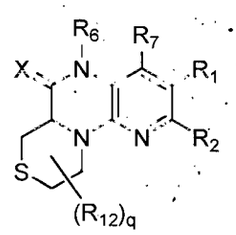


wherein

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

P_{11} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0135] In still another embodiment, PARP inhibitors of the present invention comprise:

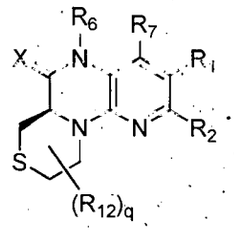


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

P_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0136] In yet another embodiment, PARP inhibitors of the present invention comprise:

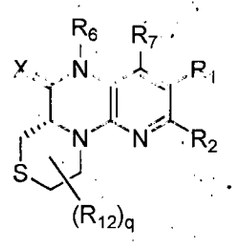


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

P_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0137] In a further embodiment, PARP inhibitors of the present invention comprise:

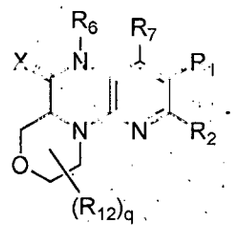


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

P_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0138] In still a further embodiment, PARP inhibitors of the present invention comprise:



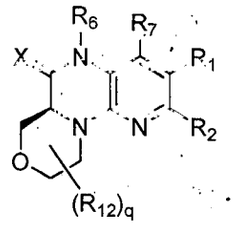
wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

P_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0139] In yet a further embodiment, PARP inhibitors of the present invention comprise:

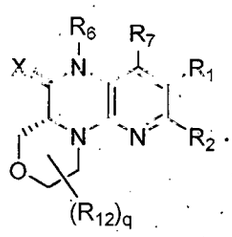


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

R_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0140] In another embodiment, PARP inhibitors of the present invention comprise:

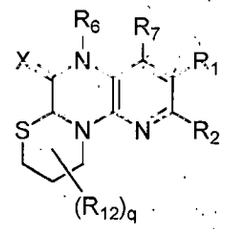


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

R_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0141] In still another embodiment, PARP inhibitors of the present invention comprise:

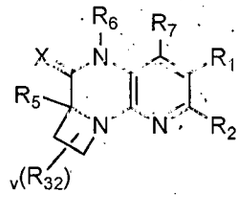


wherein

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

R_{12} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0142] In a further embodiment, PARP inhibitors of the present invention comprise:



wherein

v is selected from the group consisting of 0, 1, 2, 3 and 4; and

R_{32} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0143] In one variation of each of the above embodiments and variations, X is O.

[0144] In another variation of each of the above embodiments and variations,

R_1 is $-L_1-R_{13}$;

L_1 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{13} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0145] In still another variation of each of the above embodiments and variations,

L_1 is absent or a linker selected from the group consisting of $-(CR_{14}R_{15})_r-$, -CO-, -CS-, $-C(=NR_{16})-$, $-NR_{17}-$, -O-, -S-, -SO-, $-SO_2-$ and combinations thereof;

r is selected from the group consisting of 1, 2 and 3;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{16} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl,

amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{17} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0146] In yet another variation of each of the above embodiments and variations,

L_1 is $-CR_{14}R_{15}-$;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0147] In a further variation of each of the above embodiments and variations, L_1 is $-CH_2-$. In another variation of each of the above embodiments and variations, L_1 is $-CF_2-$. In still a further variation of each of the above embodiments and variations, L_1 is $-NR_{17}-$. In yet a further variation of each of the above embodiments and variations, L_1 is $-O-$.

[0148] In yet another variation of each of the above embodiments and variations, R_2 is hydrogen. In a further variation of each of the above embodiments and variations, R_2 is halo. In still a further variation of each of the above embodiments and variations, R_2 is a substituted or unsubstituted (C_{1-3}) alkyl.

[0149] In still another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted (C_{1-3})alkyl. In yet another variation of each of the above embodiments and variations, R_3 is methyl. In a further variation of each of the above embodiments and variations, R_3 is ethyl. In still a further variation of each of the above embodiments and variations, R_3 is propyl. In yet a further variation of each of the above embodiments and variations, R_3 is isopropyl. In another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted aryl(C_{1-3})alkyl. In still another variation of each of the above embodiments and variations, R_3 is a substituted or unsubstituted benzyl.

[0150] In yet another variation of each of the above embodiments and variations, R_3 has the formula $-L_2-R_{18}$, wherein L_2 is absent or a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{18} and the ring to which L_2 is attached, wherein the atoms of the linker providing the separation are selected from the group consisting of carbon, oxygen, nitrogen, and sulfur; and R_{18} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy,

carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0151] In a further variation of each of the above embodiments and variations,

L_2 is absent or a linker selected from the group consisting of $-(CR_{14}R_{15})_r-$, -CO-, -CS-, $-C(=NR_{16})-$, $-NR_{17}-$, -O-, -S-, -SO-, $-SO_2-$ and combinations thereof;

r is selected from the group consisting of 1, 2 and 3;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{16} is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{17} is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0152] In still a further variation of each of the above embodiments and variations,

L_2 is $-CR_{14}R_{15}-$;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0153] In yet a further variation of each of the above embodiments and variations, L_2 is –CH_2-.

[0154] In still another variation of each of the above embodiments and variations, R_4 is a substituted or unsubstituted (C_{1-3})alkyl. In yet another variation of each of the above embodiments and variations, R_4 is methyl. In a further variation of each of the above embodiments and variations, R_4 is hydrogen.

[0155] In still a further variation of each of the above embodiments and variations, R_3 and R_4, together with the atoms to which they are attached, are taken to form a substituted or unsubstituted 3, 4, 5, 6, 7 or 8 membered ring. In yet a further variation of each of the above embodiments and variations, R_3 and R_4, together with the atoms to which they are attached, are taken to form a substituted or unsubstituted 3, 4, 5, 6, 7 or 8 membered heterocycloalkyl ring. In another variation of each of the above embodiments and variations, R_3 and R_4, together with the atoms to which they are attached, are taken to form a substituted or unsubstituted 3, 4, 5, 6, 7 or 8 membered heterocycloaryl ring.

[0156] In yet another variation of each of the above embodiments and variations, R_5 is hydrogen. In a further variation of each of the above embodiments and variations, R_5 is halo. In still a further variation of each of the above embodiments and variations, R_5 is a substituted or unsubstituted (C_{1-3}) alkyl.

[0157] In yet another variation of each of the above embodiments and variations, R_6 is hydrogen. In still a further variation of each of the above embodiments and variations, R_6 is a substituted or unsubstituted (C_{1-3}) alkyl.

[0158] In yet another variation of each of the above embodiments and variations, R_7 is hydrogen. In a further variation of each of the above embodiments and variations, R_7 is halo. In still a further variation of each of the above embodiments and variations, R_7 is a substituted or unsubstituted (C_{1-3}) alkyl.

[0159] In still a further variation of each of the above embodiments and variations, R_8 is hydrogen. In yet a further variation of each of the above embodiments and variations, R_8 is a substituted or unsubstituted (C_{1-3})alkyl.

[0160] In yet a further variation of each of the above embodiments and variations, R_9 is hydrogen. In another variation of each of the above embodiments and variations, R_9 is halo. In still another variation of each of the above embodiments and variations, R_9 is a substituted or unsubstituted (C_{1-3})alkyl.

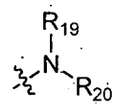
[0161] In yet a further variation of each of the above embodiments and variations, R_{10} is hydrogen. In another variation of each of the above embodiments and variations, R_{10} is halo. In still another variation of each of the above embodiments and variations, R_{10} is a substituted or unsubstituted (C_{1-3})alkyl.

[0162] In yet a further variation of each of the above embodiments and variations, R_{11} is hydrogen. In another variation of each of the above embodiments and variations, R_{11} is halo. In still another variation of each of the above embodiments and variations, R_{11} is a substituted or unsubstituted (C_{1-3})alkyl.

[0163] In yet a further variation of each of the above embodiments and variations, R_{12} is hydrogen. In another variation of each of the above embodiments and variations, R_{12} is halo. In still another variation of each of the above embodiments and variations, R_{12} is a substituted or unsubstituted (C_{1-3})alkyl.

[0164] In a further variation of each of the above embodiments and variations, R_{13} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted. In another variation of each of the above embodiments and variations, R_{13} is selected from the group consisting of hetero(C_{3-12})cycloalkyl, hetero(C_{3-12})bicycloalkyl, hetero(C_{1-10})aryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0165] In still a further variation of each of the above embodiments and variations, R_{13} has the formula:

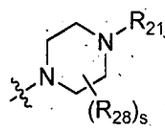


wherein

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{19} and R_{20} are taken together to form a substituted or unsubstituted ring.

[0166] In yet a further variation of each of the above embodiments and variations, R_{13} is a substituted or unsubstituted piperazinyl.

[0167] In another variation of each of the above embodiments and variations, R_{13} has the formula



wherein

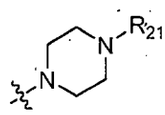
c is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8;

R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{28} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

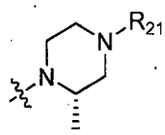
[0168] In another variation of each of the above embodiments and variations, R_{13} has the formula:



wherein

R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

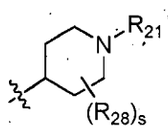
[0169] In still another variation of each of the above embodiments and variations, R_{13} has the formula:



wherein

R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0170] In yet another variation of each of the above embodiments and variations, R_{13} has the formula:



wherein

s is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8;

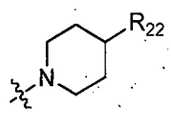
R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{23} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0171] In still another variation of each of the above embodiments and variations, R_{13} is a substituted or unsubstituted piperidinyl.

[0172] In yet another variation of each of the above embodiments and variations, R_{13} has the formula:

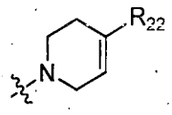


wherein

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0173] In a further variation of each of the above embodiments and variations, R_{13} is a substituted or unsubstituted 1,2,3,6-tetrahydropyridinyl.

[0174] In still a further variation of each of the above embodiments and variations, R_{13} has the formula:

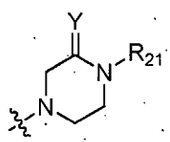


wherein

R_{22} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0175] In yet a further variation of each of the above embodiments and variations, R_{13} is a substituted or unsubstituted 3-oxo-piperazinyl.

[0176] In another variation of each of the above embodiments and variations, R_{13} has the formula:



wherein

Y is selected from the group consisting of O and S; and

R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl,

halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0177] In still another variation of each of the above embodiments and variations, Y is O.

[0178] In yet another variation of each of the above embodiments and variations, R_{14} is hydrogen. In a further variation of each of the above embodiments and variations, R_{14} is halo. In still a further variation of each of the above embodiments and variations, R_{14} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0179] In yet another variation of each of the above embodiments and variations, R_{15} is hydrogen. In a further variation of each of the above embodiments and variations, R_{15} is halo. In still a further variation of each of the above embodiments and variations, R_{15} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0180] In yet a further variation of each of the above embodiments and variations, R_{16} is hydrogen. In still another variation of each of the above embodiments and variations, R_{16} is a substituted or unsubstituted (C_{1-3})alkyl.

[0181] In another variation of each of the above embodiments and variations, R_{17} is selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted. In yet a further variation of each of the above embodiments and variations, R_{17} is hydrogen. In still another variation of each of the above embodiments and variations, R_{17} is a substituted or unsubstituted (C_{1-3})alkyl.

[0182] In another variation of each of the above embodiments and variations, R_{18} is a substituted or unsubstituted phenyl.

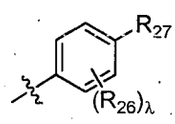
[0183] In a further variation of each of the above embodiments and variations, R_{19} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{19} is a substituted or unsubstituted (C_{1-3})alkyl.

[0184] In another variation of each of the above embodiments and variations, R_{20} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{20} is a substituted or unsubstituted (C_{1-3})alkyl.

[0185] In a further variation of each of the above embodiments and variations, R_{19} and R_{20} are taken together to form a substituted or unsubstituted ring. In still a further variation of each of the above embodiments and variations, R_{19} and R_{20} are taken together to form a substituted or unsubstituted hetero(C_{3-12})cycloalkyl. In yet a further variation of each of the above embodiments and variations, R_{19} and R_{20} are taken together to form a substituted or unsubstituted hetero(C_{3-12})bicycloalkyl. In another variation of each of the above embodiments and variations, R_{19} and R_{20} are taken together to form a substituted or unsubstituted hetero(C_{1-10})aryl. In still another variation of each of the above embodiments and variations, R_{19} and R_{20} are taken together to form a substituted or unsubstituted hetero(C_{4-12})bicycloaryl.

[0186] In still another variation of each of the above embodiments and variations, R_{21} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted. In yet another variation of each of the above embodiments and variations, R_{21} is a substituted or unsubstituted phenyl. In a further variation of each of the above embodiments and variations, R_{21} is a substituted or unsubstituted 4-chlorophenyl. In still a further variation of each of the above embodiments and variations, R_{21} is a substituted or unsubstituted pyridinyl.

[0187] In still another variation of each of the above embodiments and variations, R_{21} has the formula:



wherein

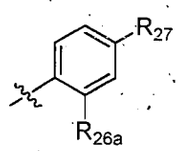
λ is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_{26} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino,

sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0188] In yet another variation of each of the above embodiments and variations, R_{21} has the formula:



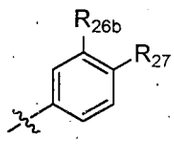
wherein

R_{26a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl,

imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0189] In a further variation of each of the above embodiments and variations, R_{21} has the formula:



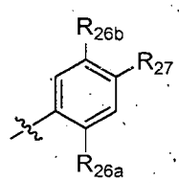
wherein

R_{26b} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0190] In still a further variation of each of the above embodiments and variations, R_{21} has the formula:



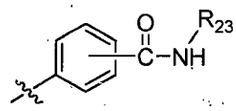
wherein

R_{26a} and R_{26b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl,

(C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

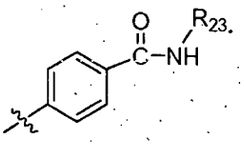
[0191] In yet a further variation of each of the above embodiments and variations, R_{21} has the formula:



wherein

R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0192] In another variation of each of the above embodiments and variations, R_{21} has the formula:

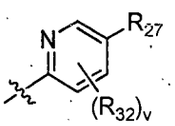


wherein

R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0193] In still another variation of each of the above embodiments and variations, R_{21} is substituted with a substituent selected from the group consisting of halo, cyano and a substituted or unsubstituted carbonyl. In yet another variation of each of the above embodiments and variations, R_{21} is substituted with a substituent having the formula –C(=O)-R_{24}, wherein R_{24} is selected from the group consisting of hydrogen, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0194] In another variation of each of the above embodiments and variations, R_{21} has the formula:



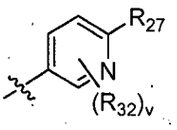
wherein

v is selected from the group consisting of 0, 1, 2 and 3;

each R_{32} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0195] In still another variation of each of the above embodiments and variations, R_{21} has the formula:



wherein

v is selected from the group consisting of 0, 1, 2 and 3;

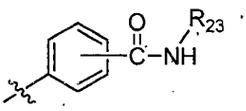
each R_{32} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0196] In a further variation of each of the above embodiments and variations, R_{22} is selected from the group consisting of (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted. In still a further variation of

each of the above embodiments and variations, R_{22} is a substituted or unsubstituted phenyl. In yet a further variation of each of the above embodiments and variations, R_{22} is a substituted or unsubstituted 4-chlorophenyl. In another variation of each of the above embodiments and variations, R_{22} is a substituted or unsubstituted pyridinyl.

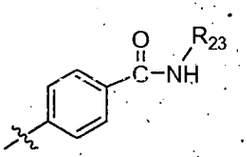
[0197] In still another variation of each of the above embodiments and variations, R_{22} has the formula:



wherein

R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0198] In yet another variation of each of the above embodiments and variations, R_{22} has the formula:



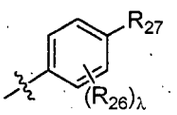
wherein

R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0199] In a further variation of each of the above embodiments and variations, R_{22} is substituted with a substituent selected from the group consisting of halo, cyano and a substituted or unsubstituted carbonyl. In still a further variation of each of the above embodiments and variations, R_{22} is substituted with a substituent having the formula –C(=O)-R_{24}, wherein R_{24} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0200] In a further variation of each of the above embodiments and variations, R_{22} has the formula:



wherein

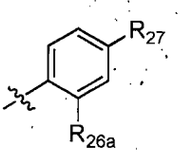
λ is selected from the group consisting of 0, 1, 2, 3 and 4;

each R_{26} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl,

(C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0201] In still a further variation of each of the above embodiments and variations, R_{22} has the formula:



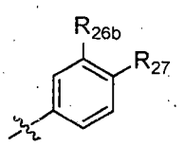
wherein

R_{26a} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl,

hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0202] In yet a further variation of each of the above embodiments and variations, R_{22} has the formula:

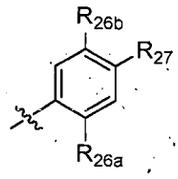


wherein

R_{26b} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0203] In another variation of each of the above embodiments and variations, R_{22} has the formula:

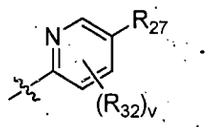


wherein

R_{26a} and R_{26b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0204] In another variation of each of the above embodiments and variations, R_{22} has the formula:



wherein

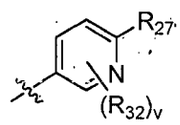
v is selected from the group consisting of 0, 1, 2 and 3;

each R_{32} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy,

carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0205] In still another variation of each of the above embodiments and variations, R_{22} has the formula:



wherein

v is selected from the group consisting of 0, 1, 2 and 3;

each R_{32} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino; (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl,

carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0206] In yet a further variation of each of the above embodiments and variations, R_{23} is a substituted or unsubstituted (C_{1-3})alkyl. In another variation of each of the above embodiments and variations, R_{23} is a substituted or unsubstituted (C_{3-5})cycloalkyl. In still another variation of each of the above embodiments and variations, R_{23} is methyl, ethyl, propyl, isopropyl or cyclopropyl.

[0207] In yet a further variation of each of the above embodiments and variations, R_{24} is hydroxyl. In another variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted (C_{1-3})alkoxy. In still another variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted (C_{1-5})alkylamino. In yet another variation of each of the above embodiments and variations, R_{24} is hydrogen. In still a further variation of each of the above embodiments and variations, R_{24} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0208] In another variation of each of the above embodiments and variations, R_{26} is hydrogen. In still another variation of each of the above embodiments and variations, R_{26} is halo. In yet another variation of each of the above embodiments and variations, R_{26} is a substituted or unsubstituted (C_{1-3}) alkyl. In a further variation of each of the above embodiments and variations, R_{26} is a substituted or unsubstituted (C_{1-3})alkoxy. In still a further variation of each of the above embodiments and variations, R_{26} is fluro, chloro, methyl or methoxy.

[0209] In another variation of each of the above embodiments and variations, R_{26a} is hydrogen. In still another variation of each of the above embodiments and variations, R_{26a} is halo. In yet another variation of each of the above embodiments and variations, R_{26a} is a substituted or unsubstituted (C_{1-3}) alkyl. In a further variation of each of the above embodiments and variations, R_{26a} is a substituted or unsubstituted (C_{1-3})alkoxy. In still a

further variation of each of the above embodiments and variations, R_{26a} is fluro, chloro, methyl or methoxy.

[0210] In another variation of each of the above embodiments and variations, R_{26b} is hydrogen. In still another variation of each of the above embodiments and variations, R_{26b} is halo. In yet another variation of each of the above embodiments and variations, R_{26b} is a substituted or unsubstituted (C_{1-3}) alkyl. In a further variation of each of the above embodiments and variations, R_{26b} is a substituted or unsubstituted (C_{1-3})alkoxy. In still a further variation of each of the above embodiments and variations, R_{26b} is fluro, chloro, methyl or methoxy.

[0211] In another variation of each of the above embodiments and variations, R_{27} is –CO-NH-R_{23}; and R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0212] In still another variation of each of the above embodiments and variations, R_{27} is –CO-O-R_{23} ; and R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0213] In yet another variation of each of the above embodiments and variations, R_{27} is –SO_2-O-R_{23} ; and R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino,

(C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

[0214] In a further variation of each of the above embodiments and variations, R_{27} is –CO-$NR_{29}R_{30}$; and R_{29} and R_{30} are each independently selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{29} and R_{30} are taken together to form a substituted or unsubstituted ring.

[0215] In still a further variation of each of the above embodiments and variations, R_{27} is cyano. In another variation of each of the above embodiments and variations, R_{27} is halo. In yet a further variation of each of the above embodiments and variations, R_{27} is chloro. In another variation of each of the above embodiments and variations, R_{27} is fluoro.

[0216] In still another variation of each of the above embodiments and variations, R_{28} is hydrogen. In yet another variation of each of the above embodiments and variations, R_{28} is halo. In a further variation of each of the above embodiments and variations, R_{28} is a substituted or unsubstituted (C_{1-3}) alkyl. In a further variation of each of the above embodiments and variations, R_{28} is a substituted or unsubstituted (C_{1-3}) alkoxy. In still a further variation of each of the above embodiments and variations, R_{28} is a substituted or unsubstituted amino. In yet a further variation of each of the above embodiments and variations, R_{28} is thio.

[0217] In still a further variation of each of the above embodiments and variations, R_{29} is hydrogen. In yet a further variation of each of the above embodiments and variations, R_{29} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0218] In another variation of each of the above embodiments and variations, R_{30} is hydrogen. In still another variation of each of the above embodiments and variations, R_{30} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0219] In yet another variation of each of the above embodiments and variations, R_{31} is hydrogen. In a further variation of each of the above embodiments and variations, R_{31} is halo. In still a further variation of each of the above embodiments and variations, R_{31} is a substituted or unsubstituted (C_{1-3}) alkyl.

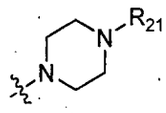
[0220] In yet another variation of each of the above embodiments and variations, R_{32} is hydrogen. In a further variation of each of the above embodiments and variations, R_{32} is halo. In still a further variation of each of the above embodiments and variations, R_{32} is a substituted or unsubstituted (C_{1-3}) alkyl.

[0221] In another variation of each of the above embodiments and variations,

R_1 is $-L_1-R_{13}$;

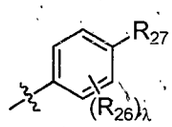
L_1 is $-CH_2-$;

R_{13} has the formula:



;

R_{21} has the formula:



;

λ is selected from the group consisting of 0, 1 and 2;

each R_{26} is independently selected from the group consisting of hydrogen, halo, (C_{1-3}) alkyl and (C_{1-3})alkoxy;

R_{27} is $-CO-NH-R_{23}$; and

R_{23} is selected from the group consisting of (C_{1-3})alkyl and (C_{3-6})cycloalkyl.

[0222] In still another variation of each of the above embodiments and variations, n is 0. In yet another variation of each of the above embodiments and variations, n is 1. In a further variation of each of the above embodiments and variations, l is 0. In still a further variation of

each of the above embodiments and variations, l is 1. In yet a further variation of each of the above embodiments and variations, l is 2. In a further variation of each of the above embodiments and variations, m is 0. In still a further variation of each of the above embodiments and variations, m is 1. In yet a further variation of each of the above embodiments and variations, p is 0. In another variation of each of the above embodiments and variations, p is 1. In still another variation of each of the above embodiments and variations, q is 0. In yet another variation of each of the above embodiments and variations, q is 1. In still a further variation of each of the above embodiments and variations, r is 1. In yet a further variation of each of the above embodiments and variations, r is 2. In a further variation of each of the above embodiments and variations, s is 0. In still a further variation of each of the above embodiments and variations, s is 1. In yet a further variation of each of the above embodiments and variations, s is 2. In another variation of each of the above embodiments and variations, t is 1. In still another variation of each of the above embodiments and variations, u is 0. In yet another variation of each of the above embodiments and variations, u is 1. In a further variation of each of the above embodiments and variations, v is 0. In still a further variation of each of the above embodiments and variations, v is 1.

[0223] In another of its aspects, the present invention relates to methods of making compounds that are useful as PARP inhibitors.

[0224] In still another of its aspects, the present invention relates to intermediates that are useful in making PARP inhibitors.

[0225] It is noted that the compounds of the present invention may be in the form of a pharmaceutically acceptable salt, biohydrolyzable ester, biohydrolyzable amide, biohydrolyzable carbamate, solvate, hydrate or prodrug thereof. For example, the compound optionally comprises a substituent that is convertible *in vivo* to a different substituent such as hydrogen.

[0226] It is further noted that the compound may be present as a mixture of stereoisomers, or the compound may be present as a single stereoisomer.

[0227] In another of its aspects, there is provided a pharmaceutical composition comprising a compound according to any one of the above embodiments and variations; and one or more pharmaceutically acceptable excipients. In one particular variation, the composition is a solid formulation adapted for oral administration. In another particular variation, the composition is a liquid formulation adapted for oral administration. In yet another particular variation, the composition is a tablet. In still another particular variation, the composition is a liquid formulation adapted for parenteral administration.

[0228] The present invention also provides a pharmaceutical composition comprising a compound according to any one of the above embodiments and variations, wherein the composition is adapted for administration by a route selected from the group consisting of orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadiposally, intraarticularly, and intrathecally.

[0229] In yet another of its aspects, there is provided a kit comprising a compound of any one of the above embodiments and variations; and instructions which comprise one or more forms of information selected from the group consisting of indicating a disease state for which the composition is to be administered, storage information for the composition, dosing information and instructions regarding how to administer the composition. In one particular variation, the kit comprises the compound in a multiple dose form.

[0230] In still another of its aspects, there is provided an article of manufacture comprising a compound of any one of the above embodiments and variations; and packaging materials. In one variation, the packaging material comprises a container for housing the compound. In one particular variation, the container comprises a label indicating one or more members of the group consisting of a disease state for which the compound is to be administered, storage information, dosing information and/or instructions regarding how to administer the compound. In another variation, the article of manufacture comprises the compound in a multiple dose form.

[0231] In a further of its aspects, there is provided a therapeutic method comprising administering a compound of any one of the above embodiments and variations to a subject.

[0232] In another of its aspects, there is provided a method of inhibiting PARP comprising contacting PARP with a compound of any one of the above embodiments and variations.

[0233] In yet another of its aspects, there is provided a method of inhibiting PARP comprising causing a compound of any one of the above embodiments and variations to be present in a subject in order to inhibit PARP in vivo.

[0234] In a further of its aspects, there is provided a method of inhibiting PARP comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits PARP in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0235] In another of its aspects, there is provided a method of treating a disease state for which PARP possesses activity that contributes to the pathology and/or symptomology of the

disease state, the method comprising causing a compound of any one of the above embodiments and variations to be present in a subject in a therapeutically effective amount for the disease state.

[0236] In yet another of its aspects, there is provided a method of treating a disease state for which PARP possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a compound of any one of the above embodiments and variations to a subject, wherein the compound is present in the subject in a therapeutically effective amount for the disease state.

[0237] In a further of its aspects, there is provided a method of treating a disease state for which PARP possesses activity that contributes to the pathology and/or symptomology of the disease state, the method comprising administering a first compound to a subject that is converted in vivo to a second compound wherein the second compound inhibits PARP in vivo, the second compound being a compound according to any one of the above embodiments and variations.

[0238] In one variation of each of the above methods the disease state is selected from the group consisting of cancers (including cancers where DNA damaging (e.g., alkylating) agents, cytotoxic drugs, radiation therapy and/or topoisomerase inhibitors are a standard of care (*e.g.*, in combination with chemo- and/or radiosensitizers for cancer treatment); cancers which are deficient in Homologous Recombination (HR) dependent DNA DSB repair; BRCA-1 and BRCA-2 deficient tumors; bladder cancer; blood-borne cancers (*e.g.*, acute lymphoblastic leukemia("ALL"), acute lymphoblastic B-cell leukemia, acute lymphoblastic T-cell leukemia, acute myeloblastic leukemia ("AML"), acute promyelocytic leukemia("APL"), acute monoblastic leukemia, acute erythroleukemic leukemia, acute megakaryoblastic leukemia, acute myelomonocytic leukemia, acute nonlymphocytic leukemia, acute undifferentiated leukemia, chronic myelocytic leukemia("CML"), chronic lymphocytic leukemia("CLL"), hairy cell leukemia and multiple myeloma); bone cancer; breast cancer; carcinomas (*e.g.*, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, small cell lung carcinoma, bladder carcinoma and epithelial carcinoma); CNS and brain cancers (*e.g.*, glioma (*e.g.*, pilocytic astrocytoma, astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme), pilocytic astrocytoma, astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma,

oligodendroglioma, meningioma, vestibular schwannoma, adenoma, metastatic brain cancer, meningioma, spinal tumor and medulloblastoma); cervical cancer; colon cancer; colorectal cancer; esophageal cancer; hepatomas; head and neck cancer; kidney cancer; acute and chronic leukemias (*e.g.*, lymphoblastic, myelogenous, lymphocytic and myelocytic leukemias); liver cancer; lung cancer; lymphomas (*e.g.*, such as Hodgkin's disease, non- Hodgkin's Lymphoma, Multiple myeloma, Waldenstrom's macroglobulinemia, Heavy chain disease and Polycythemia vera); melanomas; nasal cancer; neuroblastomas; oral cancer; ovarian cancer; pancreatic cancer; prostate cancer; retinoblastomas; skin cancer; solid tumors (*e.g.*, such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma and rhabdomyosarcoma); stomach cancer; testicular cancer; throat cancer; uterine cancer and Wilms' tumor); cardiovascular diseases (including chronic heart failure; atherosclerosis; congestive heart failure; circulatory shock; cardiomyopathy; cardiac transplant; myocardialinfarction and cardiac arrhythmia (*e.g.*, atrial fibrillation, supraventricular tachycardia, atrial flutter and paroxysmal atrial tachycardia)); vascular diseases other than cardiovascular diseases (including peripheral arterial occlusion; thromboangitis obliterans; Reynaud's disease and phenomenon; acrocyanosis; erythromelalgia; venous thrombosis; varicose veins; arteriovenous fistula; lymphedema and lipedema); metabolic diseases (including diabetes (*e.g.*, diabetes mellitus (*e.g.*, Type I diabetes (Insulin Dependent Diabetes Mellitus), Type II diabetes (Non-Insulin Dependent Diabetes Mellitus), gestational diabetes, autoimmune diabetes, insulinopathies, diabetes due to pancreatic disease, diabetes associated with other endocrine diseases (such as Cushing's Syndrome, acromegaly, pheochromocytoma, glucagonoma, primary aldosteronism or somatostatinoma), Type A insulin resistance syndrome, Type B insulin resistance syndrome, lipatrophic diabetes, and diabetes induced by β-cell toxins); and diabetic complications (*e.g.*, diabetic cataract, glaucoma, retinopathy, nephropathy (*e.g.*, microaluminuria and diabetic nephropathy), mononeuropathy, autonomic neuropathy, polyneuropathy, gangrene of the feet, atherosclerotic coronary arterial disease, peripheral arterial disease, non-ketotic hyperglycemic- hyperosmolar coma, mononeuropathies, autonomic neuropathy, foot ulcers, joint problems, skin or mucous membrane complications (*e.g.*, infection, shin spot, candidal infection or necrobiosis lipoidica diabeticorumobesity), hyperlipidemia, hypertension, syndrome of insulin resistance, coronary artery disease, foot ulcers, joint problems, fungal infections, bacterial infections, cardiomyopathy, immune- complex vasculitis and systemic lupus erythematosus (SLE))); inflammatory diseases (including conditions resulting from organ transplant rejection; chronic

inflammatory diseases of the joints (*e.g.*, arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption); inflammatory bowel diseases (*e.g.*, ileitis, ulcerative colitis, Barrett's syndrome and Crohn's disease); inflammatory lung diseases (*e.g.*, asthma, adult respiratory distress syndrome and chronic obstructive airway disease); inflammatory diseases of the eye (*e.g.*, corneal dystrophy, trachoma, onchocerciasis, uveitis, sympatheticophthalmitis and endophthalmitis); chronic inflammatory diseases of the gum (*e.g.*, gingivitis and periodontitis); tuberculosis; leprosy; inflammatory diseases of the kidney (*e.g.*, uremic complications, glomerulonephritis and nephrosis); inflammatory diseases of the skin (*e.g.*, scleroderma titis, psoriasis and eczema); inflammatory diseases of the central nervous system (*e.g.*, chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration , Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and viral or autoimmune encephalitis); inflammatory diseases of the heart (*e.g.*, cardiomyopathy, ischemic heart disease, hypercholesterolemia and atherosclerosis); diseases that can have significant inflammatory components (*e.g.*, preeclampsia, chronic liver failure, brain and spinal cord trauma and multiple organ dysfunction syndrome (MODS) (multiple organ failure (MOF))); systemic inflammation of the body, exemplified by gram-positive or gram negative shock, hemorrhagic or anaphylactic shock, or shock induced by cancer chemotherapy in response to pro-inflammatory cytokines, (*e.g.*, shock associated with pro-inflammatory cytokines; and shock induced, for example, by a chemotherapeutic agent that is administered as a treatment for cancer); reperfusion injuries, including those resulting from naturally occurring episodes and during a surgical procedure (*e.g.*, intestinal reperfusion injury; myocardial reperfusion injury; reperfusion injury resulting from cardiopulmonary bypass surgery, aortic aneurysm repair surgery, carotid endarterectomy surgery, or hemorrhagic shock; and reoxygenation injury resulting from transplantation of organs such as heart, lung, liver, kidney, pancreas, intestine or cornea); ischemic conditions, including those resulting from organ transplantation (*e.g.*, stable angina, unstable angina, myocardial ischemia, hepatic ischemia, mesenteric artery ischemia, intestinal ischemia, critical limb ischemia, chronic critical limb ischemia, cerebral ischemia, acute cardiac ischemia, ischemic kidney disease, ischemic liver disease, ischemic retinal disorder, septic shock; and an ischemic disease of the central nervous system (*e.g.*, stroke or cerebral ischemia)); neurodegenerative diseases (*e.g.*, polyglutamine-expansion-related neurodegeneration, Huntington's disease, Kennedy's disease, spinocerebellar ataxia, dentatorubral-pallidoluysian atrophy (DRPLA), protein-aggregation-related neurodegeneration, Machado-Joseph's disease, Alzheimer's disease, Parkinson's disease, amyotrophic lateral

sclerosis, spongiform encephalopathy, a prion-related disease and multiple sclerosis (MS)); tissue injuries; CNS diseases; heart attack; hematolymphoid system disorders; endocrine and neuroendocrine system disorders; urinary tract disorders; respiratory system disorders; female reproductive system disorders; male reproductive system disorders; retroviral infections; retinal damage; skin senescence; UV- induced skin damage; chronic or acute renal disease or failure; age-related cellular dysfunction; and fatty acid synthesis related diseases (*e.g.*, obesity, diabetes and cardiovascular disease).

[0239] In another variation of each of the above methods, the PARP is a PARP-1, PARP-2, PARP-3, vaultPARP or TiPARP. It is noted that the compounds of the present invention may also possess inhibitory activity for other PARP family members and thus may be used to address disease states associated with these other family members. Further, the compounds of the present invention may also possess inhibitory activity for tankyrases (*e.g.*, tankyrase-1 and tankyrase-2) and thus may be used to address disease states associated with these target proteins.

Salts, Hydrates, and Prodrugs of PARP Inhibitors

[0240] It should be recognized that the compounds of the present invention may be present and optionally administered in the form of salts, hydrates and prodrugs that are converted in vivo into the compounds of the present invention. For example, it is within the scope of the present invention to convert the compounds of the present invention into and use them in the form of their pharmaceutically acceptable salts derived from various organic and inorganic acids and bases in accordance with procedures well known in the art.

[0241] When the compounds of the present invention possess a free base form, the compounds can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid, *e.g.*, hydrohalides such as hydrochloride, hydrobromide, hydroiodide; other mineral acids and their corresponding salts such as sulfate, nitrate, phosphate, etc.; and alkyl and monoarylsulfonates such as ethanesulfonate, toluenesulfonate and benzenesulfonate; and other organic acids and their corresponding salts such as acetate, tartrate, maleate, succinate, citrate, benzoate, salicylate and ascorbate. Further acid addition salts of the present invention include, but are not limited to: adipate, alginate, arginate, aspartate, bisulfate, bisulfite, bromide, butyrate, camphorate, camphorsulfonate, caprylate, chloride, chlorobenzoate, cyclopentanepropionate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, fumarate, galacterate (from mucic acid), galacturonate, glucoheptonate, gluconate, glutamate,

glycerophosphate, hemisuccinate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isethionate, iso-butyrate, lactate, lactobionate, malate, malonate, mandelate, metaphosphate, methanesulfonate, methylbenzoate, monohydrogenphosphate, 2-naphthalenesulfonate, nicotinate, nitrate, oxalate, oleate, pamoate, pectinate, persulfate, phenylacetate, 3-phenylpropionate, phosphate, phosphonate and phthalate. It should be recognized that the free base forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base forms for the purposes of the present invention.

[0242] When the compounds of the present invention possess a free acid form, a pharmaceutically acceptable base addition salt can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Examples of such bases are alkali metal hydroxides including potassium, sodium and lithium hydroxides; alkaline earth metal hydroxides such as barium and calcium hydroxides; alkali metal alkoxides, *e.g.*, potassium ethanolate and sodium propanolate; and various organic bases such as ammonium hydroxide, piperidine, diethanolamine and N-methylglutamine. Also included are the aluminum salts of the compounds of the present invention. Further base salts of the present invention include, but are not limited to: copper, ferric, ferrous, lithium, magnesium, manganic, manganous, potassium, sodium and zinc salts. Organic base salts include, but are not limited to, salts of primary, secondary and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, *e.g.*, arginine, betaine, caffeine, chloroprocaine, choline, N,N'-dibenzylethylenediamine (benzathine), dicyclohexylamine, diethanolamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, iso-propylamine, lidocaine, lysine, meglumine, N-methyl-D-glucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethanolamine, triethylamine, trimethylamine, tripropylamine and tris-(hydroxymethyl)-methylamine (tromethamine). It should be recognized that the free acid forms will typically differ from their respective salt forms somewhat in physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid forms for the purposes of the present invention.

[0243] N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (*e.g.*, trifluoroperacetic

acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (*e.g.*, a halogenated hydrocarbon such as dichloromethane) at approximately 0 °C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

[0244] Prodrug derivatives of compounds according to the present invention can be prepared by modifying substituents of compounds of the present invention that are then converted in vivo to a different substituent. It is noted that in many instances, the prodrugs themselves also fall within the scope of the range of compounds according to the present invention. For example, prodrugs can be prepared by reacting a compound with a carbamylating agent (*e.g.*, 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like) or an acylating agent. Further examples of methods of making prodrugs are described in Saulnier et al. (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985.

[0245] Protected derivatives of compounds of the present invention can also be made. Examples of techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

[0246] Compounds of the present invention may also be conveniently prepared, or formed during the process of the invention, as solvates (*e.g.*, hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0247] A "pharmaceutically acceptable salt", as used herein, is intended to encompass any compound according to the present invention that is utilized in the form of a salt thereof, especially where the salt confers on the compound improved pharmacokinetic properties as compared to the free form of compound or a different salt form of the compound. The pharmaceutically acceptable salt form may also initially confer desirable pharmacokinetic properties on the compound that it did not previously possess, and may even positively affect the pharmacodynamics of the compound with respect to its therapeutic activity in the body. An example of a pharmacokinetic property that may be favorably affected is the manner in which the compound is transported across cell membranes, which in turn may directly and positively affect the absorption, distribution, biotransformation and excretion of the compound. While the route of administration of the pharmaceutical composition is important, and various anatomical, physiological and pathological factors can critically affect bioavailability, the solubility of the compound is usually dependent upon the character of the particular salt form thereof, which it utilized. One of skill in the art will appreciate that an aqueous solution of the

compound will provide the most rapid absorption of the compound into the body of a subject being treated, while lipid solutions and suspensions, as well as solid dosage forms, will result in less rapid absorption of the compound.

Compositions Comprising PARP Inhibitors

[0248] A wide variety of compositions and administration methods may be used in conjunction with the compounds of the present invention.. Such compositions may include, in addition to the compounds of the present invention, conventional pharmaceutical excipients, and other conventional, pharmaceutically inactive agents. Additionally, the compositions may include active agents in addition to the compounds of the present invention. These additional active agents may include additional compounds according to the invention, and/or one or more other pharmaceutically active agents.

[0249] The compositions may be in gaseous, liquid, semi-liquid or solid form, formulated in a manner suitable for the route of administration to be used. For oral administration, capsules and tablets are typically used. For parenteral administration, reconstitution of a lyophilized powder, prepared as described herein, is typically used.

[0250] Compositions comprising compounds of the present invention may be administered or coadministered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery (for example by catheter or stent), subcutaneously, intraadipocally, intraarticularly, or intrathecally. The compounds and/or compositions according to the invention may also be administered or coadministered in slow release dosage forms.

[0251] The PARP inhibitors and compositions comprising them may be administered or coadministered in any conventional dosage form. Co-administration in the context of this invention is intended to mean the administration of more than one therapeutic agent, one of which includes a PARP inhibitor, in the course of a coordinated treatment to achieve an improved clinical outcome. Such co-administration may also be coextensive, that is, occurring during overlapping periods of time.

[0252] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application may optionally include one or more of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as

ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; agents for the adjustment of tonicity such as sodium chloride or dextrose, and agents for adjusting the acidity or alkalinity of the composition, such as alkaline or acidifying agents or buffers like carbonates, bicarbonates, phosphates, hydrochloric acid, and organic acids like acetic and citric acid. Parenteral preparations may optionally be enclosed in ampules, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[0253] When compounds according to the present invention exhibit insufficient solubility, methods for solubilizing the compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

[0254] Upon mixing or adding compounds according to the present invention to a composition, a solution, suspension, emulsion or the like may be formed. The form of the resulting composition will depend upon a number of factors, including the intended mode of administration, and the solubility of the compound in the selected carrier or vehicle. The effective concentration needed to ameliorate the disease being treated may be empirically determined.

[0255] Compositions according to the present invention are optionally provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, dry powders for inhalers, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds, particularly the pharmaceutically acceptable salts, preferably the sodium salts, thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms, as used herein, refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes individually packaged tablet or capsule. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include

vials, bottles of tablets or capsules or bottles of pint or gallons. Hence, multiple dose form is a multiple of unit-doses that are not segregated in packaging.

[0256] In addition to one or more compounds according to the present invention, the composition may comprise: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum açaciagelatin, glucose, molasses, polvinylpyrrolidine, celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrine derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known in the art, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a sufficient quantity of an inhibitor of the present invention to reduce PARP activity in vivo, thereby treating the disease state of the subject.

[0257] Dosage forms or compositions may optionally comprise one or more compounds according to the present invention in the range of 0.005% to 100% (weight/weight) with the balance comprising additional substances such as those described herein. For oral administration, a pharmaceutically acceptable composition may optionally comprise any one or more commonly employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate, sodium saccharin, talcum. Such compositions include solutions, suspensions, tablets, capsules, powders, dry powders for inhalers and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparing these formulations are known to those skilled in the art. The compositions may

optionally contain 0.01%-100% (weight/weight) of one or more PARP inhibitors, optionally 0.1-95%, and optionally 1-95%.

[0258] Salts, preferably sodium salts, of the inhibitors may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The formulations may further include other active compounds to obtain desired combinations of properties.

Formulations for Oral Administration

[0259] Oral pharmaceutical dosage forms may be as a solid, gel or liquid. Examples of solid dosage forms include, but are not limited to tablets, capsules, granules, and bulk powders. More specific examples of oral tablets include compressed, chewable lozenges and tablets that may be enteric-coated, sugar-coated or film-coated. Examples of capsules include hard or soft gelatin capsules. Granules and powders may be provided in non-effervescent or effervescent forms. Each may be combined with other ingredients known to those skilled in the art.

[0260] In certain embodiments, compounds according to the present invention are provided as solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like may optionally contain one or more of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

[0261] Examples of binders that may be used include, but are not limited to, microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose, and starch paste.

[0262] Examples of lubricants that may be used include, but are not limited to, talc, starch, magnesium or calcium stearate, lycopodium and stearic acid.

[0263] Examples of diluents that may be used include, but are not limited to, lactose, sucrose, starch, kaolin, salt, mannitol, and dicalcium phosphate.

[0264] Examples of glidants that may be used include, but are not limited to, colloidal silicon dioxide.

[0265] Examples of disintegrating agents that may be used include, but are not limited to, croscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose.

[0266] Examples of coloring agents that may be used include, but are not limited to, any of the approved certified water-soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate.

[0267] Examples of sweetening agents that may be used include, but are not limited to, sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray-dried flavors.

[0268] Examples of flavoring agents that may be used include, but are not limited to, natural flavors extracted from plants such as fruits and synthetic blends of compounds that produce a pleasant sensation, such as, but not limited to peppermint and methyl salicylate.

[0269] Examples of wetting agents that may be used include, but are not limited to, propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate, and polyoxyethylene lauryl ether.

[0270] Examples of anti-emetic coatings that may be used include, but are not limited to, fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates.

[0271] Examples of film coatings that may be used include, but are not limited to, hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

[0272] If oral administration is desired, the salt of the compound may optionally be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

[0273] When the dosage unit form is a capsule, it may optionally additionally comprise a liquid carrier such as a fatty oil. In addition, dosage unit forms may optionally additionally comprise various other materials that modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents.

[0274] Compounds according to the present invention may also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may optionally comprise, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

[0275] The compounds of the present invention may also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. For example, if a compound is used for treating asthma or hypertension, it may be used with other bronchodilators and antihypertensive agents, respectively.

[0276] Examples of pharmaceutically acceptable carriers that may be included in tablets comprising compounds of the present invention include, but are not limited to binders,

lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets may be compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets may be compressed tablets that have been coated with polymers or other suitable coating. Multiple compressed tablets may be compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in tablets. Flavoring and sweetening agents may be used in tablets, and are especially useful in the formation of chewable tablets and lozenges.

[0277] Examples of liquid oral dosage forms that may be used include, but are not limited to, aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules.

[0278] Examples of aqueous solutions that may be used include, but are not limited to, elixirs and syrups. As used herein, elixirs refer to clear, sweetened, hydroalcoholic preparations. Examples of pharmaceutically acceptable carriers that may be used in elixirs include, but are not limited to solvents. Particular examples of solvents that may be used include glycerin, sorbitol, ethyl alcohol and syrup. As used herein, syrups refer to concentrated aqueous solutions of a sugar, for example, sucrose. Syrups may optionally further comprise a preservative.

[0279] Emulsions refer to two-phase systems in which one liquid is dispersed in the form of small globules throughout another liquid. Emulsions may optionally be oil-in-water or water-in-oil emulsions. Examples of pharmaceutically acceptable carriers that may be used in emulsions include, but are not limited to non-aqueous liquids, emulsifying agents and preservatives.

[0280] Examples of pharmaceutically acceptable substances that may be used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents.

[0281] Examples of pharmaceutically acceptable substances that may be used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide.

[0282] Coloring and flavoring agents may optionally be used in all of the above dosage forms.

[0283] Particular examples of preservatives that may be used include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol.

[0284] Particular examples of non-aqueous liquids that may be used in emulsions include mineral oil and cottonseed oil.

[0285] Particular examples of emulsifying agents that may be used include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate.

[0286] Particular examples of suspending agents that may be used include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin.

[0287] Particular examples of wetting agents that may be used include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether.

[0288] Particular examples of organic acids that may be used include citric and tartaric acid.

[0289] Sources of carbon dioxide that may be used in effervescent compositions include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof.

[0290] Particular examples of flavoring agents that may be used include natural flavors extracted from plants such fruits, and synthetic blends of compounds that produce a pleasant taste sensation.

[0291] For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Pat. Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

[0292] Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Pat. Nos. Re 28,819 and 4,358,603.

Injectables, Solutions, and Emulsions

[0293] The present invention is also directed to compositions designed to administer the compounds of the present invention by parenteral administration, generally characterized by subcutaneous, intramuscular or intravenous injection. Injectables may be prepared in any conventional form, for example as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions.

[0294] Examples of excipients that may be used in conjunction with injectables according to the present invention include, but are not limited to water, saline, dextrose, glycerol or ethanol. The injectable compositions may also optionally comprise minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins. Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Pat. No. 3,710,795) is also contemplated herein. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

[0295] Parenteral administration of the formulations includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products, such as the lyophilized powders described herein, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous..

[0296] When administered intravenously, examples of suitable carriers include, but are not limited to physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

[0297] Examples of pharmaceutically acceptable carriers that may optionally be used in parenteral preparations include, but are not limited to aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

[0298] Examples of aqueous vehicles that may optionally be used include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection.

[0299] Examples of nonaqueous parenteral vehicles that may optionally be used include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil.

[0300] Antimicrobial agents in bacteriostatic or fungistatic concentrations may be added to parenteral preparations, particularly when the preparations are packaged in multiple-dose containers and thus designed to be stored and multiple aliquots to be removed. Examples of antimicrobial agents that may be used include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride.

[0301] Examples of isotonic agents that may be used include sodium chloride and dextrose. Examples of buffers that may be used include phosphate and citrate. Examples of antioxidants that may be used include sodium bisulfate. Examples of local anesthetics that may be used include procaine hydrochloride. Examples of suspending and dispersing agents that may be used include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Examples of emulsifying agents that may be used include Polysorbate 80 (TWEEN 80). A sequestering or chelating agent of metal ions includes EDTA.

[0302] Pharmaceutical carriers may also optionally include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

[0303] The concentration of an inhibitor in the parenteral formulation may be adjusted so that an injection administers a pharmaceutically effective amount sufficient to produce the desired pharmacological effect. The exact concentration of an inhibitor and/or dosage to be used will ultimately depend on the age, weight and condition of the patient or animal as is known in the art.

[0304] Unit-dose parenteral preparations may be packaged in an ampoule, a vial or a syringe with a needle. All preparations for parenteral administration should be sterile, as is known and practiced in the art.

[0305] Injectables may be designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the PARP inhibitor to the treated tissue(s). The inhibitor may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage

and duration of treatment will be a function of the location of where the composition is parenterally administered, the carrier and other variables that may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens may need to be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations. Hence, the concentration ranges set forth herein are intended to be exemplary and are not intended to limit the scope or practice of the claimed formulations.

[0306] The PARP inhibitor may optionally be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease state and may be empirically determined.

Lyophilized Powders

[0307] The compounds of the present invention may also be prepared as lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. The lyophilized powders may also be formulated as solids or gels.

[0308] Sterile, lyophilized powder may be prepared by dissolving the compound in a sodium phosphate buffer solution containing dextrose or other suitable excipient. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Briefly, the lyophilized powder may optionally be prepared by dissolving dextrose, sorbitol, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent, about 1-20%, preferably about 5 to 15%, in a suitable buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art,at, typically, about neutral pH. Then, a PARP inhibitor is added to the resulting mixture, preferably above room temperature, more preferably at about 30-35 °C, and stirred until it dissolves. The resulting mixture is diluted by adding more buffer to a desired concentration. The resulting mixture is sterile filtered or treated to remove particulates and to insure sterility, and apportioned into vials for lyophilization. Each vial may contain a single dosage or multiple dosages of the inhibitor.

Topical Administration

[0309] The compounds of the present invention may also be administered as topical mixtures. Topical mixtures may be used for local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

[0310] The PARP inhibitors may be formulated as aerosols for topical application, such as by inhalation (see, U.S. Pat. Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

[0311] The inhibitors may also be formulated for local or topical application, such as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the PARP inhibitor alone or in combination with other pharmaceutically acceptable excipients can also be administered.

Formulations for Other Routes of Administration

[0312] Depending upon the disease state being treated, other routes of administration, such as topical application, transdermal patches, and rectal administration, may also be used. For example, pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum that melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3

gm. Tablets and capsules for rectal administration may be manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

Examples of Formulations

[0313] The following are particular examples of oral, intravenous and tablet formulations that may optionally be used with compounds of the present invention. It is noted that these formulations may be varied depending on the particular compound being used and the indication for which the formulation is going to be used.

ORAL FORMULATION

Compound of the Present Invention	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

Compound of the Present Invention	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of the Present Invention	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

Kits Comprising PARP Inhibitors

[0314] The invention is also directed to kits and other articles of manufacture for treating diseases associated with PARP. It is noted that diseases are intended to cover all conditions for which the PARP possess activity that contributes to the pathology and/or symptomology of the condition.

[0315] In one embodiment, a kit is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with instructions. The instructions may indicate the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also comprise packaging materials. The packaging material may

comprise a container for housing the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0316] In another embodiment, an article of manufacture is provided that comprises a composition comprising at least one inhibitor of the present invention in combination with packaging materials. The packaging material may comprise a container for housing the composition. The container may optionally comprise a label indicating the disease state for which the composition is to be administered, storage information, dosing information and/or instructions regarding how to administer the composition. The kit may also optionally comprise additional components, such as syringes for administration of the composition. The kit may comprise the composition in single or multiple dose forms.

[0317] It is noted that the packaging material used in kits and articles of manufacture according to the present invention may form a plurality of divided containers such as a divided bottle or a divided foil packet. The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. The container that is employed will depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle that is in turn contained within a box. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (*e.g.*, oral, topical, transdermal and parenteral), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

[0318] One particular example of a kit according to the present invention is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next,

the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[0319] Another specific embodiment of a kit is a dispenser designed to dispense the daily doses one at a time in the order of their intended use. Preferably, the dispenser is equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter that indicates the number of daily doses that has been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

Dosage, Host and Safety

[0320] The compounds of the present invention are stable and can be used safely. In particular, the compounds of the present invention are useful as PARP inhibitors for a variety of subjects (*e.g.*, humans, non-human mammals and non-mammals). The optimal dose may vary depending upon such conditions as, for example, the type of subject, the body weight of the subject, the route of administration, and specific properties of the particular compound being used. In general, the daily dose for oral administration to an adult (body weight of about 60 kg) is about 1 to 1000 mg, about 3 to 300 mg, or about 10 to 200 mg. It will be appreciated that the daily dose can be given in a single administration or in multiple (*e.g.*, 2 or 3) portions a day.

Combination Therapies

[0321] A wide variety therapeutic agents may have a therapeutic additive or synergistic effect with PARP inhibitors according to the present invention. Combination therapies that comprise one or more compounds of the present invention with one or more other therapeutic agents can be used, for example, to: 1) enhance the therapeutic effect(s) of the one or more compounds of the present invention and/or the one or more other therapeutic agents; 2) reduce

the side effects exhibited by the one or more compounds of the present invention and/or the one or more other therapeutic agents; and/or 3) reduce the effective dose of the one or more compounds of the present invention and/or the one or more other therapeutic agents.

[0322] In one embodiment, a method is provided for treating a cell proliferative disease state comprising treating cells with a compound according to the present invention in combination with an anti-proliferative agent, wherein the cells are treated with the compound according to the present invention before, at the same time, and/or after the cells are treated with the anti-proliferative agent, referred to herein as combination therapy. It is noted that treatment of one agent before another is refeired to herein as sequential therapy, even if the agents are also administered together. It is noted that combination therapy is intended to cover when agents are administered before or after each other (sequential therapy) as well as when the agents are administered at the same time.

[0323] Examples of therapeutic agents that may be used in combination with PARP inhibitors include, but are not limited to, anticancer agents, alkylating agents, antibiotic agents, antimetabolic agents, hormonal agents, plant-derived agents, and biologic agents.

[0324] Alkylating agents are polyfunctional compounds that have the ability to substitute alkyl groups for hydrogen ions. Examples of alkylating agents include, but are not limited to, bischloroethylamines (nitrogen mustards, e.g. chlorambucil, cyclophosphamide, ifosfamide, mechlorethamine, melphalan, uracil mustard), aziridines (e.g. thiotepa), alkyl alkone sulfonates (e.g. busulfan), nitrosoureas (e.g. carmustine, lomustine, streptozocin), nonclassic alkylating agents (altretamine, dacarbazine, and procarbazine), platinum compounds (carboplastin and cisplatin). These compounds react with phosphate, amino, hydroxyl, sulfihydryl, carboxyl, and imidazole groups. Under physiological conditions, these drugs ionize and produce positively charged ion that attach to susceptible nucleic acids and proteins, leading to cell cycle arrest and/or cell death. Combination therapy including a PARP inhibitor and an alkylating agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0325] Antibiotic agents are a group of drugs that are produced in a manner similar to antibiotics as a modification of natural products. Examples of antibiotic agents include, but are not limited to, anthracyclines (e.g. doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione), mitomycin C, bleomycin, dactinomycin, plicatomycin. These antibiotic agents interfere with cell growth by targeting different cellular components. For example, anthracyclines are generally believed to interfere with the action of DNA topoisomerase II in the regions of transcriptionally active DNA, which leads to DNA strand scissions. Bleomycin

is generally believed to chelate iron and forms an activated complex, which then binds to bases of DNA, causing strand scissions and cell death. Combination therapy including a PARP inhibitor and an antibiotic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0326] Antimetabolic agents are a group of drugs that interfere with metabolic processes vital to the physiology and proliferation of cancer cells. Actively proliferating cancer cells require continuous synthesis of large quantities of nucleic acids, proteins, lipids, and other vital cellular constituents. Many of the antimetabolites inhibit the synthesis of purine or pyrimidine nucleosides or inhibit the enzymes of DNA replication. Some antimetabolites also interfere with the synthesis of ribonucleosides and RNA and/or amino acid metabolism and protein synthesis as well. By interfering with the synthesis of vital cellular constituents, antimetabolites can delay or arrest the growth of cancer cells. Examples of antimetabolic agents include, but are not limited to, fluorouracil (5-FU), floxuridine (5-FUdR), methotrexate, leucovorin, hydroxyurea, thioguanine (6-TG), mercaptopurine (6-MP), cytarabine, pentostatin, fludarabine phosphate, cladribine (2-CDA), asparaginase, and gemcitabine. Combination therapy including a PARP inhibitor and a antimetabolic agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0327] Hormonal agents are a group of drug that regulate the growth and development of their target organs. Most of the hormonal agents are sex steroids and their derivatives and analogs thereof, such as estrogens, androgens, and progestins. These hormonal agents may serve as antagonists of receptors for the sex steroids to down regulate receptor expression and transcription of vital genes. Examples of such hormonal agents are synthetic estrogens (e.g. diethylstibestrol), antiestrogens (e.g. tamoxifen, toremifene, fluoxymesterol and raloxifene), antiandrogens (bicalutamide, nilutamide, flutamide), aromatase inhibitors (e.g., aminoglutethimide, anastrozole and tetrazole), ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone. Combination therapy including a PARP inhibitor and a hormonal agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0328] Plant-derived agents are a group of drugs that are derived from plants or modified based on the molecular structure of the agents. Examples of plant-derived agents include, but are not limited to, vinca alkaloids (e.g., vincristine, vinblastine, vindesine, vinzolidine and vinorelbine), podophyllotoxins (e.g., etopocide (VP-16) and tenipocide (VM-26)), taxanes (e.g., paclitaxel and docetaxel). These plant-derived agents generally act as antimitotic agents that bind to tubulin and inhibit mitosis. Podophyllotoxins such as etopocide are believed to

interfere with DNA synthesis by interacting with topoisomerase II, leading to DNA strand scission. Combination therapy including a PARP inhibitor and a plant-derived agent may have therapeutic synergistic effects on cancer and reduce sides affects associated with these chemotherapeutic agents.

[0329] Biologic agents are a group of biomolecules that elicit cancer/tumor regression when used alone or in combination with chemotherapy and/or radiotherapy. Examples of biologic agents include, but are not limited to, immuno-modulating proteins such as cytokines, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines. Combination therapy including a PARP inhibitor and a biologic agent may have therapeutic synergistic effects on cancer, enhance the patient's immune responses to tumorigenic signals, and reduce potential sides affects associated with this chemotherapeutic agent.

[0330] Cytokines possess profound immunomodulatory activity. Some cytokines such as interleukin-2 (IL-2, aldesleukin) and interferon have demonstrated antitumor activity and have been approved for the treatment of patients with metastatic renal cell carcinoma and metastatic malignant melanoma. IL-2 is a T-cell growth factor that is central to T-cell-mediated immune responses. The selective antitumor effects of IL-2 on some patients are believed to be the result of a cell-mediated immune response that discriminate between self and nonself. Examples of interleukins that may be used in conjunction with PARP inhibitor include, but are not limited to, interleukin 2 (IL-2), and interleukin 4 (IL-4), interleukin 12 (IL-12).

[0331] Interferon include more than 23 related subtypes with overlapping activities, all of the IFN subtypes within the scope of the present invention. IFN has demonstrated activity against many solid and hematologic malignancies, the later appearing to be particularly sensitive.

[0332] Other cytokines that may be used in conjunction with a PARP inhibitor include those cytokines that exert profound effects on hematopoiesis and immune functions. Examples of such cytokines include, but are not limited to erythropoietin, granulocyte-CSF (filgrastin), and granulocyte, macrophage-CSF (sargramostim). These cytokines may be used in conjunction with a PARP inhibitor to reduce chemotherapy-induced myelopoietic toxicity.

[0333] Other immuno-modulating agents other than cytokines may also be used in conjunction with a PARP inhibitor to inhibit abnormal cell growth. Examples of such immuno-modulating agents include, but are not limited to bacillus Calmette-Guerin, levamisole, and octreotide, a long-acting octapeptide that mimics the effects of the naturally occurring hormone somatostatin.

[0334] Monoclonal antibodies against tumor antigens are antibodies elicited against antigens expressed by tumors, preferably tumor-specific antigens. For example, monoclonal antibody HERCEPTIN® (Trastruzumab) is raised against human epidermal growth factor receptor2 (HER2) that is overexpressed in some breast tumors including metastatic breast cancer. Overexpression of HER2 protein is associated with more aggressive disease and poorer prognosis in the clinic. HERCEPTIN® is used as a single agent for the treatment of patients with metastatic breast cancer whose tumors over express the HER2 protein. Combination therapy including PARP inhibitor and HERCEPTIN® may have therapeutic synergistic effects on tumors, especially on metastatic cancers.

[0335] Another example of monoclonal antibodies against tumor antigens is RITUXAN® (Rituximab) that is raised against CD20 on lymphoma cells and selectively deplete normal and malignant $CD20^+$ pre-B and mature B cells. RITUXAN® is used as single agent for the treatment of patients with relapsed or refractory low-grade or follicular, CD20+, B cell non-Hodgkin's lymphoma. Combination therapy including PARP inhibitor and RITUXAN® may have therapeutic synergistic effects not only on lymphoma, but also on other forms or types of malignant tumors.

[0336] Tumor suppressor genes are genes that function to inhibit the cell growth and division cycles, thus preventing the development of neoplasia. Mutations in tumor suppressor genes cause the cell to ignore one or more of the components of the network of inhibitory signals, overcoming the cell cycle check points and resulting in a higher rate of controlled cell growth—cancer. Examples of the tumor suppressor genes include, but are not limited to, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1, and BRCA2.

[0337] DPC-4 is involved in pancreatic cancer and participates in a cytoplasmic pathway that inhibits cell division. NF-1 codes for a protein that inhibits Ras, a cytoplasmic inhibitory protein. NF-1 is involved in neurofibroma and pheochromocytomas of the nervous system and myeloid leukemia. NF-2 encodes a nuclear protein that is involved in meningioma, schwanoma, and ependymoma of the nervous system. RB codes for the pRB protein, a nuclear protein that is a major inhibitor of cell cycle. RB is involved in retinoblastoma as well as bone, bladder, small cell lung and breast cancer. P53 codes for p53 protein that regulates cell division and can induce apoptosis. Mutation and/or inaction of p53 is found in a wide ranges of cancers. WT1 is involved in Wilms tumor of the kidneys. BRCA1 is involved in breast and ovarian cancer, and BRCA2 is involved in breast cancer. The tumor suppressor gene can be transferred into the tumor cells where it exerts its tumor suppressing functions. Combination

therapy including a PARP inhibitor and a tumor suppressor may have therapeutic synergistic effects on patients suffering from various forms of cancers.

[0338] Cancer vaccines are a group of agents that induce the body's specific immune response to tumors. Most of cancer vaccines under research and development and clinical trials are tumor-associated antigens (TAAs). TAA are structures (i.e. proteins, enzymes or carbohydrates) which are present on tumor cells and relatively absent or diminished on normal cells. By virtue of being fairly unique to the tumor cell, TAAs provide targets for the immune system to recognize and cause their destruction. Example of TAAs include, but are not limited to gangliosides (GM2), prostate specific antigen (PSA), alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) (produced by colon cancers and other adenocarcinomas, e.g. breast, lung, gastric, and pancreas cancers), melanoma associated antigens (MART-1, gp100, MAGE 1,3 tyrosinase), papillomavirus E6 and E7 fragments, whole cells or portions/lysates of autologous tumor cells and allogeneic tumor cells.

[0339] An adjuvant may be used to augment the immune response to TAAs. Examples of adjuvants include, but are not limited to, bacillus Calmette-Guerin (BCG), endotoxin lipopolysaccharides, keyhole limpet hemocyanin (GKLH), interleukin-2 (IL-2), granulocyte-macrophage colony-stimulating factor (GM-CSF) and cytoxan, a chemotherapeutic agent which is believe to reduce tumor-induced suppression when given in low doses.

[0340] Further examples of therapeutic agents that may be used in combination with PARP inhibitors include, but are not limited to, PI3/Akt signaling inhibitors. Examples of PI3/Akt inhibitors that may be used in combination with PARP inhibitors include, but are not limited to, human epidermal growth factor receptor (HER2) inhibitors. Examples of HER2 inhibitors include, but are not limited to, Herceptin® (Trastruzumab) and Tykerb® (Lapatinib). Tykerb®, a small molecule that can be administered orally, inhibits the tyrosine kinase components of ErbB1 and ErbB2 receptors. Stimulation of ErbB1 and ErbB2 is associated with cell proliferation and with multiple processes involved in tumor progression, invasion, and metastasis. Overexpression of these receptors has been reported in a variety of human tumors and is associated with poor prognosis and reduced overall survival.

[0341] Still further examples of therapeutic agents that may be used in combination with PARP inhibitors include, but are not limited to, histone deacetylase (HDAC) inhibitors. Examples of HDAC inhibitors that may be used in combination with PARP inhibitors include, but are not limited to, suberoylanilide hydroxamic acid (SAHA).

[0342] In addition, the PARP inhibitors of the present invention may be used in combination with aminoglycide antiobiotics, CHK inhibitors, cytotoxic drugs and/or topoisomerase inhibitors.

EXAMPLES

Preparation of PARP Inhibitors

[0343] Various methods may be developed for synthesizing compounds according to the present invention. Representative methods for synthesizing these compounds are provided in the Examples. It is noted, however, that the compounds of the present invention may also be synthesized by other synthetic routes that others may devise.

[0344] It will be readily recognized that certain compounds according to the present invention have atoms with linkages to other atoms that confer a particular stereochemistry to the compound (*e.g.*, chiral centers). It is recognized that synthesis of compounds according to the present invention may result in the creation of mixtures of different stereoisomers (*i.e.*, enantiomers and diastereomers). Unless a particular stereochemistry is specified, recitation of a compound is intended to encompass all of the different possible stereoisomers.

[0345] Various methods for separating mixtures of different stereoisomers are known in the art. For example, a racemic mixture of a compound may be reacted with an optically active resolving agent to form a pair of diastereoisomeric compounds. The diastereomers may then be separated in order to recover the optically pure enantiomers. Dissociable complexes may also be used to resolve enantiomers (*e.g.*, crystalline diastereoisomeric salts). Diastereomers typically have sufficiently distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. For example, diastereomers can typically be separated by chromatography or by separation/resolution techniques based upon differences in solubility. A more detailed description of techniques that can be used to resolve stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[0346] Compounds according to the present invention can also be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound can be prepared by reacting the free acid form of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically

acceptable salts of compounds are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds can be prepared using salts of the starting materials or intermediates.

[0347] The free acid or free base forms of the compounds can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (*e.g.*, ammonium hydroxide solution, sodium hydroxide, and the like). A compound in a base addition salt form can be converted to the corresponding free acid by treating with a suitable acid (*e.g.*, hydrochloric acid, etc).

[0348] The N-oxides of compounds according to the present invention can be prepared by methods known to those of ordinary skill in the art. For example, N-oxides can be prepared by treating an unoxidized form of the compound with an oxidizing agent (*e.g.*, trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, meta-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (*e.g.*, a halogenated hydrocarbon such as dichloromethane) at approximately 0 °C. Alternatively, the N-oxides of the compounds can be prepared from the N-oxide of an appropriate starting material.

[0349] Compounds in an unoxidized form can be prepared from N-oxides of compounds by treating with a reducing agent (*e.g.*, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (*e.g.*, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80 °C.

[0350] Prodrug derivatives of the compounds can be prepared by methods known to those of ordinary skill in the art (*e.g.*, for further details see Saulnier et al.(1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound with a suitable carbamylating agent (*e.g.*, 1,1-acyloxyalkylcarbonochloridate, para-nitrophenyl carbonate, or the like).

[0351] Protected derivatives of the compounds can be made by methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

[0352] Compounds according to the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (*e.g.*, hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

[0353] Compounds according to the present invention can also be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds, dissociable complexes are preferred (*e.g.*, crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (*e.g.*, melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

[0354] As used herein the symbols and conventions used in these processes, schemes and examples are consistent with those used in the contemporary scientific literature, for example, the Journal of the American Chemical Society or the Journal of Biological Chemistry. Standard single-letter or three-letter abbreviations are generally used to designate amino acid residues, which are assumed to be in the L-configuration unless otherwise noted. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification:

µL (microliters)	Ac (acetyl)
atm (atmosphere)	ATP (Adenosine Triphophatase)
BOC (tert-butyloxycarbonyl)	BOP (bis(2-oxo-3-oxazolidinyl)phosphinic chloride)
BSA (Bovine Serum Albumin)	CBZ (benzyloxycarbonyl)
CDI (1,1-carbonyldiimidazole)	DCC (dicyclohexylcarbodiimide)
DCE (dichloroethane)	DCM (dichloromethane)
DMAP (4-dimethylaminopyridine)	DME (1,2-dimethoxyethane)
DMF (N,N-dimethylformamide)	DMPU (N,N'-dimethylpropyleneurea)
DMSO (dimethylsulfoxide)	EDCI (ethylcarbodiimide hydrochloride)
EDTA (Ethylenediaminetetraacetic acid)	Et (ethyl)
Et_2O (diethyl ether)	EtOAc (ethyl acetate)
FMOC (9-fluorenylmethoxycarbonyl)	g (grams)
h (hours)	HOAc or AcOH (acetic acid)
HOBT (1-hydroxybenzotriazole)	HOSu (N-hydroxysuccinimide)
HPLC (high pressure liquid chromatography)	Hz (Hertz)

i.v. (intravenous)	IBCF (isobutyl chloroformate)
i-PrOH (isopropanol)	L (liters)
M (molar)	mCPBA (meta-chloroperbenzoic acid)
Me (methyl)	MeOH (methanol)
mg (milligrams)	MHz (megahertz)
min (minutes)	mL (milliliters)
mM (millimolar)	mmol (millimoles)
mol (moles)	MOPS (Morpholinepropanesulfonic acid)
mp (melting point)	NaOAc (sodium acetate)
OMe (methoxy)	psi (pounds per square inch)
RP (reverse phase)	RT (ambient temperature)
SPA (Scintillation Proximity Assay)	TBAF (tetra-n-butylammonium fluoride)
TBS (t-butyldimethylsilyl)	tBu (tert-butyl)
TEA (triethylamine)	TFA (trifluoroacetic acid)
TFAA (trifluoroacetic anhydride)	THF (tetrahydrofuran)
TIPS (triisopropylsilyl)	TLC (thin layer chromatography)
TMS (trimethylsilyl)	TMSE (2-(trimethylsilyl)ethyl)
Tr (retention time)	

[0355] All references to ether or Et_2O are to diethyl ether; and brine refers to a saturated aqueous solution of NaCl. Unless otherwise indicated, all temperatures are expressed in °C (degrees Centigrade). All reactions are conducted under an inert atmosphere at RT unless otherwise noted.

[0356] ^{1}H NMR spectra were recorded on a Bruker Avance 400. Chemical shifts are expressed in parts per million (ppm). Coupling constants are in units of Hertz (Hz). Splitting patterns describe apparent multiplicities and are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[0357] Low-resolution mass spectra (MS) and compound purity data were acquired on a Waters ZQ LC/MS single quadrupole system equipped with electrospray ionization (ESI) source, UV detector (220 and 254 nm), and evaporative light scattering detector (ELSD). Thin-layer chromatography was performed on 0.25 mm E. Merck silica gel plates (60F-254), visualized with UV light, 5% ethanolic phosphomolybdic acid, Ninhydrin or p-anisaldehyde solution. Flash column chromatography was performed on silica gel (230-400 mesh, Merck).

[0358] The starting materials and reagents used in preparing these compounds are either available from commercial suppliers such as the Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), or may be prepared by methods well known to a person of ordinary skill in the art, following procedures described in such standard references as Fieser and Fieser's Reagents for Organic Synthesis, vols. 1-17, John Wiley and Sons, New York, NY, 1991; Rodd's Chemistry of Carbon Compounds, vols. 1-5 and supps.,

Elsevier Science Publishers, 1989; Organic Reactions, vols. 1-40, John Wiley and Sons, New York, NY, 1991; March J.: Advanced Organic Chemistry, 4th ed., John Wiley and Sons, New York, NY; and Larock: Comprehensive Organic Transformations, VCH Publishers, New York, 1989.

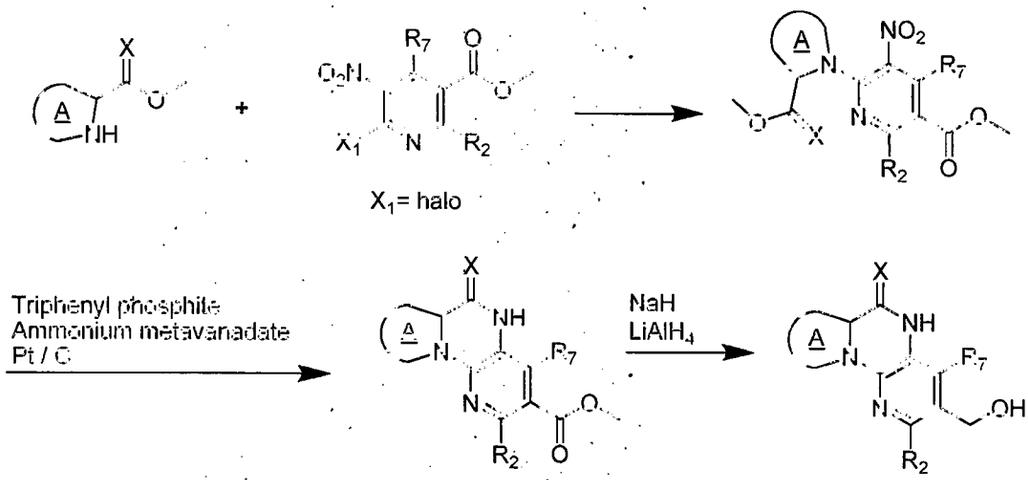
[0359] The entire disclosures of all documents cited throughout this application are incorporated herein by reference.

Synthetic Schemes for Compounds of the Present Invention

[0360] Compounds according to the present invention may be synthesized according to the reaction schemes shown below. Other reaction schemes could be readily devised by those skilled in the art. It should also be appreciated that a variety of different solvents, temperatures and other reaction conditions can be varied to optimize the yields of the reactions.

[0361] In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

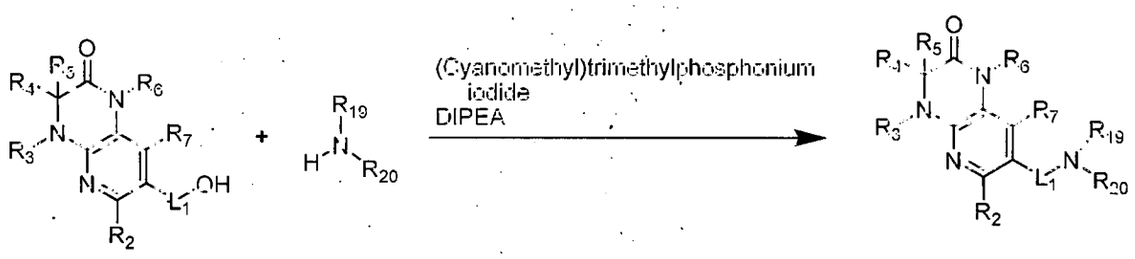
Scheme 1



[0362] An α-aminoester is condensed with a substituted 2-halo-3-nitropyridine (alternatively with or without solvent or applied heat) followed by reduction of the nitro group and ring closure to give a substituted pyridopyrazine. Alternatively the nitro reduction and cyclization can be carried out with iron dust in AcOH with heating. Reduction of the methyl

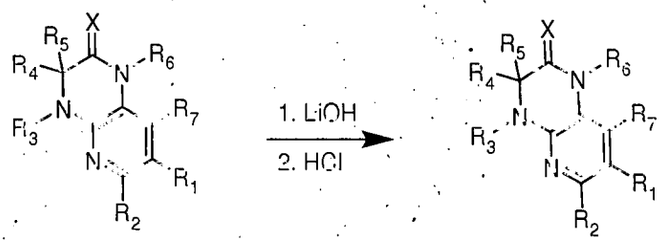
ester at the 7-position is accomplished with lithium aluminum hydride (or other hydride reducint agents) after deprotonation of the amide N-H to protect the amide.

Scheme 2



[0363] Nucleophilic substitution of the alcohol with amines is accomplished after conversion of the alcohol to the iodide. Other methods of alcohol activation may be utilized including Mitsunobu conditions among others.

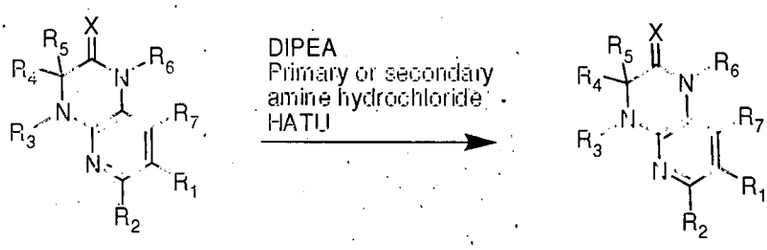
Scheme 3



wherein R_1 has a terminal ester wherein R_1 has a terminal carboxylic acid

[0364] Hydrolysis of a terminal ester is accomplished with lithium hydroxide followed by treatment with acid to give a terminal carboxylic acid. Alternatively, other hydrolysis conditions can be utilized, both basic and acidic, including sodium hydroxide, potassium hydroxide, hydrochloric acid and others.

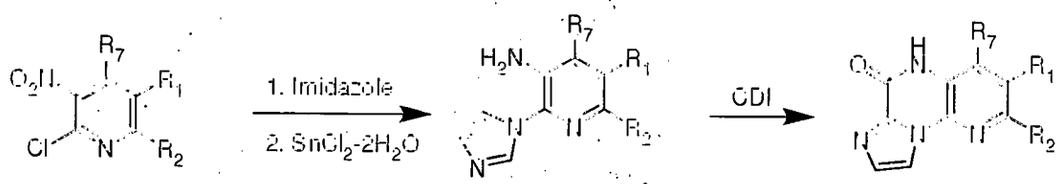
Scheme 4



wherein R_1 has a terminal carboxylic acid wherein R_1 has a terminal carboxamide

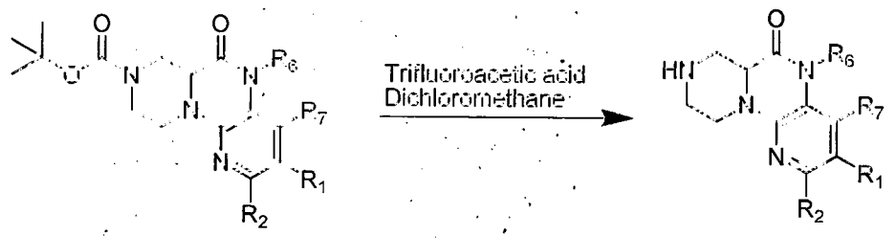
[0365] Terminal carboxylic acids are converted to terminal carboxamides through activation of the acid with HATU followed by treatment with primary or secondary amines. Alternatively, other methods exist to convert carboxylic acids to carboxamides including conversion to an intermediate acid chloride or use of other activation reagents such as EDC, HOBt, EDAC, PyBOP, TATU and others.

Scheme 5



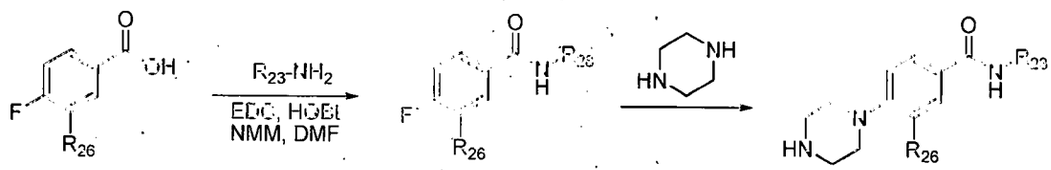
[0366] Nucleophilic aromatic substitution of a 2-halo-3-nitropyridine with imidazole is carried out followed by reduction of the nitro group. Treatment with CDI forms the pyrazinone.

Scheme 6



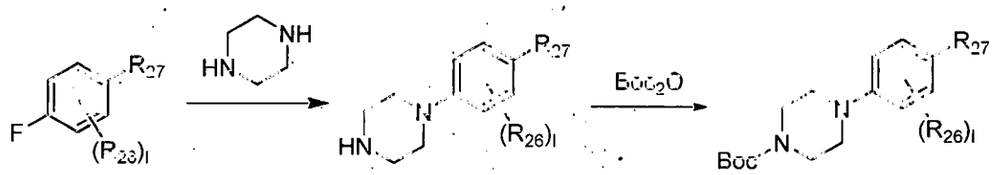
[0367] Deprotection of a Boc group is accomplished by stirring with TFA in DCM. Alternatively, other strong acids and solvents may be used including but not limited to HCl in EtOAc.

Scheme 7a: General Procedure for synthesis of substituted 4-piperazinylbenzamides



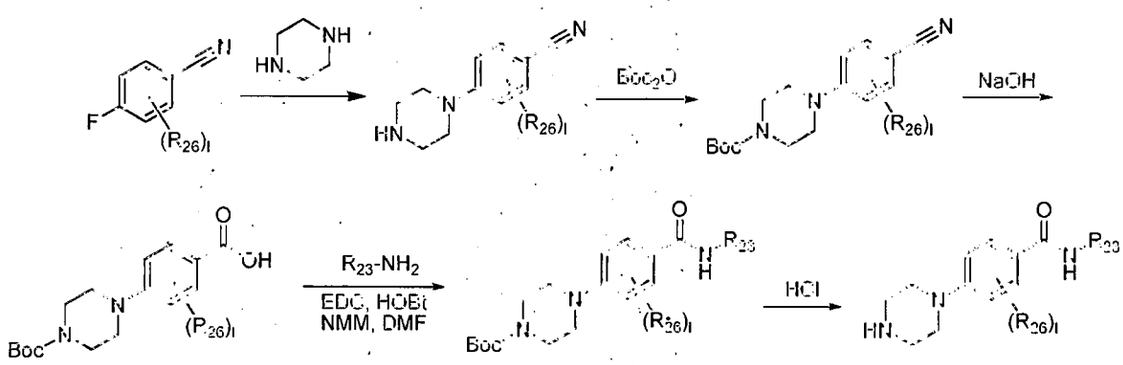
[0368] Substituted 4-fluorobenzoic acids are converted to benzamides using various amines and a coupling reagent such as EDC with HOBt. Alternatively, other coupling reagents can be used to form the amide. Subsequent nucleophilic aromatic substitution with piperazine gives the required substituted 4-piperazinylbenzamides.

Scheme 7b: Alternative General Procedure for synthesis of substituted 4-piperazinylbenzamides



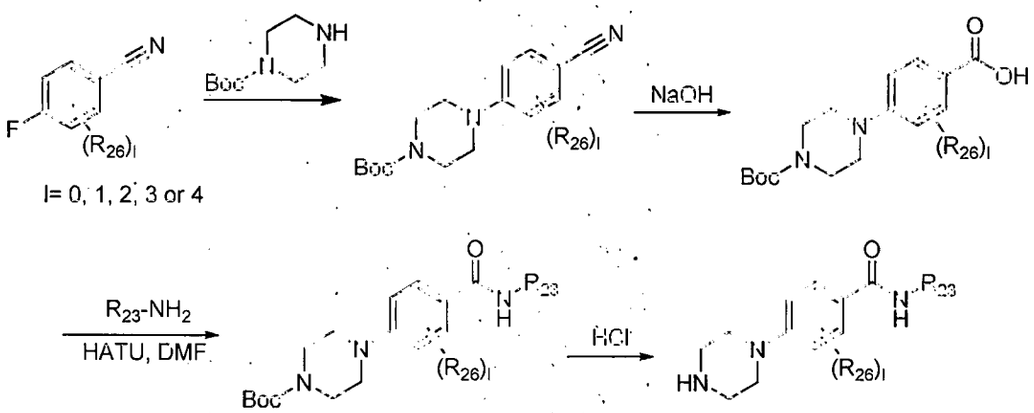
[0369] Nucleophilic aromatic substitution of aryl fluorides with piperazine gives N-arylpiperazines which can then be protected with a Boc group to allow further functionalization of the aryl substituents. Alternatively, other protecting groups can be used besides Boc.

Scheme 8



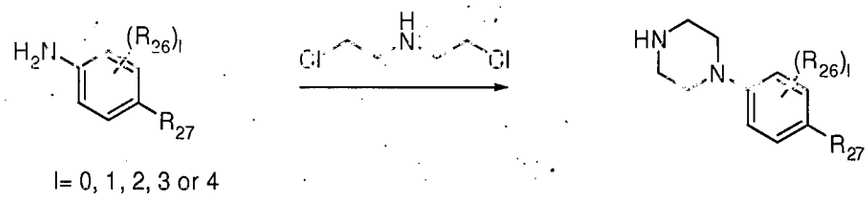
[0370] Substituted 4-fluorobenzonitriles are subjected to nucleophilic aromatic substitution with piperazine followed by protection using Boc anhydride. The nitrile is hydrolyzed to the corresponding carboxylic acid which is then coupled with an amine to give the resulting benzamide. Finally the Boc protecting group is removed by treatment with acid to furnish substituted 4-piperazinylbenzamides.

Scheme 9



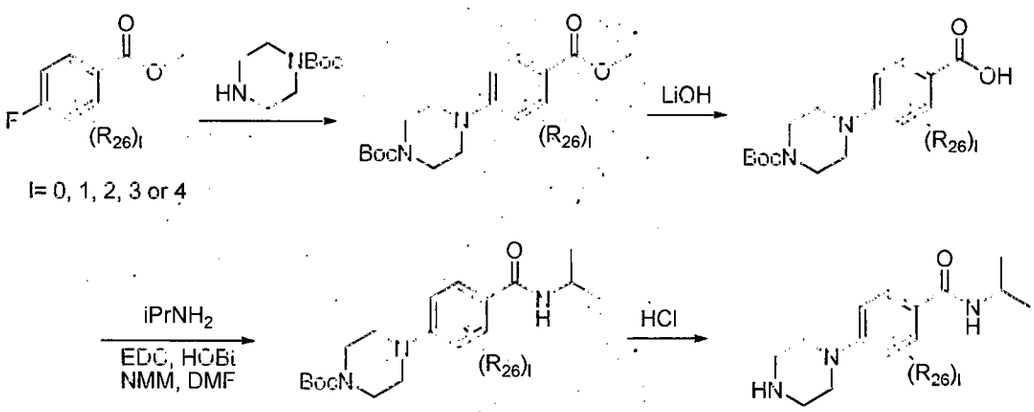
[0371] Substituted 4-fluorobenzonitriles are subjected to nucleophilic aromatic substitution with Boc-piperazine. The nitrile is hydrolyzed to the corresponding carboxylic acid which is then coupled with an amine to give the resulting benzamide. Finally the Boc protecting group is removed to furnish substituted 4-piperazinylbenzamides.

Scheme 10



[0372] Substituted anilines can be converted to substituted piperazines through alkylation of the aniline with bis(2-chloroethyl)amine. Alternatively, other halogens or leaving groups can be incorporated in the amine such as bis(2-bromoethyl)amine or others.

Scheme 11



[0373] Substituted 4-fluorobenzoates are subjected to nucleophilic aromatic substitution with N-Boc piperazine followed by hydrolysis of the ester with lithium hydroxide to give a protected 4-carboxyphenyl-N-piperazine. Alternatively, other hydrolysis conditions can be utilized, both basic and acidic, including sodium hydroxide, potassium hydroxide, hydrochloric acid and others. Amide formation of the benzoic acid with amines is mediated with coupling reagents such as EDC with HOBt followed by removal of the protecting group with HCl to give the desired substituted 4-benzamidepiperazines. Alternatively, other methods exist to convert carboxylic acids to carboxamides including conversion to an intermediate acid chloride or use of other activation reagents such as EDAC, PyBOP, TATU and others.

[0374] Chiral components can be separated and purified using any of a variety of techniques known to those skilled in the art. For example, chiral components can be purified using supercritical fluid chromatography (SFC). In one particular variation, chiral analytical SFC/MS analyses are conducted using a Berger analytical SFC system (AutoChem, Newark, DE) which consists of a Berger SFC dual pump fluid control module with a Berger FCM 1100/1200 supercritical fluid pump and FCM 1200 modifier fluid pump, a Berger TCM 2000 oven, and an Alcott 718 autosampler. The integrated system can be controlled by EI-SFC Chemstation software version 3.4. Detection can be accomplished with a Waters ZQ 2000 detector operated in positive mode with an ESI interface and a scan range from 200-300 Da with 0.5 second per scan. Chromatographic separations can be performed on a ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, or ChiralCel OJ-H column (5μ, 4.6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) with 10 to 40% methanol as the modifier and with or without ammonium acetate (10 mM). Any of a variety of flow rates can be utilized including, for example, 1.5 or 3.5 mL/min with an inlet pressure set at 100 bar. Additionally, a variety of sample injection conditions can be used including, for example, sample injections of either 5 or 10μL in methanol at 0.1 mg/mL in concentration.

[0375] In another variation, preparative chiral separations are performed using a Berger MultiGram II SFC purification system. For example, samples can be loaded onto a ChiralPak AD column (21 x 250 mm, 10μ). In particular variations, the flow rate for separation can be 70 mL/min, the injection volume up to 2 mL, and the inlet pressure set at 130 bar. Stacked injections can be applied to increase the efficiency.

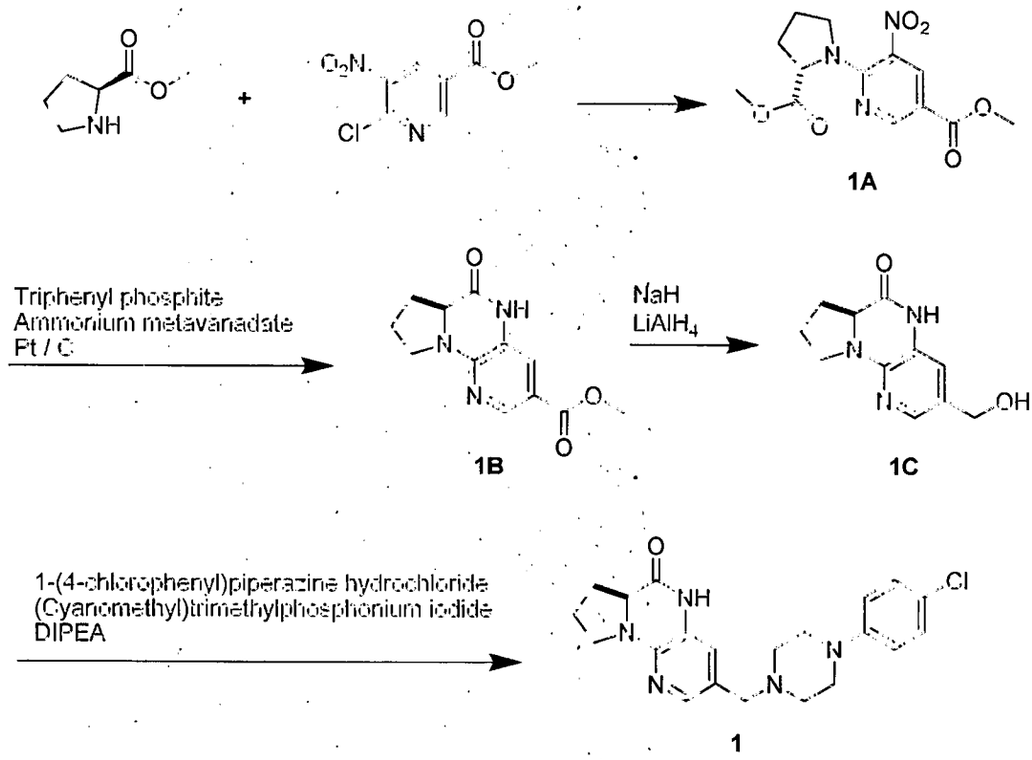
[0376] In each of the above reaction procedures or schemes, the various substituents may be selected from among the various substituents otherwise taught herein.

[0377] Descriptions of the syntheses of particular compounds according to the present invention based on the above reaction scheme are set forth herein.

Examples of PARP Inhibitors

[0378] The present invention is further exemplified, but not limited by, the following examples that describe the synthesis of particular compounds according to the invention.

Compound 1: (S)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



[0379] **Compound 1A: (S)-Methyl 6-(2-(methoxycarbonyl)pyrrolidin-1-yl)-5-nitronicotinate**: (S)-Methyl pyrrolidine-2-carboxylate (6.56 g, 50.8 mmol) was added to methyl 6-chloro-5-nitronicotinate (5.00 g, 23.1 mmol) and the reaction mixture was stirred at 90 °C for 10 min (exothermic reaction). It was cooled to room temperature, diluted with EtOAc (10 mL) and purified using flash column chromatography on silica gel (20-30% EtOAc in hexanes) to afford the title compound as a yellow oil (6.70 g, 94%). [M+H] calc'd for $C_{13}H_{15}N_3O_6$, 310; found, 310.

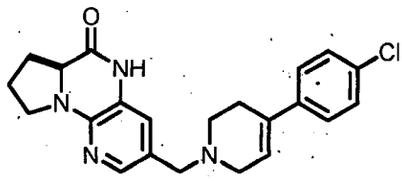
[0380] **Compound 1B: (S)-methyl 6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate**: (S)-Methyl 6-(2-(methoxycarbonyl)pyrrolidin-1-

yl)-5-nitronicotinate (1.45 g, 46.9 mmol) and triphenyl phosphite (5.00 mg, 0.0161 mmol) were dissolved in dichloromethane (12 mL). Ammonium metavanadate (50 mg, 0.427 mmol) and Pt/C (5% wt., 200 mg) were added and the reaction mixture was stirred under hydrogen (30 psi) for 5 h. The reaction mixture was filtered through a small plug of celite and the precipitate was washed multiple times with hot dichloromethane until it was free from white precipitate. The filtrate was concentrated in vacuo and crystallized with ethyl ether (15 mL). The resulting solid was filtered off and dried in vacuum to afford the title compound as an off-white solid (0.930 g, 80%). [M+H] calc'd for $C_{12}H_{13}N_3O_3$, 248; found, 248.

[0381] Compound 1C: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: (S)-methyl 6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate (3.00 g, 10.5 mmol) was suspended in THF and sodium hydride (60% suspension in mineral oil, 0.712 g, 17.8 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h and cooled to -78°C. $LiAlH_4$ (2M in THF, 12.5 mL, 25 mmol) was added dropwise over 5 min and the reaction mixture was allowed to warm to -40 °C and kept at -40-(-20) °C for 3h. The reaction mixture was cooled to -60 °C and quenched with MeOH, water and TFA until a clear mixture resulted. This was purified using HPLC (1-30% acetnitrile in water, TFA buffered). The fractions containing product were concentrated in vacuo and crystallized with ethyl ether. The solid was filtered and dried in vacuum to afford the title compound as a grey solid (2.60 g, 74%, TFA salt). [M+H] calc'd for $C_{11}H_{13}N_3O_2$, 220; found, 220.

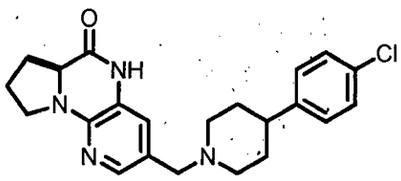
[0382] Compound 1: (S)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (200 mg, 0.912 mmol), 1-(4-chlorophenyl)piperazine hydrochloride (200 mg, 0.858 mmol), N,N-diisopropylethylamine (DIPEA; 0.50 mL), and (cyanomethyl)trimethylphosphonium iodide (220 mg, 1.08 mmol) were suspended in propionitrile (2 mL) and heated in a closed vial at 90 °C for 4h. The reaction mixture was diluted with MeOH (2 mL) and purified using preparative scale HPLC (45-95% acetonitrile in water, buffered with NH_4HCO_3). The fractions containing product were concentrated in vacuo and diluted with water (5 mL). The resulting precipitate was filtered and dried in vacuum to afford the title compound as an off-white solid (135 mg, 40%). ^{1}H NMR (DMSO-d_6) δ (ppm): 10.43 (s, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 3.91 - 4.06 (m, 1H), 3.51 - 3.66 (m, 1H), 3.37 - 3.47 (m, 1H), 3.10 (br. s., 4H), 2.46 (d, J = 4.3 Hz, 4H), 2.09 - 2.26 (m, 1H), 1.80 - 2.03 (m, 3H); [M+H] calc'd for $C_{21}H_{24}ClN_5O$, 398; found, 398; melting point 265-268 °C.

Compound 2: (S)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



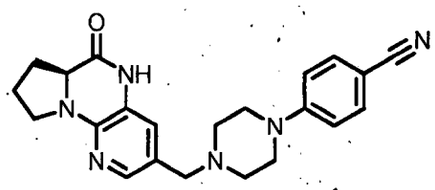
[0383] Compound 2 was prepared using a procedure analogous to that described in connection with compound 1, except that 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.77 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 7.29 - 7.33 (m, 2H), 7.26 - 7.29 (m, 2H), 7.01 (d, J = 1.8 Hz, 1H), 6.01 - 6.08 (m, 1H), 4.07 (dd, J = 9.2, 6.4 Hz, 1H), 3.72 - 3.83 (m, 1H), 3.57 - 3.66 (m, 1H), 3.44 - 3.55 (m, 2H), 3.15 (q, J = 2.8 Hz, 2H), 2.65 - 2.76 (m, 2H), 2.47 - 2.57 (m, 2H), 2.34 - 2.46 (m, 1H), 1.94 - 2.26 (m, 3H): [M+H] calc'd for $C_{22}H_{23}ClN_4O$, 395; found, 395, melting point 234-235 °C.

Compound 3: (S)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



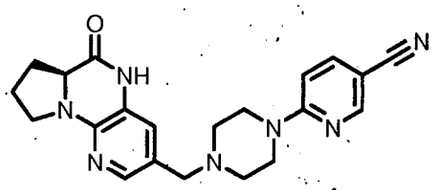
[0384] Compound 3 was prepared using a procedure analogous to that described in connection with compound 1, except that 4-(4-chlorophenyl)piperidine hydrochloride was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.92 (br. s., 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.26 (d, J = 8.3 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 1.5 Hz, 1H), 4.07 (dd, J = 9.5, 6.4 Hz, 1H), 3.69 - 3.82 (m, 1H), 3.54 - 3.66 (m, 1H), 3.33 - 3.49 (m, 2H), 3.00 (d, J = 11.4 Hz, 2H), 2.33 - 2.55 (m, 2H), 1.95 - 2.25 (m, 5H), 1.74 - 1.85 (m, 3H); [M+H] calc'd for $C_{22}H_{25}ClN_4O$, 397; found, 397.

Compound 4: (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



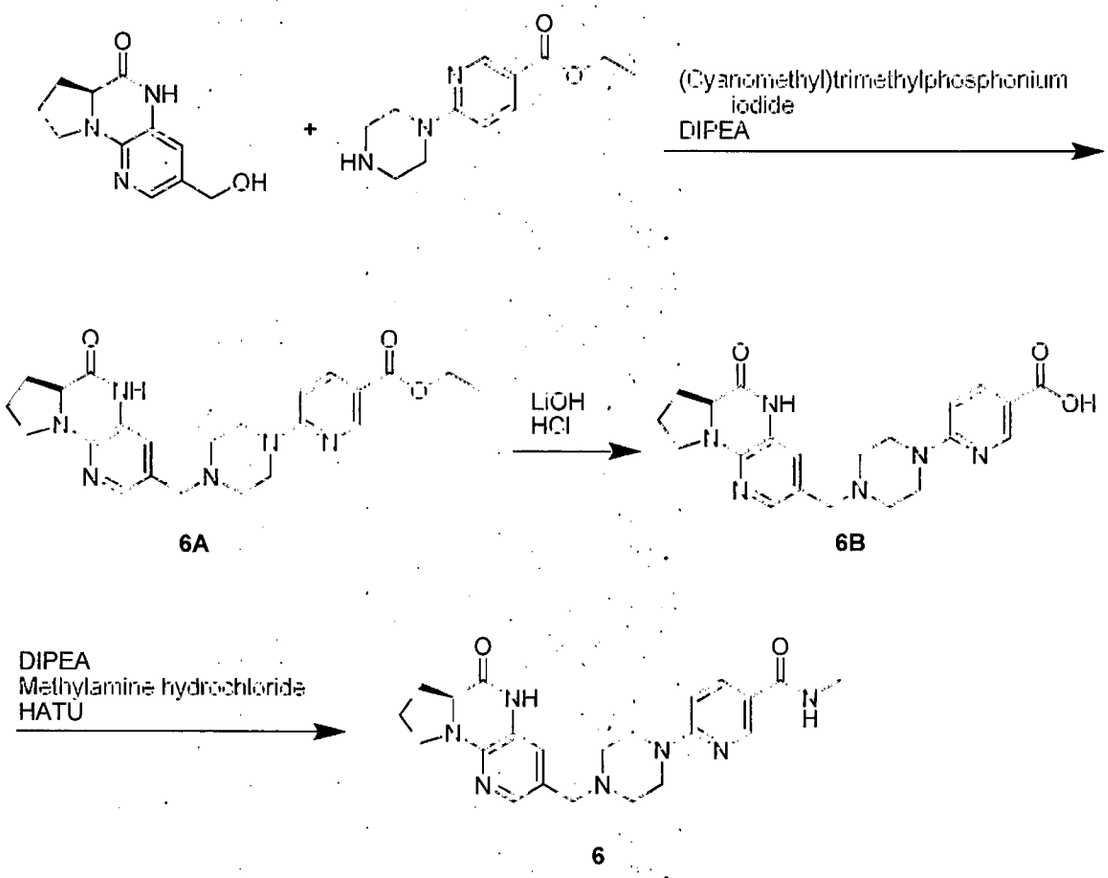
[0385] Compound 4 was prepared using a procedure analogous to that described in connection with compound 1, except that 4-(piperazin-1-yl)benzonitrile was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.44 (s, 1H), 7.59 (dd, J = 16.9, 5.3 Hz, 3H), 6.99 (dd, J = 9.3, 5.3 Hz, 3H), 3.91 - 4.07 (m, 1H), 3.51 - 3.65 (m, 1H), 3.31-3.46 (m, 7H), 2.37 - 2.47 (m, 4H), 2.10 - 2.25 (m, 1H), 1.82 - 2.01 (m, 3H); [M+H] calc'd for $C_{22}H_{24}N_6O$, 389; found, 389; melting point 252 °C.

Compound 5: (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile



[0386] Compound 5 was prepared using a procedure analogous to that described in connection with compound 1, except that 6-(piperazin-1-yl)nicotinonitrile was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.44 (s, 1H), 8.47 (d, J = 2.3 Hz, 1H), 7.84 (dd, J = 9.1, 2.3 Hz, 1H), 7.60 (d, J = 1.5 Hz, 1H), 6.98 (d, J = 1.8 Hz, 1H), 6.91 (d, J = 9.1 Hz, 1H), 3.92 - 4.06 (m, 1H), 3.57 - 3.71 (m, 5H), 3.27 - 3.48 (m, 3H), 2.40 (t, J = 4.5 Hz, 4H), 2.10 - 2.24 (m, 1H), 1.81 - 2.01 (m, 3H); [M+H] calc'd for $C_{21}H_{23}N_7O$, 390; found, 390; melting point 252-256 °C.

Compound 6: (S)-N-methyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



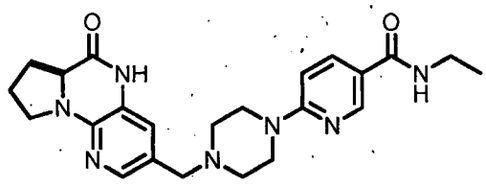
[0387] Compound 6A: (S)-ethyl 6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (233 mg, 1.06 mmol), ethyl 6-(piperazin-1-yl)nicotinate (270 mg, 0.1.15 mmol), DIPEA (0.80 mL), and (cyanomethyl)trimethylphosphonium iodide (369 mg, 01.82 mmol) were suspended in propionitrile (3 mL) and heated in a closed vial at 90 °C for 5h. The mixture was cooled, diluted with a solution of K_2CO_3 (2.50 g) in water (15 mL) and extracted with dichloromethane (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was crystallized with ethyl ether – ethanol (10:1, 22 mL) to afford the title compounds as a tan solid (0.355 mg, 77%). [M+H] calc'd for $C_{23}H_{28}N_6O_3$, 437; found, 437.

[0388] Compound 6B: (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid: (S)-ethyl 6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate (0.355 mg,

0.813 mmol) was suspended in dioxane (4 mL) and treated with LiOH (1N, 4.00 mL, 4.00 mmol). The resulting solution was stirred at room temperature for 3 h and concentrated in vacuo until most of the organic solvent was removed. The solution was acidified with HCl (4.5N) to pH=3 and the resulting precipitate was filtered off, washed with ethyl ether (5 mL) and dried in vacuum to afford the title compound as a brown solid (0.260 g, 73%). [M+H] calc'd for $C_{21}H_{24}N_6O_3$, 409; found, 409.

[0389] Compound 6: (S)-N-methyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide: (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (100 mg, 0.245 mmol) was suspended in DMF (1.5 mL) and DIPEA (0.3 mL) was added followed by methylamine hydrochloride (27 mg, 0.400 mmol) and HATU (200 mg, 0.526 mmol). The reaction mixture was stirred at ambient temperature for 4 h and diluted with MeOH (2 mL). The solution was purified using HPCL (25-95% acetonitrile in water, NH_4HCO_3 buffered). The fractions were concentrated in vacuo and the resulting residue was crystallized with MeOH – water (1:5, 15 mL) to afford the title compound as an off-white solid (52.3 mg, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.80 - 2.03 (m, 3 H) 2.09 - 2.25 (m, 1 H) 2.41 (br. s., 4 H) 2.74 (d, *J*=4.29 Hz, 3 H) 3.34 - 3.44 (m, 3 H) 3.46 - 3.64 (m, 5 H) 3.92 - 4.05 (m, 1 H) 6.82 (d, *J*=9.09 Hz, 1 H) 6.99 (d, 1 H) 6.93 - 7.04 (m, 1 H) 7.61 (s, 1 H) 7.91 (dd, *J*=8.97, 2.15 Hz, 1 H) 8.17-8.23 (m, 1H) 8.56 (d, *J*=1.77 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{22}H_{27}N_7O_2$, 422; found, 422.

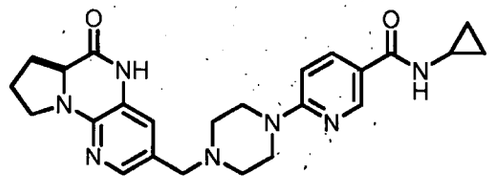
Compound 7: (S)-N-ethyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



[0390] (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (87 mg, 0.213 mmol) and ethanamine hydrochloride (17.4 mg, 0.213 mmol) were suspended in DMF (1.065 mL) and treated with DIPEA (0.186 mL, 1.065 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.426 mmol). The reaction mixture was stirred at room temperature for 3 h and purified using HPLC (10-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-ethyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-

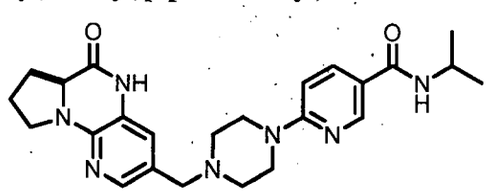
a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide (26.4 mg, 0.061 mmol, 28.5 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.09 (t, *J*=7.20 Hz, 3 H) 1.82 - 2.02 (m, 3 H) 2.18 (d, *J*=2.27 Hz, 1 H) 2.41 (t, *J*=4.80 Hz, 5 H) 3.20 - 3.29 (m, 2 H) 3.34 - 3.44 (m, 3 H) 3.51 - 3.63 (m, 5 H) 3.95 - 4.03 (m, 1 H) 6.82 (d, *J*=9.09 Hz, 1 H) 6.99 (d, *J*=1.77 Hz, 1 H) 7.61 (d, *J*=1.77 Hz, 1 H) 7.93 (dd, *J*=9.09, 2.53 Hz, 1 H) 8.23 (t, *J*=5.31 Hz, 1 H) 8.57 (d, *J*=2.27 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{23}H_{29}N_7O_2$, 422; found, 422.

Compound 8: (S)-N-cyclopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



[0391] (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (87 mg, 0.213 mmol) and cyclopropanamine (18.24 mg, 0.319 mmol) were suspended in DMF (1 ml) and treated with DIPEA (0.186 ml, 1.065 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.426 mmol). The reaction mixture was stirred at room temperature for 3 h and purified using HPLC (10-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-cyclopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide (70.3 mg, 0.157 mmol, 73.7 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 0.49 - 0.56 (m, 2 H) 0.62 - 0.70 (m, 2 H) 1.82 - 2.02 (m, 3 H) 2.11 - 2.22 (m, 1 H) 2.40 (t, *J*=4.93 Hz, 4 H) 2.78 (tq, *J*=7.34, 3.86 Hz, 1 H) 3.34 (br. s., 2 H) 3.36 - 3.44 (m, 1 H) 3.49 - 3.64 (m, 5 H) 3.94 - 4.03 (m, 1 H) 6.81 (d, *J*=8.59 Hz, 1 H) 6.98 (d,*J*=1.77 Hz, 1 H) 7.61 (d, *J*=1.77 Hz, 1 H) 7.90 (dd, *J*=9.09, 2.53 Hz, 1 H) 8.20 (d, *J*=4.04 Hz, 1 H) 8.54 (d, *J*=1.77 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{24}H_{29}N_7O_2$, 448; found, 448.

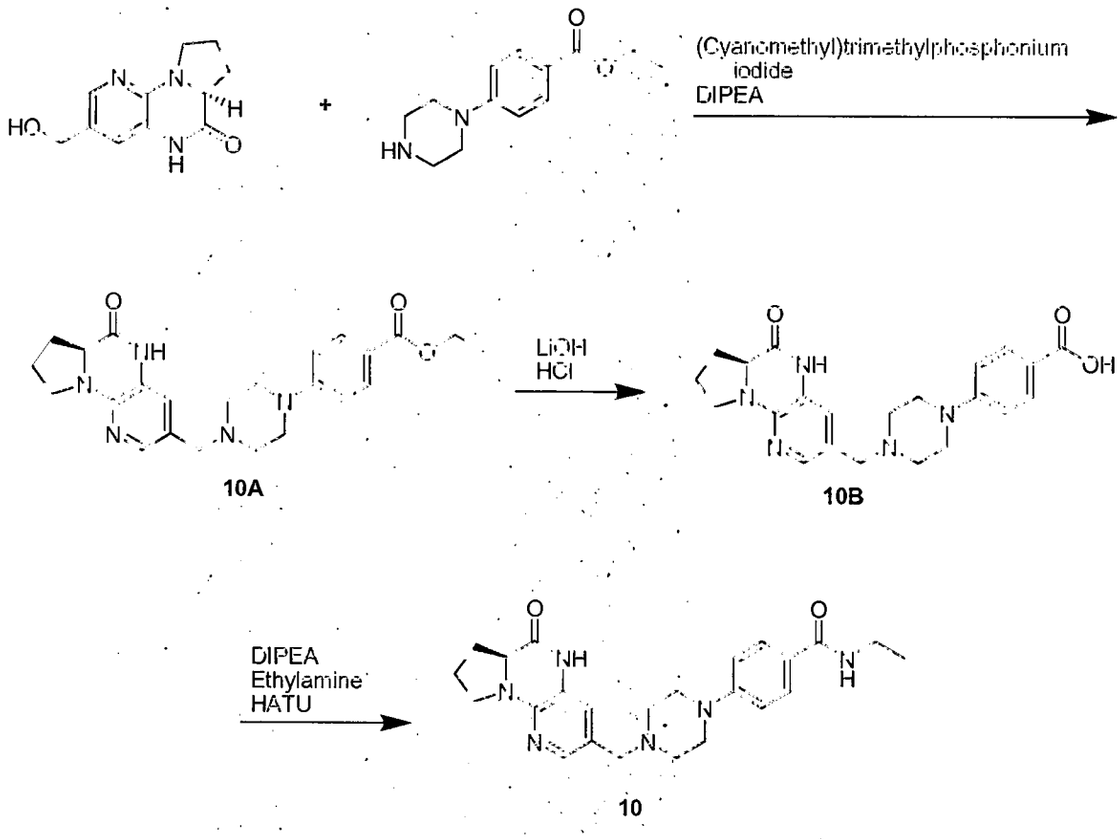
Compound 9: (S)-N-isopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



[0392] (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (37.0 mg, 0.213 mmol) and propan-2-amine (18.39 mg, 0.319 mmol) were suspended in DMF (1 ml) and treated with DIPEA (0.136 ml, 1.065 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.426 mmol). The reaction mixture was stirred at room temperature for 3 h and purified using HPLC (10-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-isopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide (62.1 mg, 0.138 mmol, 64.9 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.13 (d, *J*=6.57 Hz, 6 H) 1.84 - 2.01 (m, 3 H) 2.12 - 2.22 (m, 1 H) 2.41 (d, *J*=4.29 Hz, 4 H) 3.36 - 3.47 (m, 1H) 3.49 - 3.64 (m, 5 H) 3.95 - 4.10 (m, 2 H) 6.81 (d, *J*=8.84 Hz, 1 H) 6.99 (d, *J*=2.02 Hz, 1 H) 7.61 (d, *J*=1.77 Hz, 1 H) 7.94 (dd, *J*=9.09, 2.53 Hz, 1H) 7.97 (d, *J*=7.83 Hz, 1 H) 8.57 (d, *J*=2.53 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{24}H_{31}N_7O_2$, 450; found, 450.

Compound 10: (S)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

Method A



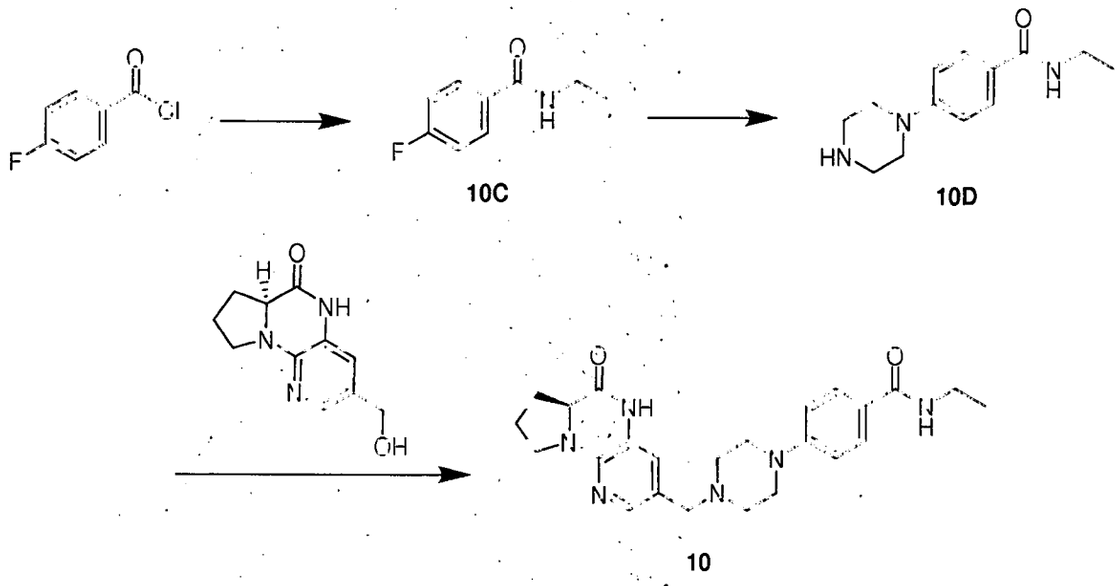
[0393] Compound 10A: (S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (187 mg, 0.854 mmol), ethyl 4-(piperazin-1-yl)benzoate (200 mg, 0.854 mmol), (cyanomethyl)trimethylphosphonium iodide (311 mg, 1.280 mmol) and N,N-diisopropylethylamine (0.745 ml, 4.27 mmol) were suspended in propionitrile (2 ml) and heated in a closed vial at 90 °C for 2h. The reaction mixture became a clear dark brown solution. The mixture was cooled to room temperature, diluted with MeOH (2 mL), filtered, the solids retained, and purified using preparative HPLC. The fractions containing product were concentrated in vacuo and crystallized from water (3 mL). The precipitate was filtered and dried in vacuum to afford the product as a light brown solid (18.3 mg). The solid from the earlier filtration was recrystallized from ether - MeOH (10 mL, 5:1). The combined products were dried in vacuum to afford (S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate (283 mg,

0.650 mmol, 76 % yield) as a brownish solid. [M+H] calc'd for $C_{24}H_{29}N_5O_3$, 436; found, 436; melting point 242 °C.

[0394] Compound 10B: (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid: (S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate (280 mg, 0.643 mmol) was suspended in 1,4-Dioxane (3.22 mL) and treated with 1N LiOH (3.215 mL, 3.22 mmol). The reaction mixture was stirred at room temperature for 23 h. The reaction mixture was concentrated in vacuo until most of the dioxane was gone and acidified with HCl (4.5 N) until a thick precipitate resulted. It was filtered off, washed with water and dried in vacuum to afford (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (225 mg, 0.552 mmol, 86 % yield) as a brown solid. [M+H] calc'd for $C_{22}H_{25}N_5O_3$, 408; found, 408.

[0395] Compound 10: (S)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (75.0 mg, 0.184 mmol) was suspended in DMF (1.0 mL) and DIPEA (0.15 mL) was added followed by ethylamine (30 mg, 0.665 mmol) and HATU (85.0 mg, 0.224 mmol). The reaction mixture was stirred at ambient temperature for 2 h and another portion of HATU (60.0 mg, 0.158 mmol) was added. The reaction mixture was stirred overnight and purified using HPCL (10-75% acetonitrile in water, NH_4HCO_3 buffered). The fractions were concentrated in vacuo and the resulting residue was crystallized with MeOH – water (1:10, 5 mL) to afford the title compound as a light green solid (24.0 mg, 30%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.09 (t, *J*=7.20 Hz, 3 H) 1.35 - 2.01 (m, 3 H) 2.18 (dt, *J*=5.37, 2.75 Hz, 1 H) 2.43 - 2.48 (m, 4 H) 3.18 - 3.28 (m, 6 H) 3.35 (s, 2 H) 3.37 - 3.45 (m, 1 H) 3.54 - 3.67 (m, 1 H) 3.94 - 4.05 (m, 1 H) 6.92 (d, *J*=9.09 Hz, 2 H) 6.99 (d, *J*=2.02 Hz, 1 H) 7.62 (d, *J*=2.02 Hz, 1 H) 7.71 (d, *J*=9.09 Hz, 2 H) 8.17 (t, *J*=5.56 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{24}H_{30}N_6O_2$, 435; found, 435.

Method B



[0396] **Compound 10C:** N-ethyl-4-fluorobenzamide: To a solution of ethylamine (69.4 mL, 139 mmol) and triethylamine (21.10 mL, 151 mmol) in DCM (Volume: 150 mL) was added p-Fluorobenzoyl chloride (15.13 mL, 126 mmol) at 0 °C. The reaction was stirred at 0 °C for 1 hr and then warmed slowly to room temperature. The reaction mixture was diluted with water. The layers were separated and the organic layer was washed with brine, dried over MgSO4, filtered, and the organic phase stripped to dryness via rotary evaporation. The organic extract was dried in vacuo to provide N-ethyl-4-fluorobenzamide (21 g, 100% yield) as a tan solid.

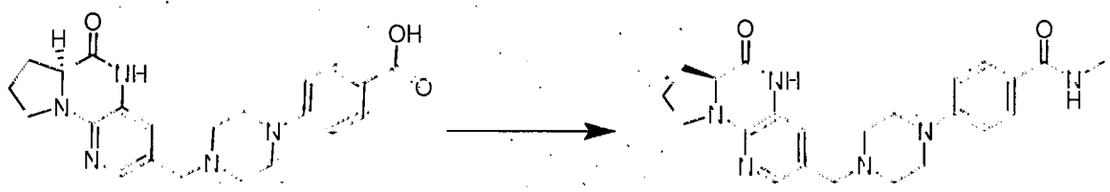
[0397] **Compound 10D:** N-ethyl-4-(piperazin-1-yl)benzamide: Using N-ethyl-4-fluorobenzamide in the general procedure for nucleophilic aromatic substitution reactions with piperazine, the title compound was obtained (77% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.07 Hz, 3 H) 2.25 (br. s., 1 H) 2.76 - 2.86 (m, 4 H) 3.09 - 3.18 (m, 4 H) 3.21 - 3.28 (m, 2 H) 6.90 (m, *J*=8.84 Hz, 2 H) 7.67 - 7.75 (m, 2 H) 8.11 (t, *J*=5.31 Hz, 1 H). ESI-MS: m/z 234.2 $(M+H)^+$. mp=131.3-134.4 °C.

[0398] **Compound 10: (S)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide:** To a suspension of (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (0.8 g, 3.65 mmol)) in propionontrile (Volume: 27.4 ml) was added (cyanomethyl)trimethylphosphonium iodide (1.064 g, 4.38 mmol), N-ethyl-4-(piperazin-1-yl)benzamide (0.851 g, 3.65 mmol) and DIEA (1.912 ml, 10.95 mmol). The vial was heated to 90 °C for 16 hours. The crude reaction

was cooled to R.T, DMSO (1 ml) was added, and the mixture was purified via HPLC (55-90, basic) to give the product as a white solid.

Compound 11: (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

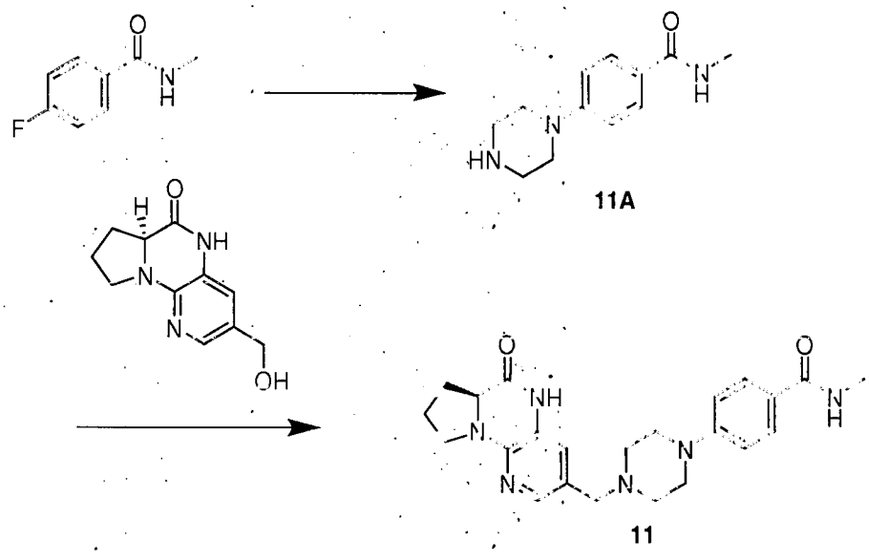
Method A



11

[0399] (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (87 mg, 0.214 mmol) and methanamine hydrochloride (21.62 mg, 0.320 mmol) were suspended in DMF (1 ml) and treated with DIPEA (0.186 ml, 1.068 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.427 mmol). The reaction mixture was stirred at room temperature for 23 h and purified using HPLC (25-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (42.4 mg, 0.101 mmol, 47.2 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.83 - 2.01 (m, 3 H) 2.11 - 2.25 (m, 1 H) 2.39 - 2.48 (m, 4 H) 2.73 (d, *J*=4.55 Hz, 3 H) 3.13 - 3.27 (m, 4 H) 3.34 - 3.44 (m, 3 H) 3.52 - 3.64 (m, 1 H) 3.96 - 4.02 (m, 1 H) 6.92 (d, *J*=9.09 Hz, 2 H) 6.98 (d, *J*=2.02 Hz, 1 H) 7.62 (d, *J*=1.77 Hz, 1 H) 7.69 (d, *J*=9.09 Hz, 2 H) 8.13 (q, *J*=4.29 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{23}H_{28}N_6O_2$, 421; found, 421.

Method B

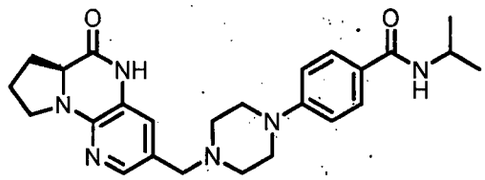


[0400] Compound 11A: N-methyl-4-(piperazin-1-yl)benzamide: To a solution of 4-fluoro-N-methylbenzamide (6 g, 39.2 mmol) in DMSO (Volume: 24.0 mL) was added piperazine (16.87 g, 196 mmol) at 23 °C. The reaction was stirred at 120 °C for 68 hr. The reaction mixture was poured into ice (261 g) and the reaction vessel was rinsed with H2O (~50 mL). Next, celite (30 g) was added to aid the filtration. The resulting suspension was warmed to 100 °C, cooled to ~40 °C, filtered, and rinsed with warm H2O (4 x 50 mL). The resulting solid was dried *in vacuo*. The filtrate was stirred at room temperature overnight affording a suspension. The suspension was filtered, rinsed with H_2O (3 x 25 mL), and the resulting solid was dried *in vacuo*. The cloudy filtrate was filtered once again through a medium fritted funnel and rinsed with H2O (3 x 10 mL). Added NaCl (200.1g) to the filtrate, cooled on ice, filtered, rinsed with cold H2O (3 x 25 mL), and dried the resulting solid *in vacuo*. Re-suspended the purified product in H2O (30 mL), stirred for 30 min at 23 °C, filtered, rinsed with H2O (3 x 5 mL), and dried the resulting solid *in vacuo*. The purified product was re-suspended in ACN (25 mL), agitated for 10 min, and dried *in vacuo*. This procedure was repeated three times to provide N-methyl-4-(piperazin-1-yl)benzamide (5.64g, 25.7 mmol, 65.7 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.29 (br. s., 1 H) 2.74 (d, *J*=4.55 Hz, 3 H) 2.77 - 2.86 (m, 4 H) 3.08 - 3.18 (m, 4 H) 6.91 (m, 2 H) 7.69 (m, 2 H) 8.13 (q, *J*=4.04 Hz, 1 H). ESI-MS: m/z 220.2 $(M+H)^+$. mp=153.9-156.5 °C.

[0401] Compound 11: (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (1.500 g, 6.34 mmol), N-

methyl-4-(piperazin-1-yl)benzamide (1.500 g, 6.84 mmol), (cyanomethyl)trimethylphosphonium iodide (2.494 g, 10.26 mmol) and N,N-diisopropylethylamine (5.97 ml, 34.2 mmol) were suspended in propiononitrile (Volume: 27.4 ml) and heated in a closed vial at 90 °C. The crude reaction was cooled to RT, DMSO (1 ml) was added, and the mixture was purified via HPLC (55-90, basic) to give the product as a white solid.

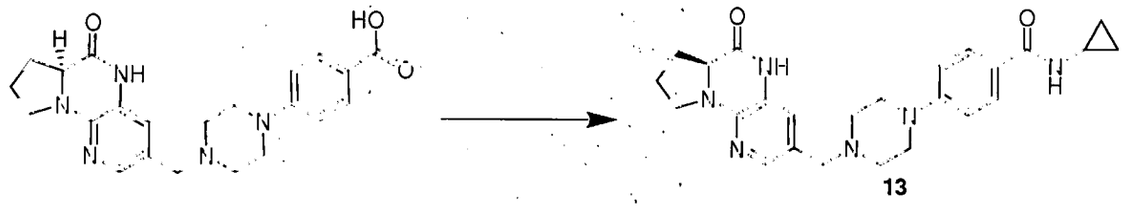
Compound 12: (S)-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0402] (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (87.0 mg, 0.214 mmol) and propan-2-amine (18.93 mg, 0.320 mmol) were suspended in DMF (1 ml) and treated with DIPEA (0.186 ml, 1.068 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.427 mmol). The reaction mixture was stirred at room temperature for 3 h and purified using HPLC (25-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (39.6 mg, 0.088 mmol, 41.3 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.13 (d, *J*=6.57 Hz, 6 H) 1.85 - 2.00 (m, 3 H) 2.11 - 2.24 (m, 1 H) 2.41 - 2.48 (m, 4 H) 3.17 - 3.27 (m, 4 H) 3.34 - 3.44 (m, 3 H) 3.53 - 3.65 (m, 1 H) 3.93 - 4.13 (m, 2 H) 6.91 (d, *J*=9.09 Hz, 2 H) 6.99 (d, *J*=2.02 Hz, 1 H) 7.62 (d, *J*=2.02 Hz, 1 H) 7.72 (d, *J*=9.09 Hz, 2 H) 7.89 (d, *J*=7.83 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{25}H_{32}N_6O_2$, 449; found, 449.

Compound 13: (S)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

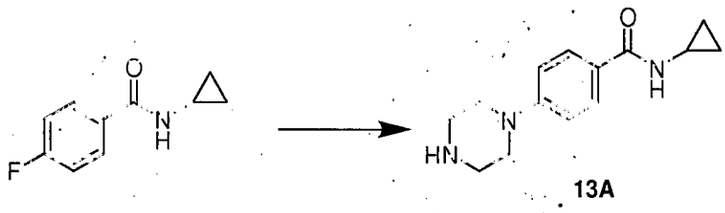
Method A



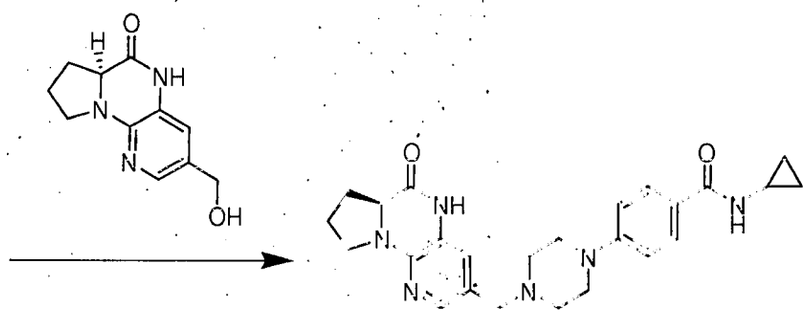
13

[0403] (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (87 mg, 0.214 mmol) and cyclopropanamine (18.29 mg, 0.320 mmol) were suspended in DMF (1 ml) and treated with DIPEA (0.186 ml, 1.068 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (162 mg, 0.427 mmol). The reaction mixture was stirred at room temperature for 3 h and purified using HPLC (25-95% acetonitrile in water, NH_4HCO_3 buffered) to afford (S)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (43.0 mg, 0.096 mmol, 45.1 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 0.46 - 0.59 (m, 2 H) 0.59 - 0.71 (m, 2 H) 1.82 - 2.02 (m, 3 H) 2.10 - 2.25 (m, 1 H) 2.46 (br. s., 4 H) 2.74 - 2.83 (m, 1 H) 3.21 (br. s., 4 H) 3.34 - 3.46 (m, 3 H) 3.53 - 3.64 (m, 1 H) 3.94 - 4.02 (m, 1 H) 6.91 (d, *J*=8.84 Hz, 2 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.61 (d, *J*=1.26 Hz, 1 H) 7.68 (d, *J*=8.84 Hz, 2 H) 8.13 (d, *J*=4.04 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{25}H_{30}N_6O_2$, 447; found, 447; melting point 265-268 °C.

Method B



13A

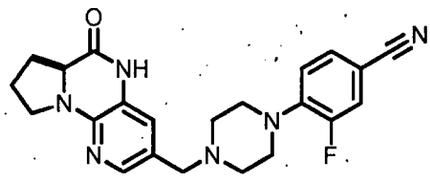


13

[0404] Compound 13A: N-cyclopropyl-4-(piperazin-1-yl)benzamide: Using N-cyclopropyl-4-fluorobenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (15% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.47 - 0.58 (m, 2 H) 0.58 - 0.73 (m, 2 H) 2.23 (br. s., 1 H) 2.70 - 2.83 (m, 5 H) 3.04 - 3.21 (m, 4 H) 6.90 (m, *J*=9.09 Hz, 2 H) 7.69 (m, *J*=8.34 Hz, 2 H) 8.12 (d, *J*=3.79 Hz, 1 H). ESI-MS: m/z 246.2 $(M+H)^+$. mp=175.1-177.2 °C.

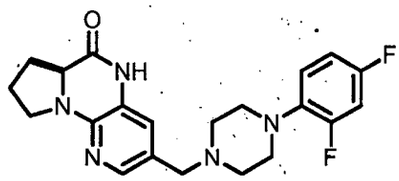
[0405] Compound 13: (S)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (300 mg, 1.368 mmol), N-cyclopropyl-4-(piperazin-1-yl)benzamide (336 mg, 1.368 mmol), (cyanomethyl)trimethylphosphonium iodide (499 mg, 2.053 mmol) and N,N-diisopropylethylamine (1195 µl, 6.84 mmol) were suspended in propionitrile (Volume: 4109 µl) and heated in a closed vial at 120 °C for 2h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (NH_4HCO_3 buffered, 20-70% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (1:1, 15 mL), and then from MeOH:EtOH:water (1:1:1, 10 mL), washed with water (3 mL) and dried in vacuum to give a light green solid.

Compound 14: (S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0406] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (150 mg, 0.684 mmol), 3-fluoro-4-(piperazin-1-yl)benzonitrile (140 mg, 0.684 mmol), (cyanomethyl)trimethylphosphonium iodide (249 mg, 1.026 mmol) and N,N-diisopropylethylamine (0.597 ml, 3.42 mmol) were suspended in propionitrile (2 ml) and heated in a closed vial at 90 °C for 2h. The reaction mixture became a clear dark brown solution. It was cooled to room temperature, diluted with DMSO (2 mL) and purified using preparative HPLC (25-95% acetonitrile in water, NH_4HCO_3 buffered). The fractions containing product were concentrated in vacuo and crystallized with water (3 mL). The precipitate was filtered and dried in vacuum to afford (S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile (60.2 mg, 0.148 mmol, 21.65 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.83 - 2.03 (m, 3 H) 2.11 - 2.24 (m, 1 H) 2.44 - 2.49 (m, 4 H) 3.07 - 3.22 (m, 4 H) 3.34 - 3.42 (m, 3 H) 3.53 - 3.65 (m, 1 H) 3.93 - 4.03 (m, 1 H) 6.97 (d, *J*=2.02 Hz, 1 H) 7.11 (t, *J*=8.72 Hz, 1 H) 7.56 (dd, *J*=8.46, 1.64 Hz, 1 H) 7.61 (d, *J*=2.02 Hz, 1 H) 7.69 (dd, *J*=13.39, 2.02 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{22}H_{23}FN_6O$, 407; found, 407; melting point 226 °C.

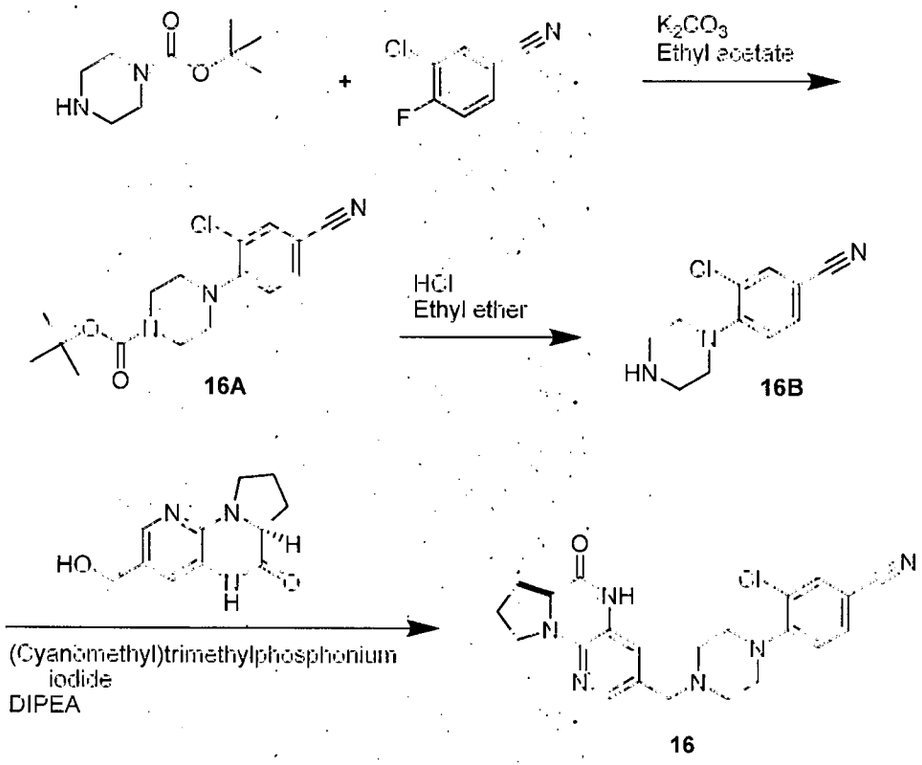
Compound 15: (S)-3-((4-(2,4-difluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



[0407] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (150 mg, 0.684 mmol), 1-(2,4-difluorophenyl)piperazine (136 mg, 0.684 mmol), (cyanomethyl)trimethylphosphonium iodide (249 mg, 1.026 mmol) and N,N-diisopropylethylamine (0.597 ml, 3.42 mmol) were suspended in propionitrile (2 ml) and heated in a closed vial at 90 °C for 2h. The reaction mixture became a clear dark brown

solution. It was cooled to room temperature, diluted with DMSO (2 mL) and purified using preparative HPLC (25-95% acetonitrile in water, NH_4HCO_3 buffered). The fractions containing product were concentrated in vacuo and crystallized from water (3 mL). The precipitate was filtered and dried in vacuum to afford (S)-3-((4-(2,4-difluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (63.2 mg, 0.158 mmol, 23.13 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.84 - 2.03 (m, 3 H) 2.09 - 2.26 (m, 1 H) 2.41 - 2.49 (m, 4 H) 2.88 - 2.99 (m, 4 H) 3.34 - 3.43 (m, 3 H) 3.54 - 3.63 (m, 1 H) 3.94 - 4.02 (m, 1 H) 6.93 - 7.09 (m, 3 H) 7.18 (ddd, J=12.44, 9.16, 2.91 Hz, 1 H) 7.61 (d, J=1.77 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{21}H_{23}F_2N_5O$, 400; found, 400.

Compound 16: (S)-3-chloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



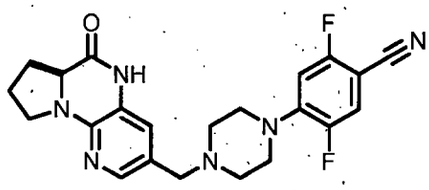
[0408] Compound 16A: tert-Butyl 4-(2-chloro-4-cyanophenyl)piperazine-1-carboxylate: Tert-Butyl piperazine-1-carboxylate (0.931 g, 5 mmol) and 3-chloro-4-fluorobenzonitrile (0.735 g, 5.00 mmol) were combined, K_2CO_3 (0.898 g, 6.50 mmol) was added and the reaction mixture was stirred at 90 °C for 1 d. The mixture was triturated with ethyl acetate (3 × 5 mL) and the combined organic extracts were filtered. This was concentrated down to about 5-10 mL and subjected to flash column chromatography on silica

gel (120 g SiO2, hexanes : ethyl acetate 1:0 to 4:1) to afford tert-butyl 4-(2-chloro-4-cyanophenyl)piperazine-1-carboxylate (1.264 g, 3.93 mmol, 79 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.42 (s, 9 H) 3.00 - 3.09 (m, 4 H) 3.42 - 3.53 (m, 4 H) 7.25 (d, *J*=8.59 Hz, 1 H) 7.77 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.97 (d, *J*=2.02 Hz, 1 H); [M+H] calc'd for $C_{16}H_{20}ClN_3O_2$, 322; found, 322.

[0409] Compound 16B: 3-chloro-4-(piperazin-1-yl)benzonitrile hydrochloride: Tert-Butyl 4-(2-chloro-4-cyanophenyl)piperazine-1-carboxylate (0.322 g, 1 mmol) was diluted with 4.0M HCl in dioxane (3 mL) and stirred for 30 min. The thick white precipitate that formed was diluted with ethyl ether (10 mL) and stirred until a fine suspension resulted. The precipitate was filtered under nitrogen and dried in vacuum to afford 3-chloro-4-(piperazin-1-yl)benzonitrile hydrochloride (0.242 g, 0.937 mmol, 94 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 3.14 - 3.29 (m, 4 H) 3.27 - 3.38 (m, 4 H) 7.33 (d, *J*=8.34 Hz, 1 H) 7.80 (dd, *J*=8.46, 1.89 Hz, 1 H) 8.02 (d, *J*=2.02 Hz, 1 H) 9.37 (br. s., 2 H); 4 H) 7.25 (d, *J*=8.59 Hz, 1 H) 7.77 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.97 (d, *J*=2.02 Hz, 1 H); [M+H] calc'd for $C_{11}H_{12}ClN_3$, 222; found, 222.

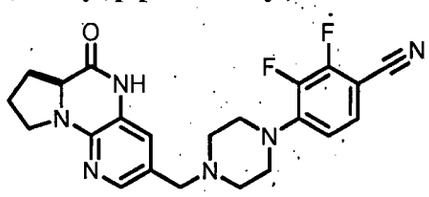
[0410] Compound 16: (S)-3-chloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-chloro-4-(piperazin-1-yl)benzonitrile hydrochloride (118 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propionitrile (2 ml) and heated in a closed vial at 90 °C for 2h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo and purified using flash column chromatography on silica gel (30g SiO_2, dichloromethane - methanol 100:0 - 95:5). The resulting solid was suspended in ether (7 mL), stirred until a fine suspension resulted, filtered and the solid was dried in vacuum to afford (S)-3-chloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile (135.4 mg, 0.320 mmol, 70.2 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.80 - 2.03 (m, 3 H) 2.10 - 2.25 (m, 1 H) 2.39 - 2.61 (m, 4 H) 2.94 - 3.19 (m, 4 H) 3.35 - 3.46 (m, 3 H) 3.51 - 3.65 (m, 1 H) 3.91 - 4.05 (m, 1 H) 6.97 (d, *J*=1.77 Hz, 1 H) 7.22 (d, *J*=8.59 Hz, 1 H) 7.62 (d, *J*=1.52 Hz, 1 H) 7.74 (dd, *J*=8.46, 1.89 Hz, 1 H) 7.93 (d, *J*=1.77 Hz, 1 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{22}H_{23}ClN_5O$, 423; found, 423; melting point 213-215 °C.

Compound 17: (S)-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



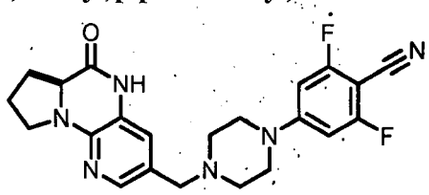
[0411] Compound 17 was prepared using a procedure analogous to that described in connection with compound 16, except that 2,4,5-trifluorobenzonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.81 - 2.01 (m, 3 H) 2.11 - 2.25 (m, 1 H) 2.47 (br. s., 4 H) 3.22 (br. s., 4 H) 3.34 - 3.44 (m, 3 H) 3.52 - 3.65 (m, 1 H) 3.92 - 4.05 (m, 1 H) 6.97 (d, *J*=1.52 Hz, 1 H) 7.08 (dd, *J*=12.00, 7.20 Hz, 1 H) 7.61 (d, *J*=1.52 Hz, 1 H) 7.77 (dd, *J*=13.14, 6.32 Hz, 1 H) 10.45 (s, 1 H); [M+H] calc'd for $C_{22}H_{22}F_2N_6O$, 425; found, 425; melting point 224-227 °C.

Compound 18: (S)-2,3-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



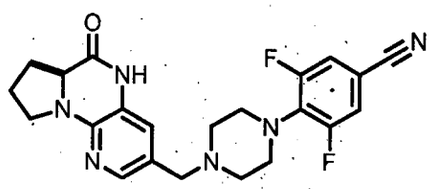
[0412] Compound 18 was prepared using a procedure analogous to that described in connection with compound 16, except that 2,3,4-trifluorobenzonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.82 - 2.03 (m, 3 H) 2.09 - 2.28 (m, 1 H) 2.38 - 2.49 (m, 4 H) 3.24 (br. s., 4 H) 3.34 - 3.45 (m, 3 H) 3.52 - 3.63 (m, 1 H) 3.93 - 4.03 (m, 1 H) 6.88 - 6.99 (m, 2 H) 7.52 - 7.63 (m, 2 H) 10.45 (s, 1 H); [M+H] calc'd for $C_{22}H_{22}F_2N_6O$, 425; found, 425.

Compound 19: (S)-2,6-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



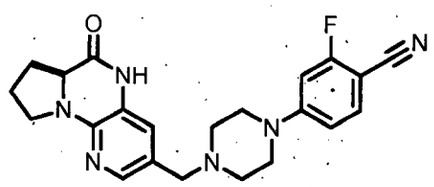
[0413] Compound 19 was prepared using a procedure analogous to that described in connection with compound 16, except that 2,4,6-trifluorobenzonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.83 - 2.04 (m, 3 H) 2.09 - 2.26 (m, 1 H) 2.33 - 2.47 (m, 4 H) 3.35 (s, 2 H) 3.37 - 3.49 (m, 5 H) 3.53 - 3.66 (m, 1 H) 3.94 - 4.06 (m, 1 H) 6.86 (d, *J*=12.63 Hz, 2 H) 6.97 (d, *J*=1.77 Hz, 1 H) 7.61 (d, *J*=1.52 Hz, 1 H) 10.45 (s, 1 H); [M+H] calc'd for $C_{22}H_{22}F_2N_6O$, 425; found, 425.

Compound 20: (S)-3,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



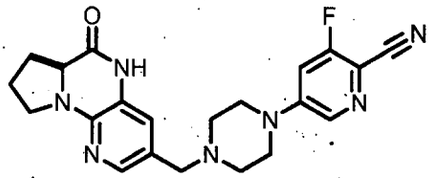
[0414] Compound 20 was prepared using a procedure analogous to that described in connection with compound 16, except that 3,4,5-trifluorobenzonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.81 - 2.04 (m, 3 H) 2.11 - 2.25 (m, 1 H) 2.43 (br. s., 4 H) 3.23 (br. s., 4 H) 3.34 - 3.47 (m, 3 H) 3.53 - 3.64 (m, 1 H) 3.94 - 4.01 (m, 1 H) 6.98 (d, *J*=1.52 Hz, 1 H) 7.61 (d, *J*=1.77 Hz, 1 H) 7.62 - 7.72 (m, 2 H) 10.43 (s, 1 H); [M+H] calc'd for $C_{22}H_{22}F_2N_6O$, 425; found, 425.

Compound 21: (S)-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



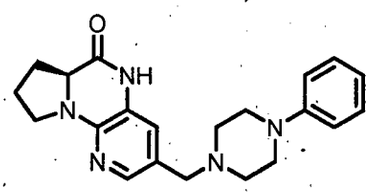
[0415] Compound 21 was prepared using a procedure analogous to that described in connection with compound 16, except that 2,4-difluorobenzonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.84 - 2.01 (m, 3 H) 2.10 - 2.23 (m, 1 H) 2.36 - 2.47 (m, 4 H) 3.34 - 3.44 (m, 7 H) 3.54 - 3.63 (m, 1 H) 6.83 (dd, *J*=9.09, 2.53 Hz, 1 H) 6.93 (dd, *J*=14.27, 2.40 Hz, 1 H) 6.97 (d, *J*=2.02 Hz, 1 H) 7.55 - 7.62 (m, 2 H) 10.44 (s, 1 H); [M+H] calc'd for $C_{22}H_{23}FN_6O$, 407; found, 407; melting point 251-255 °C.

Compound 22: (S)-3-fluoro-5-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)picolinonitrile



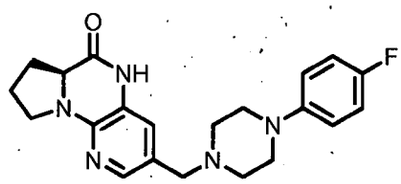
[0416] Compound 22 was prepared using a procedure analogous to that described in connection with compound 16, except that 3,5-difluoropicolinonitrile was used instead of 3-chloro-4-fluorobenzonitrile. ^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1.33 - 2.02 (m, 3 H) 2.10 - 2.24 (m, 1 H) 2.35 - 2.47 (m, 4 H) 3.34 - 3.51 (m, 7 H) 3.52 - 3.65 (m, 1 H) 3.94 - 4.03 (m, 1 H) 6.97 (d, *J*=1.77 Hz, 1 H) 7.38 (dd, *J*=13.52, 2.15 Hz, 1 H) 7.61 (d, *J*=1.52 Hz, 1 H) 8.29 (s, 1 H) 10.45 (s, 1 H); [M+H] calc'd for $C_{21}H_{22}FN_7O$, 408; found, 408.

Compound 23: (S)-3-((4-phenylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



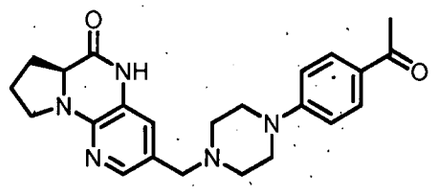
[0417] 1-Phenylpiperazine hydrochloride (11.9 mg, 0.060 mmol), (cyanomethyl)trimethylphosphonium iodide (0.025 g, 0.102 mmoles), and (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (0.014 g, 0.063 mmoles) were diluted with propionitrile (0.5 ml) and treated with DIPEA (0.017 ml, 0.100 mmol). The reaction mixture was stirred at 90 °C overnight. The reaction mixture was washed with water (1 mL) and concentrated. The residue was dissolved in DMSO (1 mL) and purified using HPLC (acetonitrile-water, NH_4HCO_3 buffered). The fractions were concentrated in vacuo, dissolved in dioxane-water (1:1:, 2 mL) and lyophilized to yield the title compound as a white solid (5.1 mg, 23%). [M+H] calc'd for $C_{21}H_{25}N_5O$ 364; found, 364.

Compound 24: (S)-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



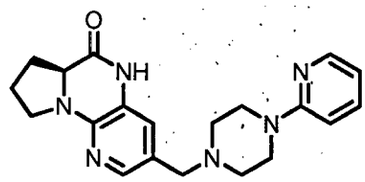
[0418] Compound 24 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{24}FN_5O$ 382; found, 382.

Compound 25: (S)-3-((4-(4-acetylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



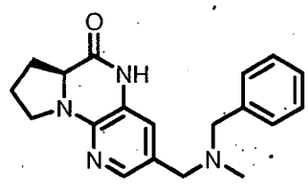
[0419] Compound 25 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{23}H_{27}N_5O_2$ 406; found, 406.

Compound 26: (S)-3-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



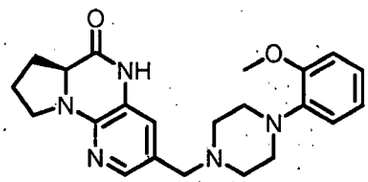
[0420] Compound 26 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{20}H_{24}N_6O$ 365; found, 365.

Compound 27: (S)-3-((benzyl(methyl)amino)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



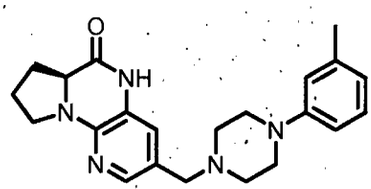
[0421] Compound 27 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{19}H_{22}N_4O$ 323; found, 323.

Compound 28: (S)-3-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



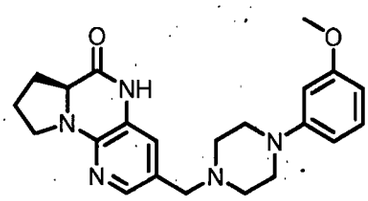
[0422] Compound 28 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{27}N_5O_2$ 394; found, 394.

Compound 29: (S)-3-((4-m-tolylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



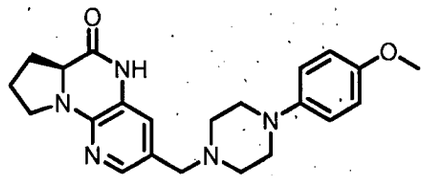
[0423] Compound 29 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{27}N_5O$ 378; found, 378.

Compound 30: (S)-3-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



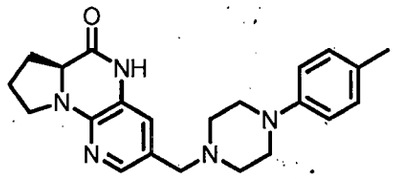
[0424] Compound 30 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{27}N_5O_2$ 394; found, 394.

Compound 31: (S)-3-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



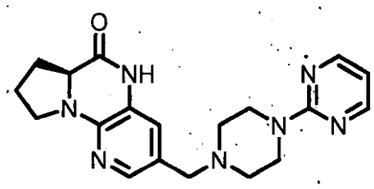
[0425] Compound 31 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{27}N_5O_2$ 394; found, 394.

Compound 32: (S)-3-((4-p-tolylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



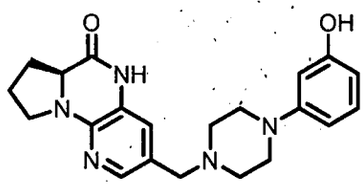
[0426] Compound 32 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{27}N_5O$ 378; found, 378.

Compound 33: (S)-3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



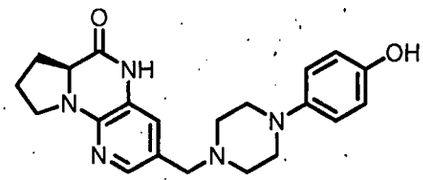
[0427] Compound 33 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{19}H_{23}N_7O$ 366; found, 366.

Compound 34: (S)-3-((4-(3-hydroxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



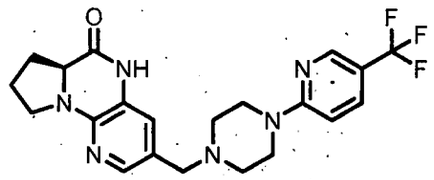
[0428] Compound 34 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{25}N_5O_2$ 380; found, 380.

Compound 35: (S)-3-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



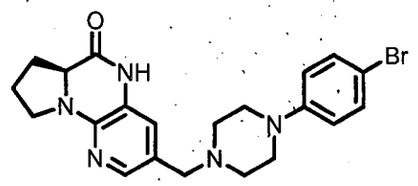
[0429] Compound 35 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{25}N_5O_2$ 380; found, 380.

Compound 36: (S)-3-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



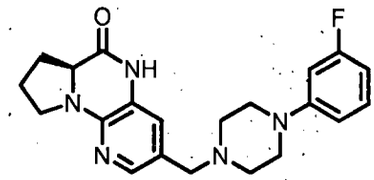
[0430] Compound 36 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{23}F_3N_6O$ 433; found, 433.

Compound 37: (S)-3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



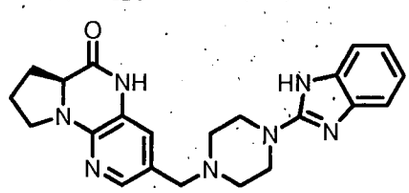
[0431] Compound 37 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{24}BrN_5O$ 444; found, 444.

Compound 38: (S)-3-((4-(3-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



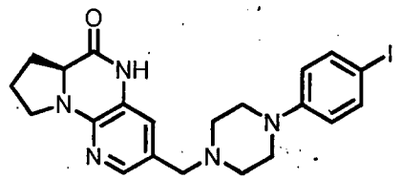
[0432] Compound 38 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{24}FN_5O$ 382; found, 382.

Compound 39: (S)-3-((4-(1H-benzo[d]imidazol-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



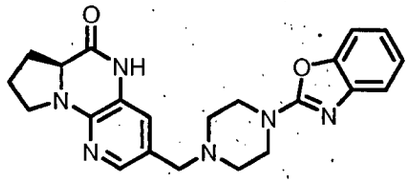
[0433] Compound 39 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{25}N_7O$ 404; found, 404.

Compound 40: (S)-3-((4-(4-iodophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



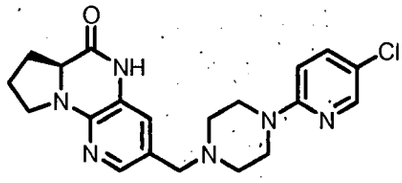
[0434] Compound 40 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{24}IN_5O$ 490; found, 490.

Compound 41: (S)-3-((4-(benzo[d]oxazol-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



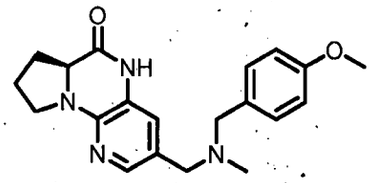
[0435] Compound 41 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{24}N_6O_2$ 405; found, 405.

Compound 42: (S)-3-((4-(5-chloropyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



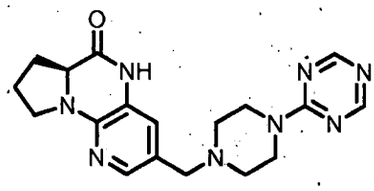
[0436] Compound 42 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{20}H_{23}ClN_6O$ 399; found, 399.

Compound 43: (S)-3-(((4-methoxybenzyl)(methyl)amino)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



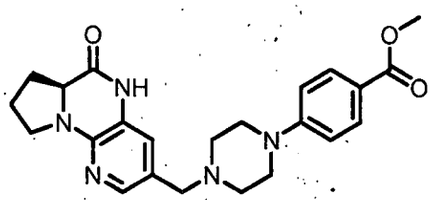
[0437] Compound 43 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{20}H_{24}N_4O_2$ 353; found, 353.

Compound 44: (S)-3-((4-(1,3,5-triazin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



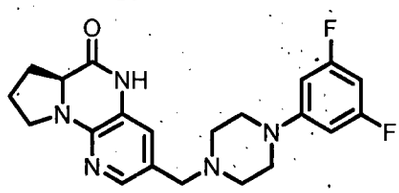
[0438] Compound 44 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{19}H_{22}N_8O$ 367; found, 367.

Compound 45: (S)-methyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate



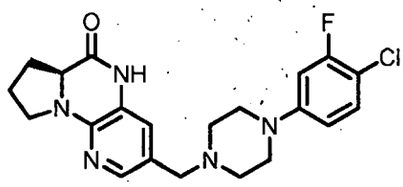
[0439] Compound 45 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{23}H_{27}N_5O_3$ 422; found, 422.

Compound 46: (S)-3-((4-(3,5-difluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



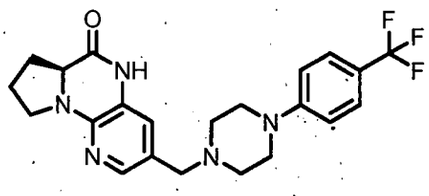
[0440] Compound 46 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{23}F_2N_5O$ 400; found, 400.

Compound 47: (S)-3-((4-(4-chloro-3-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



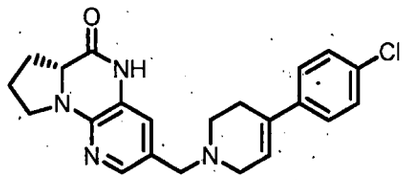
[0441] Compound 47 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{21}H_{23}ClFN_5O$ 416; found, 416.

Compound 48: (S)-3-((4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



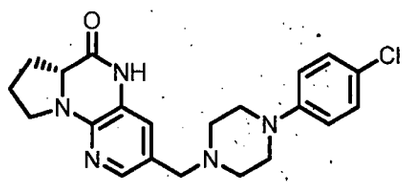
[0442] Compound 48 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{22}H_{24}F_3N_5O$ 432; found, 432.

Compound 49: (R)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



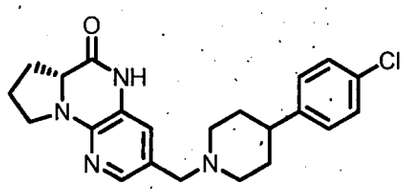
[0443] Compound 49 was prepared using a procedure analogous to that described in connection with compound 2, except that (R)-methyl pyrrolidine-2-carboxylate was used instead of (S)-methyl pyrrolidine-2-carboxylate. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.43 (s, 1H), 7.62 (d, J = 1.8 Hz, 1H), 7.40 - 7.48 (m, 2H), 7.29 - 7.40 (m, 2H), 6.99 (d, J = 1.8 Hz, 1H), 6.18 (br. s., 1H), 3.91 - 4.06 (m, 1H), 3.52 - 3.67 (m, 1H), 3.40 - 3.49 (m, 3H), 3.01 (d, J = 2.3 Hz, 2H), 2.56 - 2.65 (m, 2H), 2.43 (br. s., 2H), 2.10 - 2.24 (m, 1H), 1.77 - 2.01 (m, 3H); [M+H] calc'd for $C_{22}H_{23}ClN_4O$, 395; found, 395.

Compound 50: (R)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



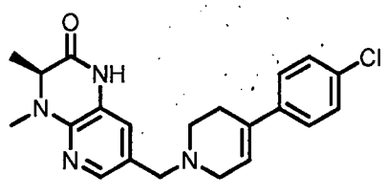
[0444] Compound 50 was prepared using a procedure analogous to that described in connection with compound 1, except that (R)-methyl pyrrolidine-2-carboxylate was used instead of (S)-methyl pyrrolidine-2-carboxylate. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.43 (s, 1H), 7.61 (d, J = 1.5 Hz, 1H), 7.21 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 3.89 - 4.05 (m, 1H), 3.52 - 3.66 (m, 1H), 3.37 - 3.48 (m, 3H), 3.10 (br. s., 4H), 2.46 (d, J = 4.5 Hz, 4H), 2.07 - 2.25 (m, 1H), 1.78 - 2.04 (m, 3H); [M+H] calc'd for $C_{21}H_{24}ClN_5O$, 398; found, 398.

Compound 51: (R)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



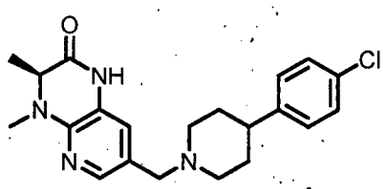
[0445] Compound 51 was prepared using a procedure analogous to that described in connection with compound 3, except that (R)-methyl pyrrolidine-2-carboxylate was used instead of (S)-methyl pyrrolidine-2-carboxylate. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.42 (s, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.19 - 7.29 (m, 2H), 6.97 (d, J = 1.8 Hz, 1H), 3.90 - 4.05 (m, 1H), 3.51 - 3.65 (m, 1H), 3.35 - 3.45 (m, 1H), 2.88 (d, J = 10.9 Hz, 2H), 2.08 - 2.25 (m, 1H), 1.82 - 2.05 (m, 5H), 1.64 - 1.78 (m, 2H), 1.48 - 1.64 (m, 2H); [M+H] calc'd for $C_{22}H_{25}ClN_4O$, 397; found, 397.

Compound 52: (S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



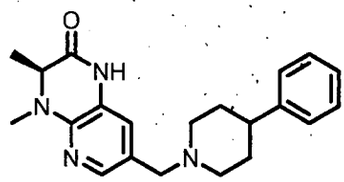
[0446] Compound 52 was prepared using a procedure analogous to that described in connection with compound 2, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.30 (d, J = 1.3 Hz, 1H), 7.60 (br. s., 1H), 7.28 - 7.33 (m, 4H), 6.96 - 7.06 (m, 1H), 6.01 - 6.08 (m, 1H), 4.13 (q, J = 6.6 Hz, 1H), 3.47 - 3.58 (m, J = 3.3 Hz, 2H), 3.13 (d, J = 2.3 Hz, 2H), 3.08 (s, 3H), 2.69 - 2.79 (m, 2H), 2.55 (br. s., 2H), 1.36 (d, J = 7.1 Hz, 3H); [M+H] calc'd for $C_{21}H_{23}ClN_4O$, 383; found, 383.

Compound 53: (S)-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



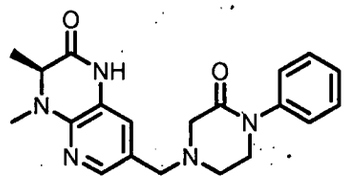
[0447] Compound 53 was prepared using a procedure analogous to that described in connection with compound 3, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.82 - 7.94 (m, 1H), 7.78 (d, J = 1.8 Hz, 1H), 7.27 (d, J = 8.6 Hz, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.00 (br. s., 1H), 4.13 (q, J = 7.0 Hz, 1H), 3.48 (br. s., 2H), 3.08 (s, 3H), 2.51 (br. s., 1H), 2.14 (d, J = 2.0 Hz, 2H), 1.81 (br. s., 4H), 1.37 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{21}H_{25}ClN_4O$, 385; found, 385.

Compound 54: (S)-3,4-dimethyl-7-((4-phenylpiperidin-1-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0448] Compound 54 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 4-phenylpiperidine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (d, *J*=6.82 Hz, 3 H) 1.82 (m, *J*=13.89 Hz, 2 H) 2.00 (d, *J*=12.38 Hz, 2 H) 2.74 - 2.85 (m, 1 H) 2.94 - 3.11 (m, 5 H) 3.47 (t, *J*=13.77 Hz, 2 H) 4.22 (d, *J*=5.05 Hz, 2 H) 7.06 (d, *J*=2.27 Hz, 1 H) 7.18 - 7.26 (m, 3 H) 7.29 - 7.36 (m, 2 H) 7.85 (d, *J*=2.02 Hz, 1 H) 9.30 (br. s., 1 H) 10.83 (s, 1 H); [M+H] calc'd for $C_{21}H_{26}N_4O$, 351; found, 351.

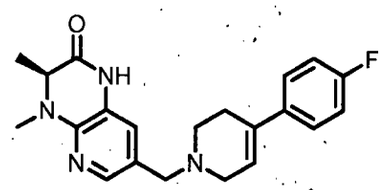
Compound 55: (S)-3,4-dimethyl-7-((3-oxo-4-phenylpiperazin-1-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0449] Compound 55 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 1-phenylpiperazin-2-one was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.81 (d, J = 1.8 Hz, 1H), 7.68 (s, 1H), 7.37 - 7.45 (m, 2H), 7.29 (d, J = 8.1 Hz, 3H), 6.93 (d, J = 1.8 Hz, 1H), 4.14

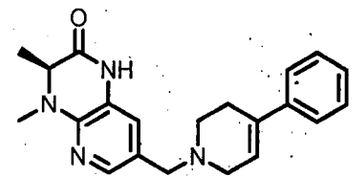
(q, J = 6.8 Hz, 1H), 3.70 (t, J = 5.3 Hz, 2H), 3.51 (s, 2H), 3.26 - 3.38 (m, 2H), 3.08 (s, 3H), 2.83 (t, J = 5.4 Hz, 2H), 1.38 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{20}H_{23}N_5O_2$, 366; found, 366.

Compound 56: (S)-7-((4-(4-fluorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



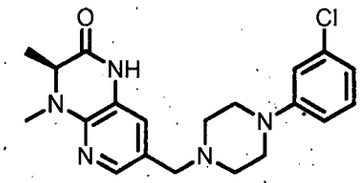
[0450] Compound 56 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.26 (s, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.29 - 7.33 (m, 2H), 6.93 - 7.05 (m, 3H), 5.95 - 6.03 (m, 1H), 4.03 - 4.17 (m, 1H), 3.46 - 3.55 (m, 2H), 3.14 (d, J = 2.8 Hz, 2H), 3.07 (s, 3H), 2.66 - 2.75 (m, 2H), 2.48 - 2.57 (m, 2H), 1.35 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{21}H_{23}FN_4O$, 367; found, 367.

Compound 57: (S)-3,4-dimethyl-7-((4-phenyl-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



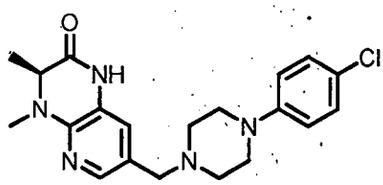
[0451] Compound 57 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 4-phenyl-1,2,3,6-tetrahydropyridine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.49 (s, 1H), 7.68 (d, J = 1.5 Hz, 1H), 7.41 (d, J = 7.3 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.17 - 7.27 (m, 1H), 7.00 (d, J = 1.8 Hz, 1H), 6.13 (br. s., 1H), 4.05 (q, J = 6.8 Hz, 1H), 3.43 (q, J = 12.9 Hz, 2H), 3.02 (d, J = 2.5 Hz, 2H), 2.94 (s, 3H), 2.57 - 2.65 (m, 2H), 2.47 (br. s., 2H), 1.17 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{21}H_{24}N_4O$, 349; found, 349.

Compound 58: (S)-7-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



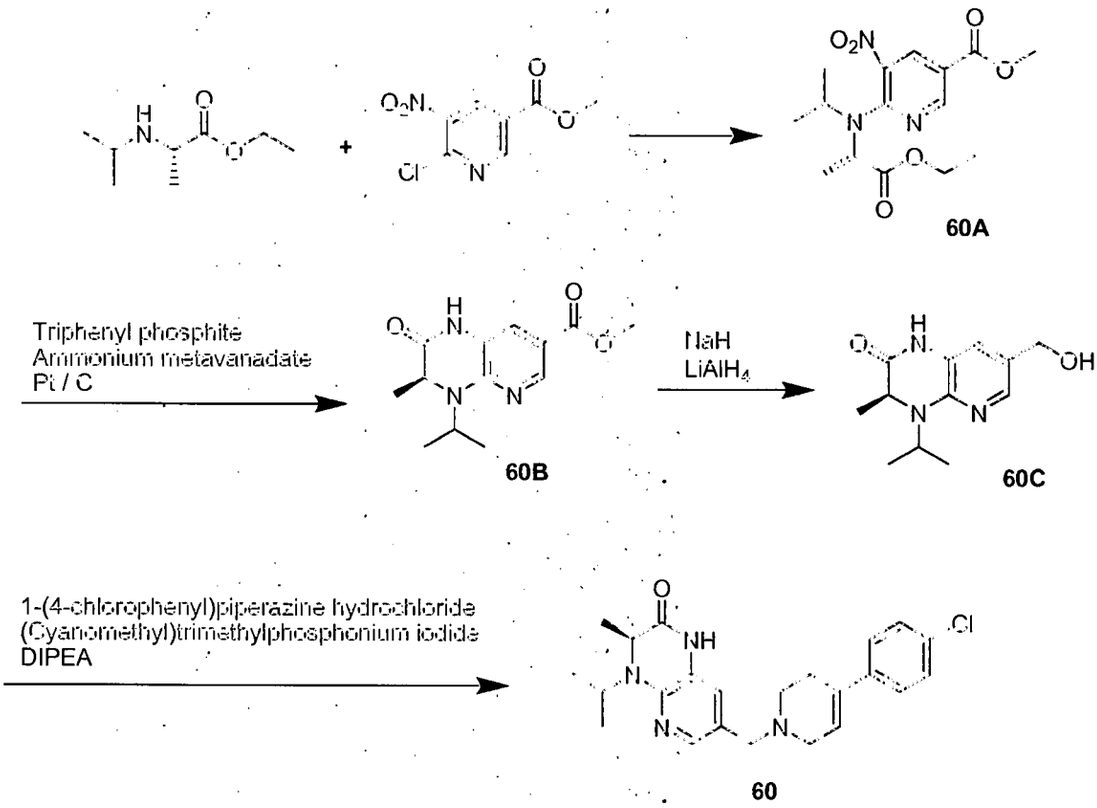
[0452] Compound 58 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 1-(3-chlorophenyl)piperazine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.79 (d, J = 1.5 Hz, 1H), 7.63 (br. s., 1H), 7.17 (t, J = 8.1 Hz, 1H), 6.89 - 7.06 (m, 1H), 6.87 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 7.3 Hz, 1H), 6.78 (dd, J = 8.3, 2.0 Hz, 1H), 4.13 (q, J = 6.8 Hz, 1H), 3.45 (br. s., 2H), 3.21 (br. s., 4H), 3.08 (s, 3H), 2.60 (br. s., 4H), 1.37 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{20}H_{24}ClN_5O$, 386; found, 386.

Compound 59: (S)-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0453] Compound 59 was prepared using a procedure analogous to that described in connection with compound 1, except that (S)-methyl 2-(methylamino)propanoate was used instead of (S)-methyl pyrrolidine-2-carboxylate and 1-(4-chlorophenyl)piperazine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.79 (d, J = 1.8 Hz, 1H), 7.72 - 7.78 (m, 1H), 7.17 - 7.24 (m, 2H), 6.89 - 7.02 (m, 1H), 6.79 - 6.88 (m, 2H), 4.13 (q, J = 7.0 Hz, 1H), 3.45 (br. s., 2H), 3.17 (br. s., 4H), 3.08 (s, 3H), 2.60 (br. s., 4H), 1.37 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{20}H_{24}ClN_5O$, 386; found, 386.

Compound 60: (S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0454] Compound 60A: (S)-methyl 6-((1-ethoxy-1-oxopropan-2-yl)(isopropyl)amino)-5-nitronicotinate: (S)-ethyl 2-(isopropylamino)propanoate (2.33 g, 17.8 mmol) was added to methyl 6-chloro-5-nitronicotinate (1.72 g, 7.94 mmol) and the reaction mixture was stirred in a closed vial at 90 °C for 20 h. It was cooled and diluted with EtOAc (25 mL). The resulting precipitate was filtered off, the filtrate was concentrated in vacuo and purified using flash column chromatography on silica gel (220 g SiO2, hexanes : ethyl acetate 4:1) to afford the title compound as yellow oil (1.12 g, 42%). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ (ppm): 1.18 (t, *J*=7.07 Hz, 3 H) 1.30 (d, *J*=6.32 Hz, 3 H) 1.36 (d, *J*=6.57 Hz, 3 H) 1.66 (d, *J*=6.82 Hz, 3 H) 3.48 - 3.62 (m, 1 H) 3.90 (s, 3 H) 4.03 (q, *J*=6.65 Hz, 1 H) 4.06 - 4.21 (m, 2 H) 8.54 (d, *J*=2.02 Hz, 1 H) 8.70 (d, *J*=2.02 Hz, 1 H); [M+H] calc'd for $C_{15}H_{21}N_3O_6$, 340; found, 340.

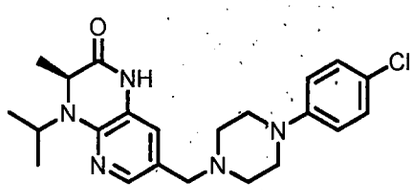
[0455] Compound 60B: (S)-methyl 4-isopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,2-b]pyrazine-7-carboxylate: (S)-methyl 6-((1-ethoxy-1-oxopropan-2-yl)(isopropyl)amino)-5-nitronicotinate (0.900 g, 2.65 mmol) was dissolved in dichloromethane (10 mL). To this solution was added triphenyl phosphite (3.0 mg, 9.7 umol), ammonium metavanadate (30 mg, 0.265 mmol) and Pt/C (5% wt., 0.120 g). The reaction mixture was

hydrogenated at 30 psi at 25 °C for 6 h. The mixture was filtered through a small pad of celite and the pad was washed with dichloromethane (20 mL). The combined filtrates were concentrated in vacuo and crystallized with ethyl ether to afford the title compounds as a white solid (0.653 g, 94%). ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ (ppm): 1.33 (d, *J*=6.82 Hz, 3 H) 1.36 - 1.41 (m, 6 H) 3.90 (s, 3 H) 4.34 (q, *J*=6.65 Hz, 1 H) 4.36 (m, 1 H) 7.52 (d, *J*=1.77 Hz, 1 H) 8.59 (d, *J*=1.77 Hz, 1 H) 8.73 (br. s., 1 H); [M+H] calc'd for $C_{13}H_{17}N_3O_3$, 264; found, 264.

[0456] Compound 60C: (S)-7-(hydroxymethyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one: (S)-methyl 4-isopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,2-b]pyrazine-7-carboxylate (0.649 g, 2.46 mmol) was dissolved in THF (8 mL) and cooled to 0 °C under nitrogen atmosphere. Sodium hydride (60% susp. in mineral oil, 0.112 g, 2.80 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. It was then cooled to -50 °C and $LiAlH_4$ (1M in THF, 9.80 mL, 9.80 mmol) was added dropwise over 10 min. The reaction mixture was kept at -30-(-20) °C for 1 h, cooled to below -50 °C and slowly quenched with MeOH (5 mL). The resulting solution was warmed to room temperature and subjected to preparative HPLC (1-30% acetonitrile in water, TFA buffered) to afford the title compound as a grey solid (TFA salt, 450 mg, 52%). [M+H] calc'd for $C_{12}H_{17}N_3O_2$, 236; found, 236.

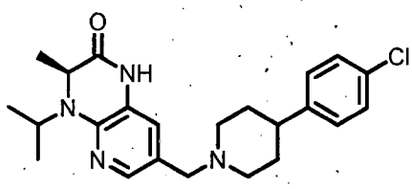
[0457] Compound 60: (S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one: Compound 60 was prepared using a procedure analogous to that described in connection with compound 1D, except that (S)-7-(hydroxymethyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one was used instead of (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one and 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.33 (s, 1H), 7.84 (d, J = 1.3 Hz, 1H), 7.21 - 7.36 (m, 4H), 7.04 (d, J = 4.5 Hz, 1H), 6.06 (br. s., 1H), 4.64 - 4.84 (m, 1H), 4.28 (q, J = 6.7 Hz, 1H), 3.52 (s, 2H), 3.05 - 3.27 (m, 2H), 2.65 - 2.79 (m, 2H), 2.54 (br. s., 2H), 1.37 (d, J = 6.8 Hz, 3H), 1.25 - 1.33 (m, 6H); [M+H] calc'd for $C_{23}H_{27}ClN_4O$, 411; found, 411.

Compound 61: (S)-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



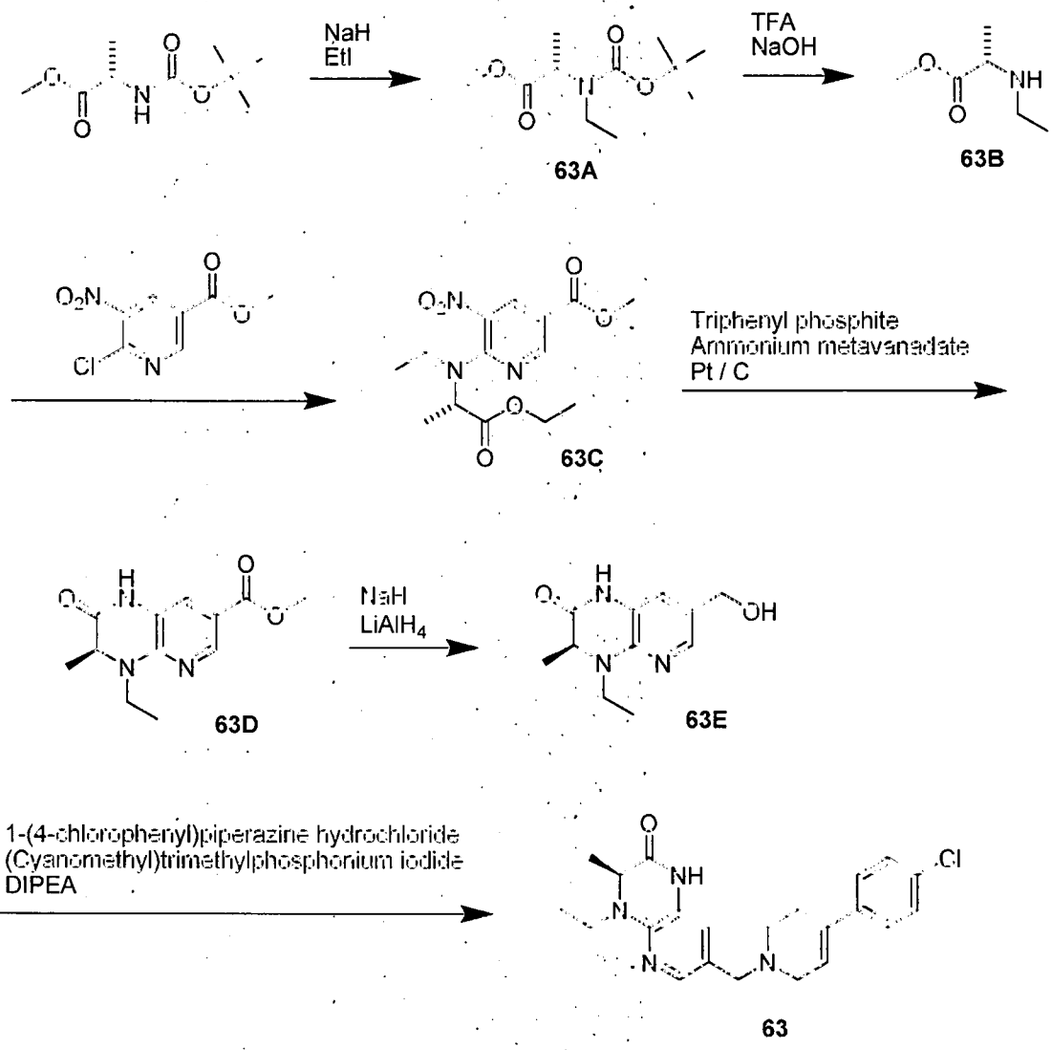
[0458] Compound 61 was prepared using a procedure analogous to that described in connection with compound 60, except that 1-(4-chlorophenyl)piperazine was used instead of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.58 (s, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.17 - 7.23 (m, 2H), 7.00 (d, J = 2.0 Hz, 1H), 6.80 - 6.86 (m, 2H), 4.67 - 4.81 (m, 1H), 4.28 (q, J = 6.7 Hz, 1H), 3.45 (s, 2H), 3.12 - 3.21 (m, 4H), 2.54 - 2.66 (m, 4H), 1.37 (d, J = 6.8 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 7.1 Hz, 3H); [M+H] calc'd for $C_{22}H_{28}ClN_5O$, 414; found, 414.

Compound 62: (S)-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0459] Compound 62 was prepared using a procedure analogous to that described in connection with compound 60, except that 4-(4-chlorophenyl)piperidine was used instead of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.15 (s, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.22 - 7.30 (m, 2H), 7.13 - 7.19 (m, 2H), 7.00 (s, 1H), 4.66 - 4.82 (m, 1H), 4.28 (q, J = 6.8 Hz, 1H), 3.43 (s, 2H), 3.01 (br. s., 2H), 2.41 - 2.56 (m, 1H), 2.08 (t, J = 11.4 Hz, 2H), 1.57 - 1.87 (m, 4H), 1.36 (d, J = 6.8 Hz, 3H), 1.31 (d, J = 6.8 Hz, 3H), 1.29 (d, J = 6.8 Hz, 3H); [M+H] calc'd for $C_{23}H_{29}ClN_4O$, 413; found, 413.

Compound 63: (S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-ethyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one



[0460] Compound 63A: (S)-methyl 2-(tert-butoxycarbonyl(ethyl)amino)propanoate: (S)-methyl 2-(tert-butoxycarbonylamino)propanoate.(10.0 g, 49.2 mmol) was dissolved in THF (100 mL) and cooled to 0 °C under nitrogen. Sodium hydride (60% susp. in mineral oil, 3.00 g, 75.1 mmol) was added in portions over 2 min. The reaction mixture was stirred for 5 min at 0 °C and EtI (4.80 mL, 59.5 mmol) was added. It was allowed to warm to room temperature over the period of 1 h, stirred at room temperature overnight and at 70 °C for 7 d. The reaction mixture was cooled, filtered and concentrated in vacuo. The solid was triturated with hexanes (2 × 70 mL), the triturates were concentrated in vacuo and the residue was purified using flash column chromatography on silica gel (330 g SiO_2, hexanes : ethyl acetate 19:1 – 9:1) to afford the title compounds as an oil (4.40 g, 39%). [M+H] calc'd for $C_{11}H_{21}NO_4$, 232; found, 232.

[0461] Compound 63B: (S)-methyl 2-(ethylamino)propanoate: (S)-methyl 2-(tert-butoxycarbonyl(ethyl)amino)propanoate (4.40 g, 19.0 mmol) was dissolved in dichloromethane and treated with TFA (10 mL). The reaction mixture was stirred for 2 h at room temperature and concentrated in vacuo. The residue was diluted with brine and NaOH (aq. 50%) was added dropwise until pH = 12.5. This was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (MgSO4), filtered and concentrated in vacuo to afford the title compound as an opaque liquid (1.85 g, 74%). [M+H] calc'd for $C_6H_{13}NO_2$, 132; found, 132.

[0462] Compound 63C: (S)-methyl 6-((1-ethoxy-1-oxopropan-2-yl)(ethyl)amino)-5-nitronicotinate: (S)-methyl 2-(ethylamino)propanoate (1.33 g, 14.0 mmol) was added to methyl 6-chloro-5-nitronicotinate (1.30 g, 6.00 mmol) and the reaction mixture was stirred in a closed vial at 90 °C for 1 h. It was cooled and diluted with EtOAc (25 mL). The resulting precipitate was filtered off, the filtrate was concentrated in vacuo and purified using flash column chromatography on silica gel (220 g SiO_2, ethyl acetate in hexanes 0-50%) to afford the title compound as a yellow oil (1.23 g, 66%). [M+H] calc'd for $C_{14}H_{19}N_3O_6$, 326; found, 326.

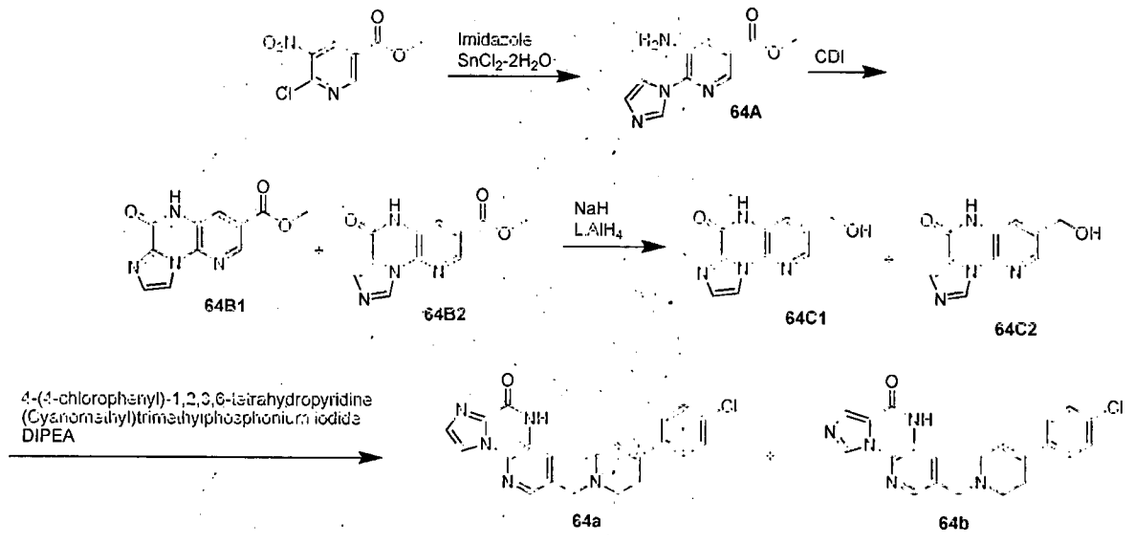
[0463] Compound 63D: (S)-methyl 4-ethyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate: (S)-methyl 6-((1-ethoxy-1-oxopropan-2-yl)(ethyl)amino)-5-nitronicotinate (1.22 g, 3.92 mmol) was dissolved in dichloromethane (12 mL). To this solution were added triphenyl phosphite (5.0 mg, 16 umol), ammonium metavanadate (50.0 mg, 0.427 mmol) and Pt/C (5% wt., 0.200 g). The reaction mixture was hydrogenated at 100 psi at 25 °C for 13 h. The mixture was filtered through a small pad of celite and the pad was washed with dichloromethane (20 mL). The combined filtrates were concentrated in vacuo and crystallized with ethyl ether (50 mL) to afford the title compound as a white solid (0.560 g, 57%). [M+H] calc'd for $C_{12}H_{15}N_3O_3$, 250; found, 250.

[0464] Compound 63E: (S)-4-ethyl-7-(hydroxymethyl)-3-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: (S)-methyl 4-ethyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate (0.560 g, 2.25 mmol) was dissolved in THF (5 mL) and cooled to 0 °C under nitrogen atmosphere. Sodium hydride (60% susp. in mineral oil, 0.135 g, 3.38 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. It was then cooled to -50 °C and $LiAlH_4$ (2M in THF, 3.40 mL, 6.80 mmol) was added dropwise over 10 min. The reaction mixture was kept at -30-(-20) °C for 1 h, cooled to below -50 °C and slowly quenched with MeOH (5 mL). The resulting solution was warmed to room temperature and subjected to preparative HPLC (1-30%

acetonitrile in water, TFA buffered) to afford the title compound as a dark oil (TFA salt, 0.587 mg, 78%). [M+H] calc'd for $C_{11}H_{15}N_3O_2$, 222; found, 222.

[0465] Compound 63: (S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-ethyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one: Compound 63 was prepared using a procedure analogous to that described in connection with compound 1D, except that (S)-4-ethyl-7-(hydroxymethyl)-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one was used instead of (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one and 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.79 (d, J = 1.5 Hz, 1H), 7.68 (br. s., 1H), 7.27 - 7.34 (m, 4H), 7.02 (s, 1H), 6.06 (br. s., 1H), 4.21 (q, J = 6.8 Hz, 1H), 3.98 - 4.12 (m, 1H), 3.44 - 3.61 (m, 2H), 3.07 - 3.26 (m, 3H), 2.75 (t, J = 5.2 Hz, 2H), 2.55 (br. s., 2H), 1.36 (d, J = 6.8 Hz, 3H), 1.26 (t, J = 7.2 Hz, 3H); [M+H] calc'd for $C_{22}H_{25}ClN_4O$, 397; found, 397.

Compounds 64a and 64b: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one and 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one



[0466] Compound 64A: Methyl 5-amino-6-(1H-imidazol-1-yl)nicotinate: Methyl 6-chloro-5-nitronicotinate (2.17 g, 10.0 mmol) was dissolved in ethyl acetate (55 mL) and imidazole (4.09 g, 60 mmol) was added. The reaction mixture was stirred at room temperature for 2h and treated with $SnCl_2$-$2H_2O$ (13.5 g, 60.0 mmol). It was heated to 70°C for 2 h, diluted with potassium carbonate (sat. aq.) and extracted with ethyl acetate (5 × 20 mL). The

combined organic extracts were dried (MgSO4), filtered and concentrated in vacuo to afford the title compound as a crude yellow solid, which was used in the next step without further purification. [M+H] calc'd for $C_{10}H_{10}N_4O_2$, 219; found, 219.

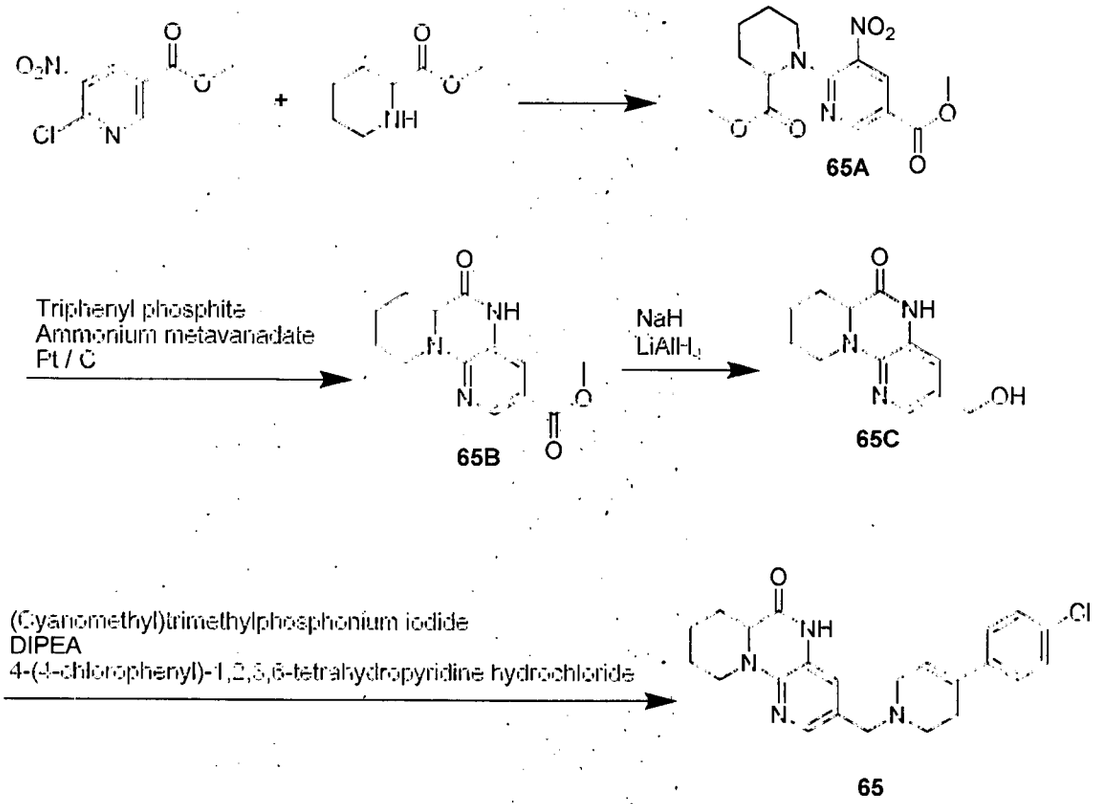
[0467] Compounds 64B1 and 64B2: Methyl 6-oxo-5,6-dihydroimidazo[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate and Methyl 6-oxo-5,6-dihydroimidazo[1,5-a]pyrido[3,2-e]pyrazine-3-carboxylate: Crude methyl 5-amino-6-(1H-imidazol-1-yl)nicotinate from the step above (max 10.0 mmol) was suspended in 1,2-dichlorobenzene 90 mL and N,N'-carbonyl diimidazole (CDI; 2.43 g, 15.0 mmol) was added. The reaction mixture was heated in a closed vial at 170°C for 2 h. The reaction mixture was cooled, poured into ethyl ether : hexanes (1:1, 300 mL) and the resulting solid was filtered and subjected to flash column chromatography on silica gel (330 g SiO2, dichloromethane : methanol 19:1 – 6:1). The solid was suspended in ethyl ether (30 mL), filtered off and dried in vacuum to afford the title compound as a yellow solid (0.467 g, 19%, ~2:1mixture of imidazole regioisomers). [M+H] calc'd for $C_{11}H_8N_4O_3$, 245; found, 245.

[0468] Compounds 64C1 and 64C2: 3-(Hydroxymethyl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one and 3-(Hydroxymethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one: Methyl 6-oxo-5,6-dihydroimidazo[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate (0.410 g, 1.68 mmol) was suspended in THF (20 mL) and sodium hydride (60% susp. in mineral oil, 0.112 g, 2.80 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h, cooled to -50 °C and $LiAlH_4$ (2M in THF, 1.7 mL, 3.4 mmol) was added dropwise over 2 min. The reaction mixture was kept at –30-(-10) °C for 3 h and more $LiAlH_4$ (2M in THF, 0.7 mL and 1.0 mL, 3.4 mmol combined) was added. The reaction mixture was cooled to -60 °C and slowly quenched with MeOH, warmed to room temperature and TFA and water were added until a clear solution resulted. The solution was subjected to preparative HPLC (1-30% acetonitrile in water, TFA buffered) to afford the title compound as a grey solid (147 mg, 40%; ~2:1 mixture of imidazole regioisomers). [M+H] calc'd for $C_{10}H_8N_4O_2$, 217; found, 217.

[0469] Compounds 64a and 64b: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one and 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one: Compound 64 was prepared as a mixture using a procedure analogous to that described in connection with compound 1D, except that a mixture of 3-(hydroxymethyl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one and 3-(hydroxymethyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one was used instead of (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-

e]pyrrolo[1,2-a]pyrazin-6(5H)-one and 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine was used instead of 1-(4-chlorophenyl)piperazine. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.51 - 2.53 (m, 2 H) 2.63 - 2.76 (m, 2 H) 3.12 (br. s., 2 H) 3.72 (br. s., 2 H) 6.20 – 6.23 (m, 1 H) 7.37 - 7.40 (m, 2 H) 7.45 - 7.48 (m, 2 H) 7.61 (d, *J*=1.26 Hz, 1 H) 7.76 (d, *J*=2.02 Hz, 1 H) 7.91 (s, 1 H) 8.27 (d, *J*=1.77 Hz, 1 H) 8.38 (d, *J*=1.26 Hz, 1 H); [M+H] calc'd for $C_{21}H_{18}ClN_5O$, 392; found, 392. Minor regioisomer: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.50 - 2.53 (m, 2 H) 2.63 - 2.76 (m, 2 H) 3.12 (br. s., 2 H) 3.70 (br. s., 2 H) 6.20 – 6.23 (m, 1 H) 7.37 - 7.40 (m, 2 H) 7.45 - 7.48 (m, 2 H) 7.70 (d, *J*=1.77 Hz, 1 H) 7.91 (d, *J*= 0.76 Hz, 1 H) 8.21 (d, *J*=1.77 Hz, 1 H) 8.91 (d, *J*= 0.76 Hz, 1 H); [M+H] calc'd for $C_{21}H_{18}ClN_5O$, 392; found, 392.

Compound 65: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



[0470] Compound 65A: Methyl 6-(2-(methoxycarbonyl)piperidin-1-yl)-5-nitronicotinate: Methyl 6-chloro-5-nitronicotinate (2.0 g, 9.23 mmol) was added to methyl piperidine-2-carboxylate (5.2 g, 36.92 mmol) while stirring at room temperature. The viscous yellow reaction was heated to 90°C for one h and then allowed to cool back to room temperature. The reaction was diluted with dichloromethane (20 mL) and purified via column

chromatography (220 g SiO2, 20-30% gradient, ethyl acetate in hexanes) to yield the title compound (2.95 g, 99% yield) as a yellow oil. [M+H] calc'd for C14H17N3O6, 324; found, 324.

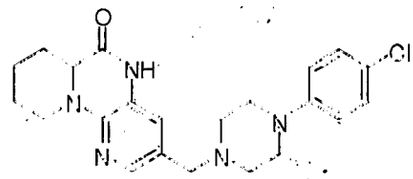
[0471] Compound 65B: Methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate: Methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate (2.95 g, 9.12 mmol) was dissolved in dichloromethane (20 mL). To the yellow solution was added ammonium metavanadate (20.0 mg, 0.171 mmol), triphenyl phosphite (aprox 30 ul, 0.097 mmol), and Pt/C (300 mg, 5% w/w). The reaction mixture was pressurized with hydrogen gas (110 psi) and stirred at room temperature for 16 h. The reaction was then depressurized and diluted with dichloromethane (100 mL) which was then refluxed for 30 min. The hot solution was filtered through a pad of celite and washed with hot dichloromethane (3 x 20 mL). The filtrate was concentrated to yield the title compound (1.91 g, 80%) as a white solid. [M+H] calc'd for C13H15N3O3, 262; found, 262.

[0472] Compound 65C: 3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one: Methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate (500 mg, 1.91 mmol) was taken up in tetrahydrofuran (23 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (60% dispersion in mineral oil, 114.7 mg, 2.87 mmol) and stirred 30 min. The reaction was then cooled to -45 °C and lithium aluminum hydride (2M in THF, 1.91 mL, 3.82 mmol) was added. The reaction was stirred at a temperature between -20 and -10°C for 1 h. The reaction was then cooled back to -60°C and MeOH (1 mL) followed by water (1 mL) was added. The reaction was allowed to stir at ambient temperature for 2 h and then poured into ethyl acetate (300 mL) and water (200 mL). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried with sodium sulfate and concentrated to yield the title compound (429.4 mg, 96%) as a white solid. [M+H] calc'd for C12H15N3O2, 234; found, 234.

[0473] Compound 65: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one: 3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.43 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (103 mg, 0.41 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (94.0 mg, 0.41 mmol). The reaction was heated to 90°C with stirring 2 h. The

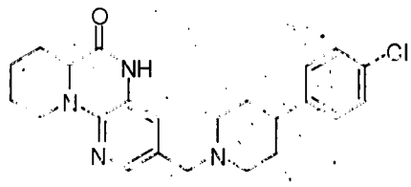
reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (31.3 mg, 18%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.41 - 7.48 (m, 2H), 7.33 - 7.40 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.18 (s, 1H), 4.43 - 4.57 (m, 1H), 3.84 (d, J = 11.4 Hz, 1H), 3.42 (s, 2H), 3.01 (d, J = 2.8 Hz, 2H), 2.55 - 2.66 (m, 3H), 2.44 (br. s., 2H), 1.98 - 2.09 (m, 1H), 1.78 - 1.92 (m, 1H), 1.57 - 1.70 (m, 1H), 1.33 - 1.56 (m, 3H). [M+H] calc'd for C23H25ClN4O, 409; found, 409.

Compound 66: 3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



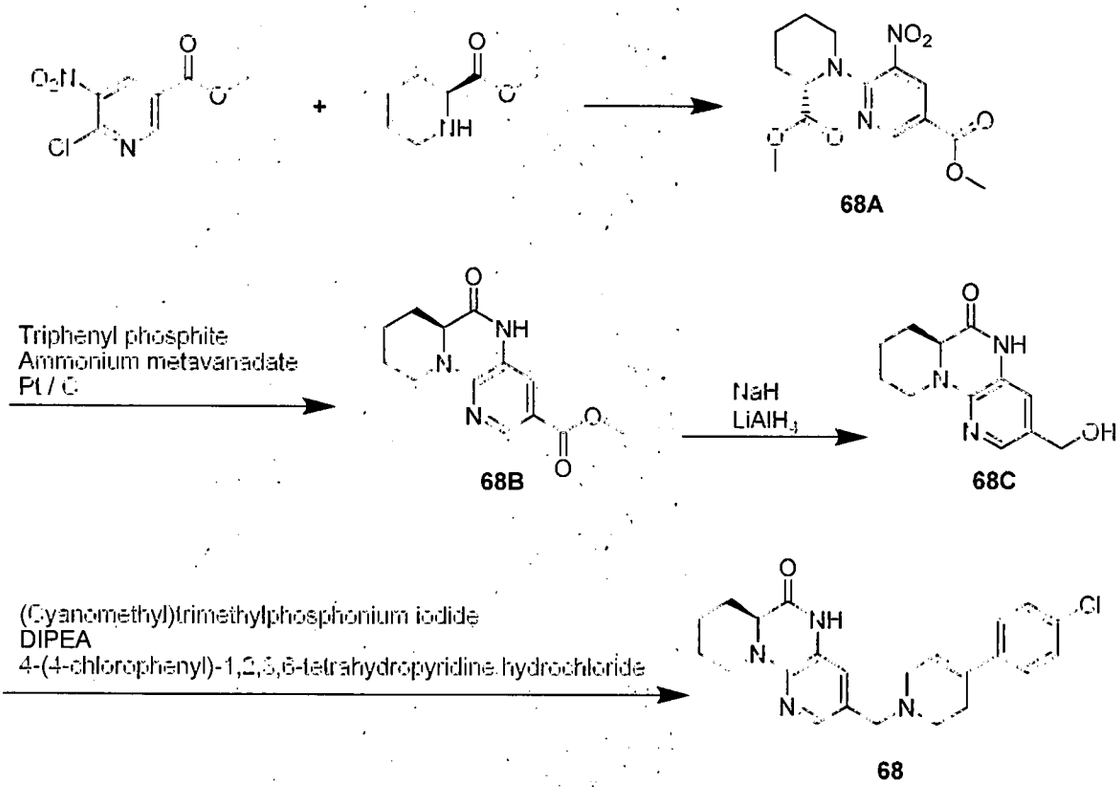
[0474] 3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.43 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (103 mg, 0.41 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 1-(4-chlorophenyl)piperazine hydrochloride (94.0 mg, 0.41 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The solids were collected to afford the title compound (69.9 mg, 39%) as a white solid.. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 9.1 Hz, 2H), 6.97 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 4.50 (d, J = 12.9 Hz, 1H), 3.83 (dd, J = 11.2, 2.7 Hz, 1H), 3.34 (d, J = 5.6 Hz, 2H), 3.01 - 3.17 (m, 4H), 2.55 - 2.65 (m, 1H), 2.37 - 2.48 (m, 4H), 1.98 - 2.08 (m, 1H), 1.85 (d, J = 12.4 Hz, 1H), 1.63 (d, J = 12.6 Hz, 1H), 1.32 - 1.56 (m, 3H). [M+H] calc'd for C22H26ClN5O, 412; found, 412.

Compound 67: 3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



[0475] 3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.43 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (103 mg, 0.41 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)piperidine hydrochloride (95.0 mg, 0.41 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was cooled to room temperature and purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield the title compound (57.3 mg, 32%) as a white solid. ^1H NMR (DMSO-d_6) δ: 13.44 (br. s., 1H), 10.82 (s, 1H), 9.52 (br. s., 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.36 - 7.42 (m, 2H), 7.24 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 2.0 Hz, 1H), 4.53 (d, J = 13.1 Hz, 1H), 4.21 (d, J = 4.5 Hz, 2H), 3.97 (dd, J = 11.6, 2.3 Hz, 1H), 3.46 (d, J = 11.6 Hz, 2H), 2.96 - 3.07 (m, 2H), 2.79 - 2.85 (m, 1H), 2.67 (td, J = 12.8, 2.7 Hz, 1H), 2.06 - 2.10 (m, 1H), 1.95 - 2.02 (m, 2H), 1.72 - 1.91 (m, 3H), 1.64 - 1.67 (m, 1H), 1.33 - 1.58 (m, 3H). [M+H] calc'd for C23H27ClN4O, 411; found, 411.

Compound 68: (S)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



[0476] Compound 68A: (S)-methyl 6-(2-(methoxycarbonyl)piperidin-1-yl)-5-nitronicotinate: Methyl 6-chloro-5-nitronicotinate (2.333 g, 10.77 mmol) was added to (S)-methyl piperidine-2-carboxylate (2.93 g, 20.46 mmol) neat while stirring. The reaction was stirred 1h at 90 °C, cooled to room temperature and taken up in ethyl acetate (10 mL). The mixture was purified by SiO_2 (330 g, 20-30% EA in Hexanes) to yield 3.4 g (98%) of the title compound as a yellow oil. [M+H] calc'd for C14H17N3O6, 324; found, 324.

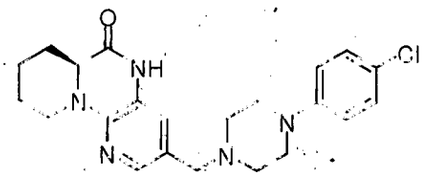
[0477] Compound 68B: (S)-methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate: In a bomb hydroginator, (S)-methyl 6-(2-(methoxycarbonyl)piperidin-1-yl)-5-nitronicotinate (1.95 g, 6.03 mmol), triphenyl phosphite (0.019 ml, 0.060 mmol), ammonium vanadate (0.056 g, 0.483 mmol) and platinum (5% on carbon, 0.235 g, 0.060 mmol) were mixed in dichloromethane (Volume: 30.2 ml) to give a suspension. The bomb was sealed and pressurized to 110 psi with hydrogen gas. The reaction was stirred at 110 psi 16h, depressurized, diluted with DCM (100 mL) and refluxed 10 minutes. The hot mixture was filtered through celite and washed with DCM (50 mL). The

filtrate was concentrated in vacuo to yield 1.4 g (39%) of the product as a white solid and used without further purification. [M+H] calc'd for C13H15N3O3, 262; found, 262.

[0478] Compound 68C: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one: In round-bottomed flask, (S)-methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate (860 mg, 3.29 mmol) was dissolved in Tetrahydrofuran (Volume: 41 mL) to give a clear solution. The solution was cooled to 0 °C and NaH (197 mg, 4.94 mmol) was added. The reaction was allowed to stir at RT for 0.5 hour. The translucent solution was then cooled to -78 °C and LAH was added over two minutes. The reaction temperature was maintained between -30 °C and -20 °C for 3 hours while stirring, then cooled to -78 °C. Methanol (3ml, gas evolution) and water (1 ml) were added. The reaction was stirred at room temperature for 30 minutes. The crude product was added to 400ml ethyl acetate. Water (100ml) was added and the mixture stirred for 1 hr. The mixture was filtered through medium frit to remove tan solids which were discarded. The aqueous layer was extracted with ethyl acetate (1 X 100 mL). The organic fractions were combined, washed once with brine and dried with sodium sulfate and concentrated to yield 743 mg (97%) of the product as a white residue. [M+H] calc'd for C12H15N3O2, 234; found, 234.

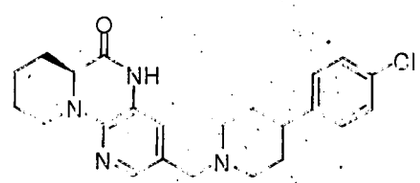
[0479] Compound 68: (S)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-on: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (125.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (225 ul, 1.3 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (109 mg, 0.472 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was then cooled to room temperature, diluted with EtOH (3 ml) and water (~ 300 ul), then filtered. The solids were collected and refluxed in ethanol (5 mL) for 2 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (75.1 mg, 43%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.40 - 7.48 (m, 2H), 7.34 - 7.40 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.18 (s, 1H), 4.45 - 4.55 (m, 1H), 3.84 (d, J = 11.4 Hz, 1H), 3.42 (s, 2H), 3.01 (d, J = 2.8 Hz, 2H), 2.56 - 2.66 (m, 3H), 2.44 (br. s., 2H), 1.98 - 2.08 (m, 1H), 1.80 - 1.89 (m, 1H), 1.59 - 1.68 (m, 1H), 1.34 - 1.57 (m, 3H). [M+H] calc'd for C23H25ClN4O, 409; found, 409. MP: 201.6 °C

Compound 69: (S)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



[0480] (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (125.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (225 ul, 1.3 mmol). To the stirred mixture was then added 1-(4-chlorophenyl)piperazine hydrochloride (110 mg, 0.472 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was then cooled to room temperature, diluted with EtOH (3 ml) and water (~ 300 ul), then filtered. The solids were collected and refluxed in ethanol (5 mL) for 2 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (67.3 mg, 43%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.47 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 9.1 Hz, 2H), 6.97 (d, J = 2.0 Hz, 1H), 6.88 - 6.95 (m, 2H), 4.45 - 4.55 (m, 1H), 3.83 (dd, J = 11.4, 2.3 Hz, 1H), 3.35 (s, 2H), 3.05 - 3.16 (m, 5H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.38 - 2.48 (m, 3H), 2.03 (d, J = 12.6 Hz, 1H), 1.77 - 1.91 (m, 1H), 1.63 (d, J = 12.6 Hz, 1H), 1.33 - 1.56 (m, 3H). [M+H] calc'd for C22H26ClN5O, 412; found, 412.

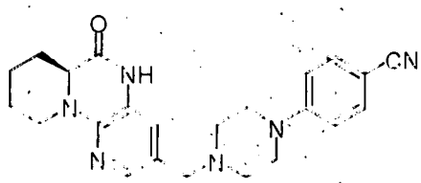
Compound 70: (S)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



[0481] (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (125.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (225 ul, 1.3 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)piperidine hydrochloride (109 mg, 0.472 mmol). The reaction was heated to

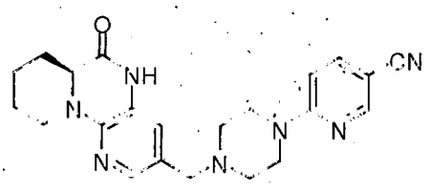
90°C with stirring for 16 h. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in 3mL DMSO and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (22.1 mg, 12.5%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.46 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.21 - 7.28 (m, 2H), 6.96 (d, J = 2.0 Hz, 1H), 4.42 - 4.58 (m, 1H), 3.83 (dd, J = 11.4, 2.8 Hz, 1H), 3.32 (s, 2H), 2.80 - 2.95 (m, 2H), 2.54 - 2.66 (m, 1H), 1.92 - 2.08 (m, 3H), 1.83 (br. s., 1H), 1.66 - 1.77 (m, 2H), 1.33 - 1.66 (m, 6H). [M+H] calc'd for C23H27ClN4O, 411; found, 411.

Compound 71: (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0482] (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (86.0 mg, 0.369 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (103.0 mg, 0.442 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (193 ul, 1.1 mmol). To the stirred mixture was then added 4-(piperazin-1-yl)benzonitrile (76 mg, 0.406 mmol). The reaction was heated to 90°C with stirring for 16 h. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in 3mL DMSO and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (29.7 mg, 20.0%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.48 (s, 1H), 7.65 (s, 1H), 7.57 (d, J = 8.8 Hz, 2H), 6.94 - 7.04 (m, 3H), 4.44 - 4.55 (m, 1H), 3.79 - 3.88 (m, 1H), 3.35 (br. s., 2H), 3.30 (br. s., 4H), 2.54 - 2.69 (m, 1H), 2.45 (br. s., 4H), 1.97 - 2.09 (m, 1H), 1.80 - 1.90 (m, 1H), 1.57 - 1.69 (m, 1H), 1.32 - 1.56 (m, 3H). [M+H] calc'd for C23H26N6O, 403; found, 403. MP: 212.2 °C

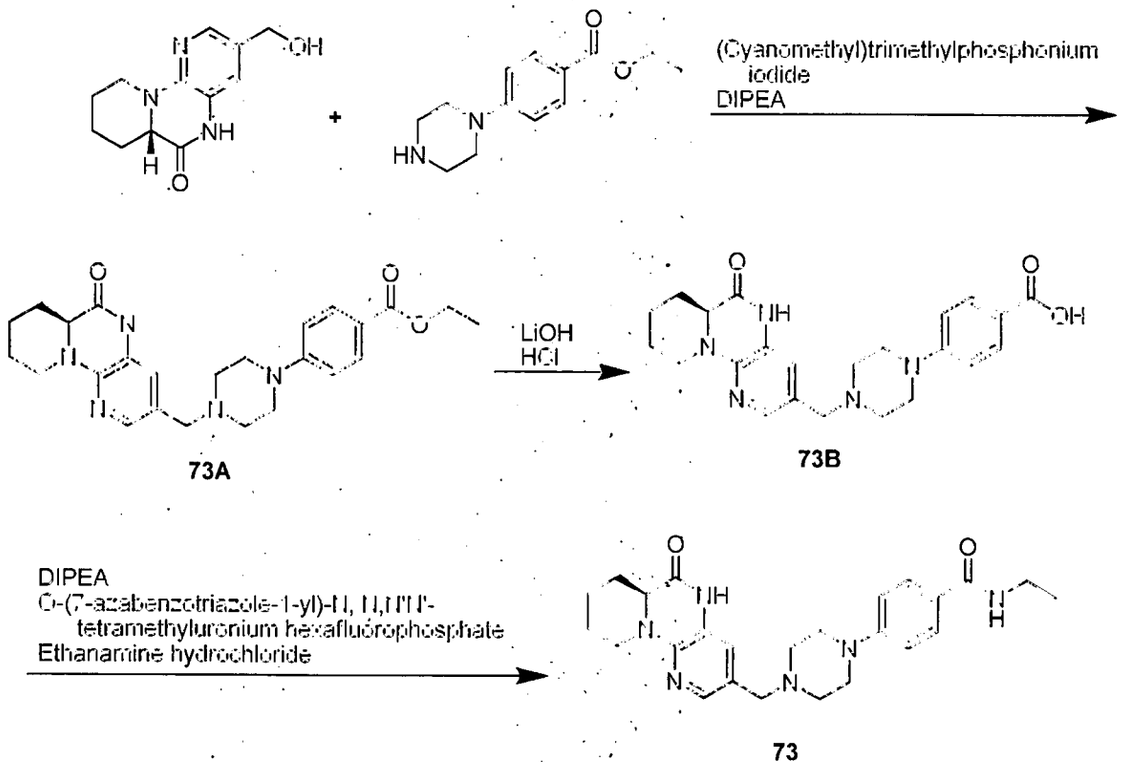
Compound 72: (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile



[0483] (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (39.0 mg, 0.382 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (111.0 mg, 0.458 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (200 ul, 1.1 mmol). To the stirred mixture was then added 6-(piperazin-1-yl)nicotinonitrile (79 mg, 0.420 mmol). The reaction was heated to 90°C with stirring for 16 h. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in 3mL DMSO and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (54.2 mg, 35.2%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.43 (br. s., 1H), 8.46 (d, J = 2.3 Hz, 1H), 7.83 (dd, J = 9.1, 2.5 Hz, 1H), 7.64 (d, J = 2.0 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 6.90 (d, J = 9.1 Hz, 1H), 4.50 (d, J = 12.9 Hz, 1H), 3.83 (dd, J = 11.4, 2.8 Hz, 1H), 3.55 - 3.70 (m, 4H), 3.34 (s, 2H), 2.59 (td, J = 12.6, 2.4 Hz, 1H), 2.40 (t, J = 4.8 Hz, 4H), 2.03 (d, J = 12.6 Hz, 1H), 1.84 (d, J = 12.1 Hz, 1H), 1.63 (d, J = 13.6 Hz, 1H), 1.29 - 1.56 (m, 3H). [M+H] calc'd for C22H25N7O, 404; found, 404.

Compound 73: (S)-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

Method A



73A 73B 73

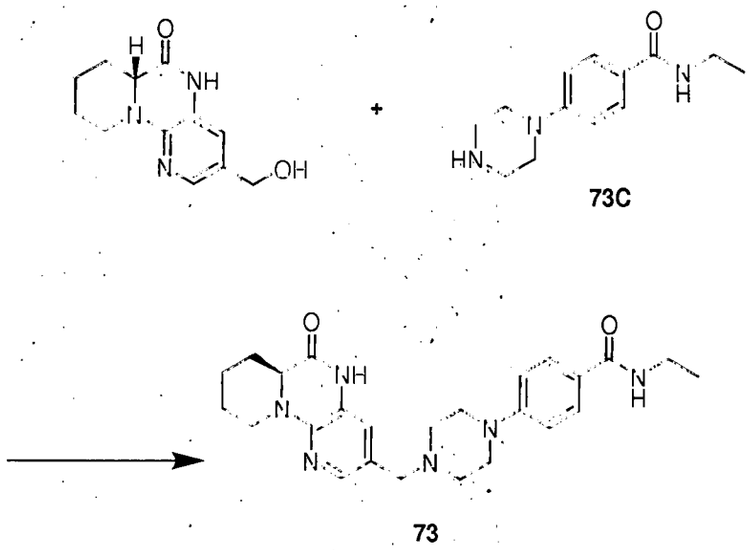
[0484] Compound 73A: (S)-ethyl 4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (400 mg, 1.715 mmol) was suspended in propionitrile (4.3 mL) and (cyanomethyl)trimethylphosphonium iodide (500.0 mg, 2.06 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (398 ul, 5.1 mmol). To the stirred mixture was then added ethyl ethyl 4-(piperazin-1-yl)benzoate (402 mg, 1.715 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was then cooled to room temperature, diluted with EtOH (8 ml) and water (1 mL), then filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (508 mg, 65.9%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.43 (s, 1H), 7.77 (d, J = 9.1 Hz, 2H), 7.65 (d, J = 2.0 Hz, 1H), 6.90 - 7.01 (m, 3H), 4.50 (d, J = 12.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.84 (dd, J = 11.4, 2.3 Hz, 1H), 3.35 (s, 2H), 3.23 (br. s., 4H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.40 - 2.47 (m, 4H), 2.03 (d, J = 12.9 Hz, 1H), 1.80 -

1.89 (m, 1H), 1.64 (d, J = 12.6 Hz, 1H), 1.33 - 1.57 (m, 3H), 1.28 (t, J = 7.1 Hz, 3H). [M+H] calc'd for C25H31N5O3, 450; found, 450.

[0485] Compound 73B: (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid: (S)-methyl 4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate (152 mg, 0.349 mmol) was taken up in dioxane (2 ml) and LiOH (1N, 2 ml, 2.000 mmol) was added. The reaction was stirred 16h at room temperature. The reaction was concentrated in-vacuo and the residue was taken up in water (5 mL) and acidified (4.5N HCl) to pH 4. A white precipitate formed. The precipitate was filtered off and dried in vacuum to afford the title compound (122.3 mg, 83%) as a white solid. [M+H] calc'd for C23H27N5O3, 422; found, 422.

[0486] Compound 73: (S)-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (122 mg, 0.29 mmol) was taken up in DMF (2.9 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (152 µl, 0.87 mmol), O-(7-azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (165 mg, 0.434 mmol), and ethanamine hydrochloride (26.0 mg, 0.318 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield 135 mg (85%) of the product as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.32 (s, 1H), 9.83 (br. s., 1H), 8.25 (t, J = 5.6 Hz, 1H), 7.84 (d, J = 2.0 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 6.94 - 7.12 (m, 3H), 4.59 (d, J = 13.1 Hz, 1H), 4.27 (br. s., 2H), 3.85 - 4.10 (m, 3H), 3.43 (d, J = 10.4 Hz, 2H), 3.21 - 3.30 (m, 2H), 2.95 - 3.19 (m, 4H), 2.61 - 2.72 (m, 1H), 2.05 (d, J = 11.8 Hz, 1H), 1.87 (d, J = 12.4 Hz, 1H), 1.66 (d, J = 12.1 Hz, 1H), 1.31 - 1.62 (m, 3H), 1.09 (t, J = 7.2 Hz, 3H). [M+H] calc'd for C23H27N5O3, 449; found, 449. MP: 232.6 °C.

Method B

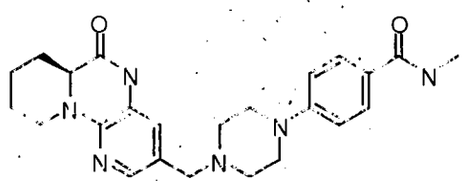


73C

73

[0487] Compound 73: (S)-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: To a suspension of (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (300 mg, 3.43 mmol) was added (cyanomethyl)trimethylphosphonium iodide (1000 mg, 4.12 mmol) and DIEA (1797 µl, 10.29 mmol) and N-ethyl-4-(piperazin-1-yl)benzamide (800 mg, 3.43 mmol)). The vial was heated to 90 °C for 16 hours. The crude reaction was cooled to RT and filtered. The resulting solid were collected and suspended in EtOH (24 mL), heated to reflux, then cooled to RT and filtered. The resulting material was rinsed with EtOH to give a white solid.

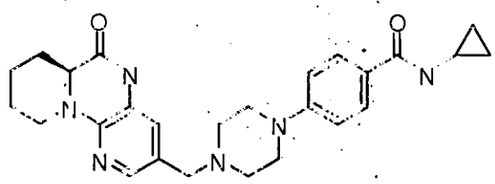
Compound 74: (S)-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0488] (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (50 mg, 0.119 mmol) was taken up in DMF (0.5 mL). To the mixture was added N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (34.1mg, 0.178 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (27.2 mg, 0.178 mmol), 4-methylmorpholine (0.065 mL, 0.593 mmol) and methanamine hydrochloride (8.01

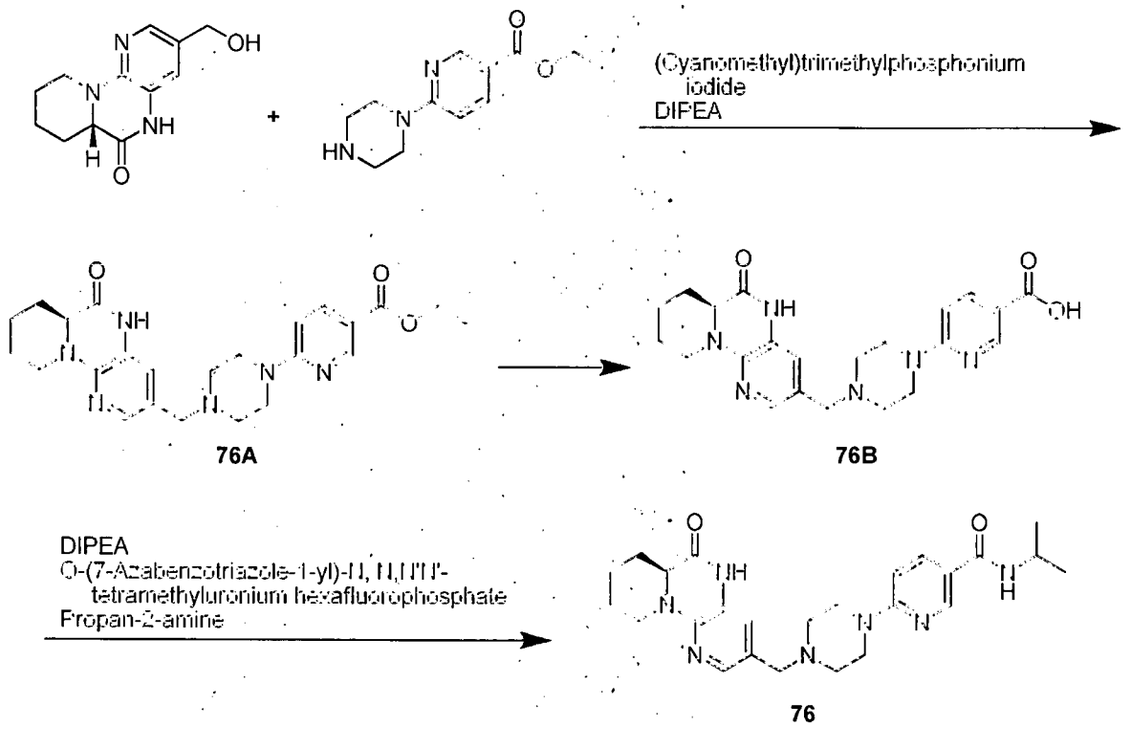
mg, 0.119 mmol). The reaction was stirred at room temperature overnight. To the stirred solution was added water (2 mL) and the precipitate was filtered, collected, and dried in vacuum to afford the title compound (23.8 mg, 46.2%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.49 (s, 1H), 8.14 (q, J = 4.5 Hz, 1H), 7.53 - 7.80 (m, 3H), 6.82 - 7.04 (m, 3H), 4.51 (d, J = 12.9 Hz, 1H), 3.84 (dd, J = 11.2, 2.7 Hz, 1H), 3.30 - 3.51 (m, 3H), 3.23 (br. s., 4H), 2.74 (d, J = 4.5 Hz, 3H), 2.61 (td, J = 12.7, 2.7 Hz, 1H), 2.49 (br. s., 3H), 2.04 (d, J = 12.6 Hz, 1H), 1.85 (d, J = 12.1 Hz, 1H), 1.64 (d, J = 12.6 Hz, 1H), 1.33 - 1.59 (m, 3H). [M+H] calc'd for C24H30N6O2, 435; found, 435.

Compound 75: (S)-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0489] (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (50 mg, 0.119 mmol) was taken up in DMF (0.5 mL). To the mixture was added N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (34.1mg, 0.178 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (27.2 mg, 0.178 mmol), 4-methylmorpholine (0.065 mL, 0.593 mmol) and cyclopropanamine (6.77 mg, 0.119 mmol). The reaction was stirred at room temperature overnight. To the stirred solution was added water (2 mL) and the precipitate was filtered, collected, and dried in vacuum to afford the title compound (41.2 mg, 75.0%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.48 (s, 1H), 8.13 (d, J = 4.0 Hz, 1H), 7.57 - 7.76 (m, 3H), 6.80 - 7.02 (m, 3H), 4.50 (d, J = 13.1 Hz, 1H), 3.84 (dd, J = 11.4, 2.8 Hz, 1H), 3.35 (br. s., 2H), 3.22 (br. s., 4H), 2.79 (td, J = 7.3, 3.9 Hz, 1H), 2.60 (td, J = 12.6, 2.7 Hz, 1H), 2.46 (br. s., 4H), 2.03 (d, J = 12.9 Hz, 1H), 1.83 (br. s., 1H), 1.64 (d, J = 12.9 Hz, 1H), 1.31 - 1.57 (m, 3H), 0.61 - 0.69 (m, 2H), 0.48 - 0.56 (m, 2H). [M+H] calc'd for C26H32N6O2, 461; found, 461.

Compound 76: (S)-N-isopropyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide

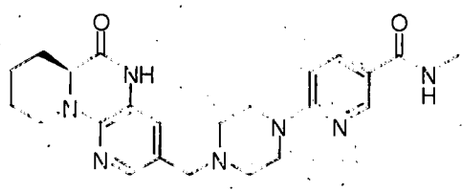


[0490] Compound 76A: (S)-ethyl 6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (330 mg, 1.415 mmol) was suspended in propionitrile (3.5 mL) and (cyanomethyl)trimethylphosphonium iodide (413.0 mg, 1.70 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (741 ul, 4.2 mmol). To the stirred mixture was then added ethyl 6-(piperazin-1-yl)nicotinate (366 mg, 1.56 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was then cooled to room temperature, diluted with EtOH (8 ml) and water (1 mL), then filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (567 mg, 39%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.48 (s, 1H), 8.63 (d, J = 2.0 Hz, 1H), 7.93 (dd, J = 9.1, 2.3 Hz, 1H), 7.65 (d, J = 1.8 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 9.1 Hz, 1H), 4.44 - 4.56 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.84 (dd, J = 11.4, 2.8 Hz, 1H), 3.53 - 3.73 (m, 4H), 3.35 (s, 2H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.41 (t, J = 4.8 Hz, 4H), 2.05 (br. s., 1H), 1.85 (d, J = 12.4 Hz, 1H), 1.64 (d, J = 12.4 Hz, 1H), 1.34 - 1.57 (m, 3H), 1.28 (t, 3H) [M+H] calc'd for C24H30N6O3, 451; found, 451.

[0491] Compound 76B: (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid: Compound 76B was prepared using a procedure analogous to that described in connection with Compound 73B except that (S)-ethyl 6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate was used instead of (S)-ethyl 4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate to yield the title compound as a white solid. [M+H] calc'd for C22H26N6O3, 423; found, 423.

[0492] Compound 76: (S)-N-isopropyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide: (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (75 mg, 0.178 mmol) was taken up in DMF (0.9 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (93 µl, 0.53 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (101 mg, 0.266 mmol), and propan-2-amine (11.5 mg, 0.195 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield 64.8 mg (65%) of the product as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.84 (s, 1H), 9.93 (br. s., 1H), 8.64 (d, J = 2.0 Hz, 1H), 8.02 - 8.11 (m, 2H), 7.82 (d, J = 2.0 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.96 (d, J = 9.1 Hz, 1H), 4.43 - 4.63 (m, 3H), 4.25 (s, 2H), 4.07 (dd, J = 14.1, 6.6 Hz, 1H), 3.93 - 4.02 (m, 1H), 3.37 - 3.55 (m, 1H), 2.96 - 3.25 (m, 4H), 2.68 (td, J = 12.9, 2.5 Hz, 1H), 2.02 - 2.11 (m, 1H), 1.87 (d, J = 12.4 Hz, 1H), 1.33 - 1.72 (m, 4H), 1.14 (d, J = 6.8 Hz, 6H). [M+H] calc'd for C25H33N7O2, 464; found, 464.

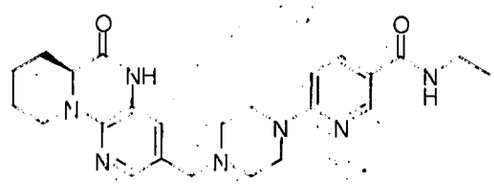
Compound 77: (S)-N-methyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



[0493] (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (75 mg, 0.178 mmol) was taken up in DMF (0.9 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (93 µl, 0.53 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (101 mg, 0.266 mmol), and methanamine hydrochloride (13.2 mg, 0.195 mmol). The reaction was stirred at

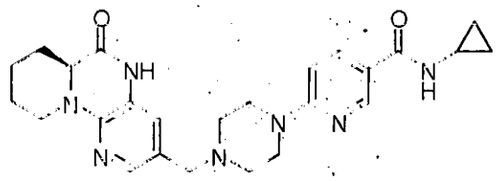
room temperature overnight. The reaction was purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield 23.3 mg (30%) of the product as a white solid. ^1H NMR (DMSO-d_6) δ (ppm): 10.43 (s, 1H), 8.56 (d, J = 2.3 Hz, 1H), 8.20 (d, J = 4.5 Hz, 1H), 7.92 (dd, J = 9.0, 2.1 Hz, 1H), 7.65 (s, 1H), 6.98 (d, J = 1.5 Hz, 1H), 6.82 (d, J = 8.8 Hz, 1H), 4.50 (d, J = 12.9 Hz, 1H), 3.77 - 3.94 (m, 1H), 3.56 (d, J = 2.3 Hz, 4H), 3.34 (s, 2H), 2.74 (d, J = 4.5 Hz, 3H), 2.53 - 2.69 (m, 1H), 2.41 (br. s., 4H), 1.99 - 2.08 (m, 1H), 1.84 (br. s., 1H), 1.59 - 1.69 (m, 1H), 1.31 - 1.57 (m, 3H). [M+H] calc'd for C25H33N7O2, 436; found, 436.

Compound 78: (S)-N-ethyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



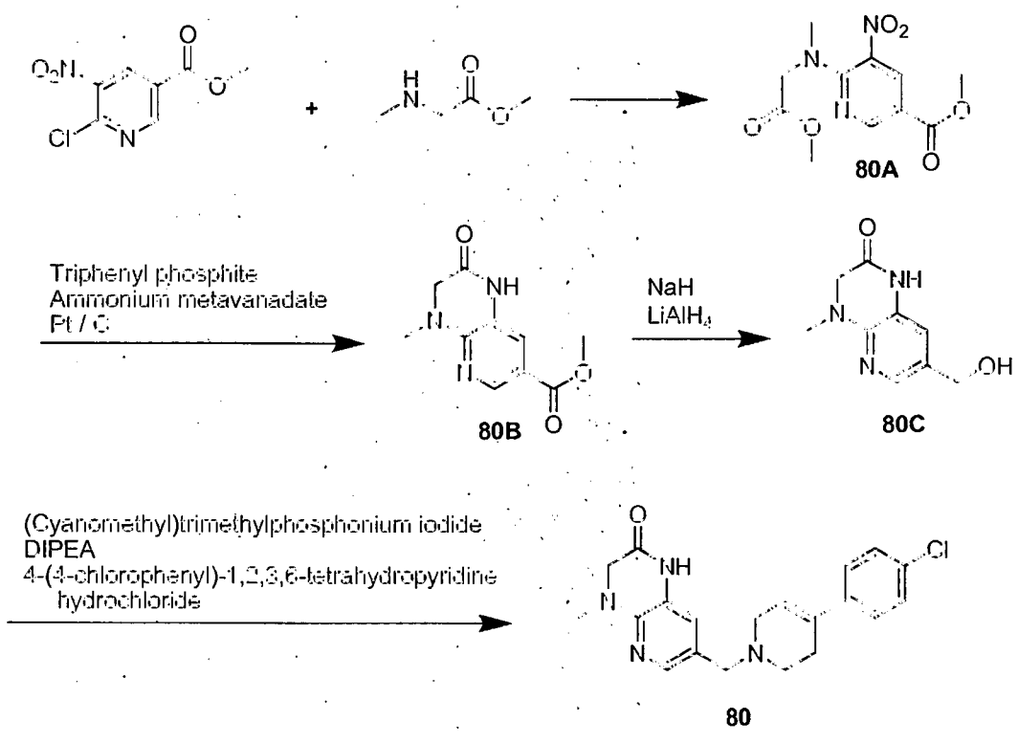
[0494] (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (75 mg, 0.173 mmol) was taken up in DMF (0.9 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (93 µl, 0.53 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (101 mg, 0.266 mmol), and ethanamine hydrochloride (15.9 mg, 0.195 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield 27.4 mg (34%) of the title compound as a white solid. ^1H NMR (DMSO-d_6) δ (ppm): 10.34 (s, 1H), 10.03 (br. s., 1H), 8.64 (s, 1H), 8.35 (t, J = 5.2 Hz, 1H), 8.04 (d, J = 9.1 Hz, 1H), 7.33 (s, 1H), 6.90 - 7.11 (m, 2H), 4.40 - 4.71 (m, 3H), 4.26 (s, 2H), 3.93 (d, J = 11.1 Hz, 1H), 2.96 - 3.57 (m, 8H), 2.61 - 2.74 (m, 1H), 2.08 (d, J = 11.9 Hz, 1H), 1.87 (d, J = 12.4 Hz, 1H), 1.33 - 1.73 (m, 4H), 1.11 (t, 3H). [M+H] calc'd for C24H31N7O2, 450; found, 450.

Compound 79: (S)-N-cyclopropyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide



[0495] (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid (75 mg, 0.178 mmol) was taken up in DMF (0.9 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (93 µl, 0.53 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (101 mg, 0.266 mmol), and cyclopropanamine (11.15 mg, 0.195 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (10-80 MeCN/H_2O, TFA buffered). The fractions were collected and lyophilized to yield 41.2 mg (50%) of the product as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.31 (s, 1H), 9.85 (br. s., 1H), 8.61 (d, J = 2.3 Hz, 1H), 8.30 (d, J = 4.0 Hz, 1H), 8.01 (dd, J = 9.0, 2.4 Hz, 1H), 7.82 (d, J = 2.0 Hz, 1H), 7.04 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.42 - 4.64 (m, 3H), 4.24 (br. s., 2H), 3.92 - 4.01 (m, 1H), 3.42 (br. s., 2H), 2.94 - 3.26 (m, 4H), 2.75 - 2.86 (m, 1H), 2.58 - 2.73 (m, 1H), 2.03 - 2.12 (m, 1H), 1.87 (d, J = 12.4 Hz, 1H), 1.66 (d, J = 12.6 Hz, 1H), 1.31 - 1.61 (m, 3H), 0.62 - 0.73 (m, 2H), 0.46 - 0.57 (m, 2H). [M+H] calc'd for C25H31N7O2, 462; found, 462.

Compound 80: 7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0496] Compound 80A: Methyl 6-((2-methoxy-2-oxoethyl)(methyl)amino)-5-nitronicotinate: Methyl 6-chloro-5-nitronicotinate (2.0 g, 9.23 mmol) was added to methyl 2-(methylamino)acetate (1.9 g, 18.47 mmol) neat while stirring at room temperature. The viscous yellow reaction was heated to 90°C for one hour and then allowed to cool back to room temperature. The reaction was diluted with dichloromethane (20 mL) and purified using flash column chromatography (220 g SiO_2, 20-30% gradient, ethyl acetate in hexanes) to yield 2.60 g (99% yield) of the title compound as a yellow oil. [M+H] calc'd for C11H13N3O6, 284; found, 284.

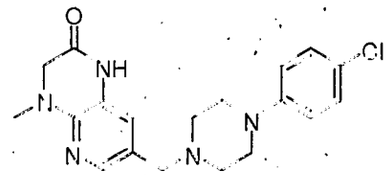
[0497] Compound 80B: Methyl 4-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate: Methyl 6-((2-methoxy-2-oxoethyl)(methyl)amino)-5-nitronicotinate (2.7 g, 9.53 mmol) was dissolved in dichloromethane (10 mL). To the yellow solution was added ammonium metavanadate (30.0 mg, 0.256 mmol), triphenyl phosphite (aprox 30 ul, 0.097 mmol), and Pt/C (300 mg, 5% w/w). The reaction mixture was pressurized with hydrogen gas (110 psi) and stirred at room temperature for 16 h. The reaction was then depressurized and diluted with dichloromethane (100 mL) which was then refluxed for 30 min. The hot solution was filtered through a pad of celite and washed with hot dichloromethane (3 x

20 mL). The filtrate was concentrated in vacuo to yield the title compound (1.45 g, 68%) as a white solid. [M+H] calc'd for C10H11N3O3, 222; found, 222.

[0498] Compound 80C: 7-(hydroxymethyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: Methyl 4-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate (500 mg, 2.25 mmol) was taken up in tetrahydrofuran (25 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (60% dispersion in mineral oil, 136 mg, 3.40 mmol) and stirred 30 min. The reaction was then cooled to -45°C and lithium aluminum hydride (2M in THF, 3.3 mL, 6.6 mmol) was added. The reaction was stirred at a temperature between -20 and -10°C for 1 h. The reaction was then cooled back to -60 °C and MeOH (1 mL) followed by water (1 mL) was added. The reaction was allowed to stir at ambient temperature for 2 h and then poured into ethyl acetate (300 mL) and water (200 mL). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, washed with brine (100 mL), dried with sodium sulfate and concentrated to yield the title compound (415 mg, 95%) as a white solid. [M+H] calc'd for C9H11N3O2, 194; found, 194.

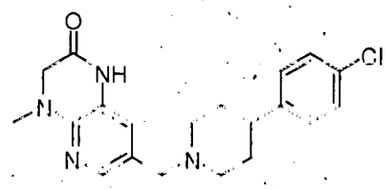
[0499] Compound 80: 7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: 7-(hydroxymethyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (35.0 mg, 0.44 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (103.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (30.2 mg, 19%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.51 (s, 1H), 7.64 (s, 1H), 7.41 - 7.47 (m, 2H), 7.34 - 7.40 (m, 2H), 6.97 (d, J = 1.3 Hz, 1H), 6.13 (s, 1H), 3.93 (s, 2H), 3.41 (s, 2H), 3.01 (br. s., 2H), 2.91 (s, 3H), 2.60 (br. s., 2H), 2.39 - 2.47 (m, J = 7.3 Hz, 2H). [M+H] calc'd for C20H21ClN4O, 369; found, 369.

Compound 81: 7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0500] 7-(hydroxymethyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (85.0 mg, 0.44 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 1-(4-chlorophenyl) piperazine hydrochloride (104.8 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (14.7 mg, 8%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.50 (s, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.21 (d, J = 9.1 Hz, 2H), 6.96 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 3.93 (s, 2H), 3.34 (s, 2H), 3.10 (br. s., 4H), 2.91 (s, 3H), 2.46 (br. s., 4H). [M+H] calc'd for C19H22ClN5O, 372; found, 372.

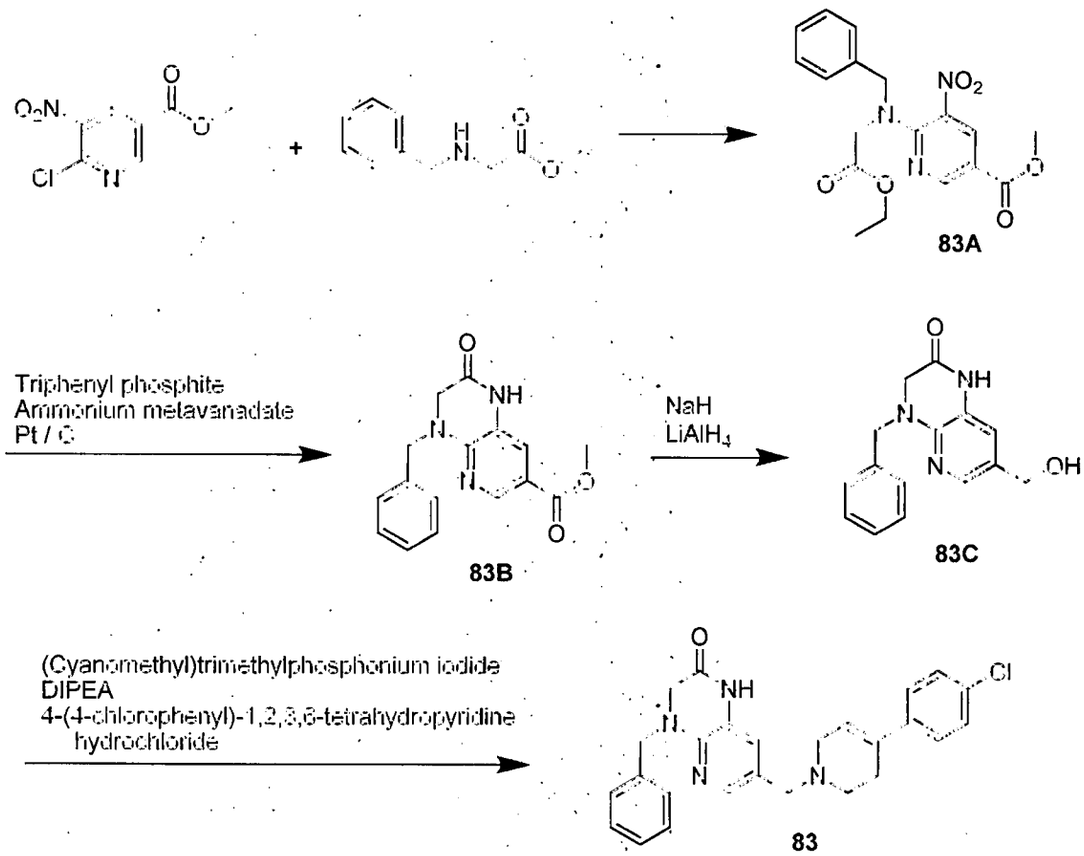
Compound 82: 7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0501] 7-(hydroxymethyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (85.0 mg, 0.44 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl) piperidine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (18.1 mg, 11%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm):

10.49 (s, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.30 - 7.36 (m, 2H), 7.23 - 7.29 (m, 2H), 6.95 (d, J = 2.0 Hz, 1H), 3.92 (s, 2H), 3.32 (s, 3H), 2.84 - 2.92 (m, 5H), 1.93 (t, J = 10.7 Hz, 2H), 1.66 - 1.75 (m, 2H), 1.50 - 1.64 (m, 2H). [M+H] calc'd for C20H23ClN4O, 371; found, 371.

Compound 83: 4-benzyl-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0502] Compound 83A: Methyl 6-(benzyl(2-ethoxy-2-oxoethyl)amino)-5-nitronicotinate: Methyl 6-chloro-5-nitronicotinate (2.0 g, 9.23 mmol) was added to methyl 2-(benzylamino)acetate (6.0 g, 31.05 mmol) neat while stirring at room temperature. The viscous yellow reaction was heated to 90°C for one h and then allowed to cool back to room temperature. The reaction was diluted with dichloromethane (20 mL) and purified via column chromatography (220 g SiO2, 20-30% gradient, ethyl acetate in hexanes) to yield the title compound (3.10 g, 90% yield) as a yellow oil. [M+H] calc'd for C18H19N3O6, 374; found, 374.

[0503] Compound 83B: Methyl 4-benzyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate: Methyl 6-(benzyl(2-ethoxy-2-oxoethyl)amino)-5-nitronicotinate

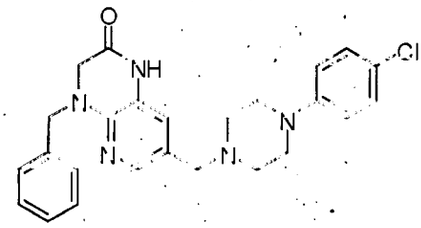
(445 mg g, 1.19 mmol) was dissolved in dichloromethane (5 mL). To the yellow solution was added ammonium metavanadate (10.0 mg, 0.085 mmol), triphenyl phosphite (aprox 10 ul, 0.032 mmol), and Pt/C (50 mg, 5% w/w). The reaction mixture was pressurized with hydrogen gas (75 psi) and stirred at room temperature for 48 h. The reaction was then depressurized and diluted with dichloromethane (20 mL) which was then refluxed for 30 min. The hot solution was filtered through a pad of celite and washed with hot dichloromethane (3 x 10 mL). The filtrate was concentrated to yield the title compound (250 mg, 71%) as a white solid. [M+H] calc'd for C16H15N3O3, 298; found, 298.

[0504] Compound 83C: 4-benzyl-7-(hydroxymethyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: Methyl 4-benzyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate (600 mg, 2.02 mmol) was taken up in tetrahydrofuran (25 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (60% dispersion in mineral oil, 121 mg, 3.03 mmo) and stirred 30 min. The reaction was then cooled to -78°C and lithium aluminum hydride (3 mL, 2M in THF) was added. The reaction was stirred at a temperature between -20 and -10°C for 2 h. The reaction was then cooled back to -78°C and MeOH (1 mL) followed by water (1 mL) was added. The reaction was allowed to stir at ambient temperature for 2 h and then poured into ethyl acetate (200 mL) and water (100 mL). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried with sodium sulfate and concentrated to afford the title compound (540 mg, 99%) as a white solid. [M+H] calc'd for C15H15N3O2, 270; found, 270.

[0505] Compound 83: 4-benzyl-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: 4-benzyl-7-(hydroxymethyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.37 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (130 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (45.3 mg, 27%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.57 (s, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.41 - 7.48 (m, 2H), 7.23 - 7.41 (m, 7H), 7.03 (d, J = 2.0 Hz, 1H), 6.19 (s, 1H), 4.72 (s,

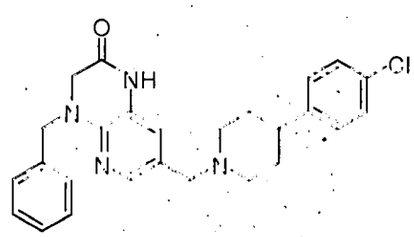
2H), 3.36 (s, 2H), 3.43 (s, 2H), 3.03 (d, J = 2.3 Hz, 2H), 2.58 - 2.65 (m, 2H), 2.44 (br. s., 2H). [M+H] calc'd for C26H25ClN4O, 445; found, 445.

Compound 84: 4-benzyl-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0506] 4-benzyl-7-(hydroxymethyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.37 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 1-(4-chlorophenyl)piperazine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (66.6 mg, 40%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.57 (s, 1H), 7.64 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 4.5 Hz, 4H), 7.25 - 7.30 (m, 1H), 7.19 - 7.24 (m, 2H), 7.01 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 4.72 (s, 2H), 3.36 (s, 2H), 3.36 (s, 2H), 3.07 - 3.15 (m, 4H), 2.44 - 2.49 (m, 4H). [M+H] calc'd for C25H26ClN5O, 448; found, 448.

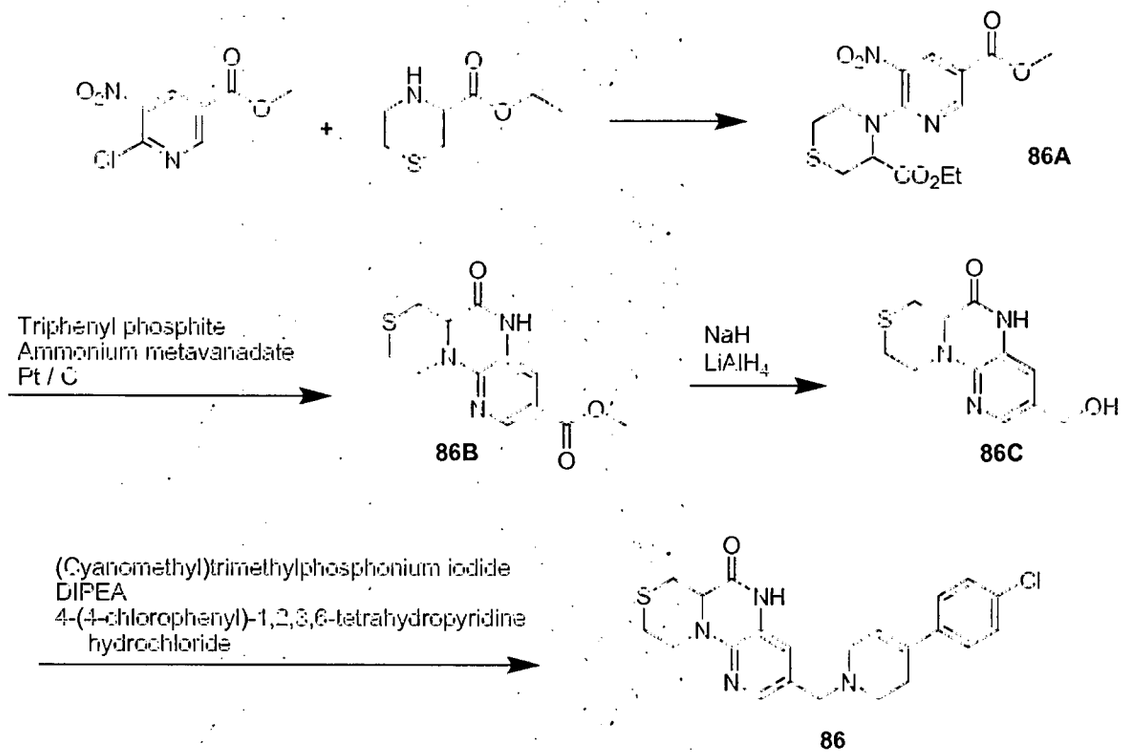
Compound 85: 4-benzyl-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one



[0507] 4-benzyl-7-(hydroxymethyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.37 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine

(180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)piperidine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered and dried in vacuum to afford the title compound (69.9 mg, 42%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.56 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.30 - 7.37 (m, 6H), 7.23 - 7.30 (m, 3H), 7.00 (d, J = 2.0 Hz, 1H), 4.71 (s, 2H), 3.35 (s, 2H), 3.33 (s, 3H), 2.89 (d, J = 11.4 Hz, 2H), 1.99 (t, J = 10.6 Hz, 2H), 1.67 - 1.73 (m, 2H), 1.48 - 1.66 (m, 2H). [M+H] calc'd for C11H15Cl2N, 447; found, 447.

Compound 86: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one



[0508] Compound 86A: Ethyl 4-(5-(methoxycarbonyl)-3-nitropyridin-2-yl)thiomorpholine-3-carboxylate: Methyl 6-chloro-5-nitronicotinate (1.1 g, 5.10 mmol) was added to ethyl thiomorpholine-3-carboxylate (2.0 g, 11.41 mmol) neat while stirring at room temperature. The viscous yellow reaction was heated to 90°C for one hour and then allowed to cool back to room temperature. The reaction was diluted with dichloromethane (20 mL) and purified via column chromatography (220 g SiO2, 20-30% gradient, ethyl acetate in hexanes)

to yield the title compound (1.71 g, 95%) as a yellow oil. [M+H] calc'd for C15H13N2O6S, 356; found, 356.

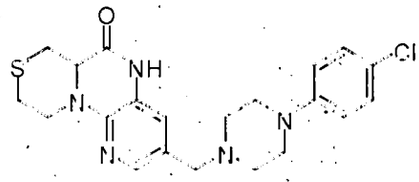
[0509] Compound 86B: methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate: Ethyl 4-(5-(methoxycarbonyl)-3-nitropyridin-2-yl)thiomorpholine-3-carboxylate (600 mg g, 1.69 mmol) was dissolved in dichloromethane (5 mL). To the yellow solution was added ammonium metavanadate (10.0 mg, 0.085 mmol), triphenyl phosphite (aprox 10 ul, 0.032 mmol), and Pt/C (50 mg, 5% w/w). The reaction mixture was pressurized with hydrogen gas (110 psi) and stirred at room temperature for 16 h. The reaction was then depressurized and diluted with dichloromethane (20 mL) which was refluxed for 30 min. The hot solution was filtered through a pad of celite and washed with hot dichloromethane (3 x 10 mL). The filtrate was concentrated to yield the title compound (452 mg, 96%) as a white solid. [M+H] calc'd for C12H13N3O3S, 280; found, 280.

[0510] Compound 86C: 3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one: Methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate (336 mg, 1.33 mmol) was taken up in tetrahydrofuran (25 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (60% dispersion in mineral oil, 121 mg, 3.03 mmol) and stirred 30 min. The reaction was cooled to -78°C and lithium aluminum hydride (3 mL, 2M in THF) was added. The reaction was stirred at a temperature between -20 and -10 °C for 3 h. The reaction was cooled back to -78°C and MeOH (1 mL) followed by water (1 mL) was added. The reaction was allowed to stir at ambient temperature for 2 h and then poured into ethyl acetate (200 mL) and water (100 mL). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The organic layers were combined, washed with brine (100 mL), dried with sodium sulfate and concentrated to afford the title compound (497 mg, 98%) as a white solid. [M+H] calc'd for C11H13N3O2S, 252; found, 252.

[0511] Compound 86: 3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one: 3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (100 mg, 0.36 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (180 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room

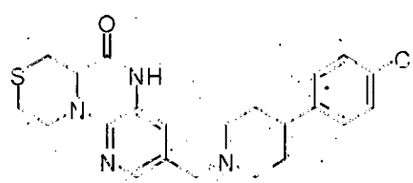
temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The solids were collected to afford the title compound (79.5 mg, 19%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.66 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.41 - 7.47 (m, 2H), 7.33 - 7.40 (m, 2H), 7.02 (d, J = 2.0 Hz, 1H), 6.18 (br. s., 1H), 4.33 (dt, J = 13.6, 2.7 Hz, 1H), 4.27 (dd, J = 10.6, 3.0 Hz, 1H), 3.43 (d, J = 3.5 Hz, 2H), 2.98 - 3.07 (m, 3H), 2.66 - 2.83 (m, 3H), 2.53 - 2.65 (m, 2H), 2.39 - 2.48 (m, 3H). [M+H] calc'd for C22H23ClN4OS, 427; found, 427.

Compound 87: 3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one



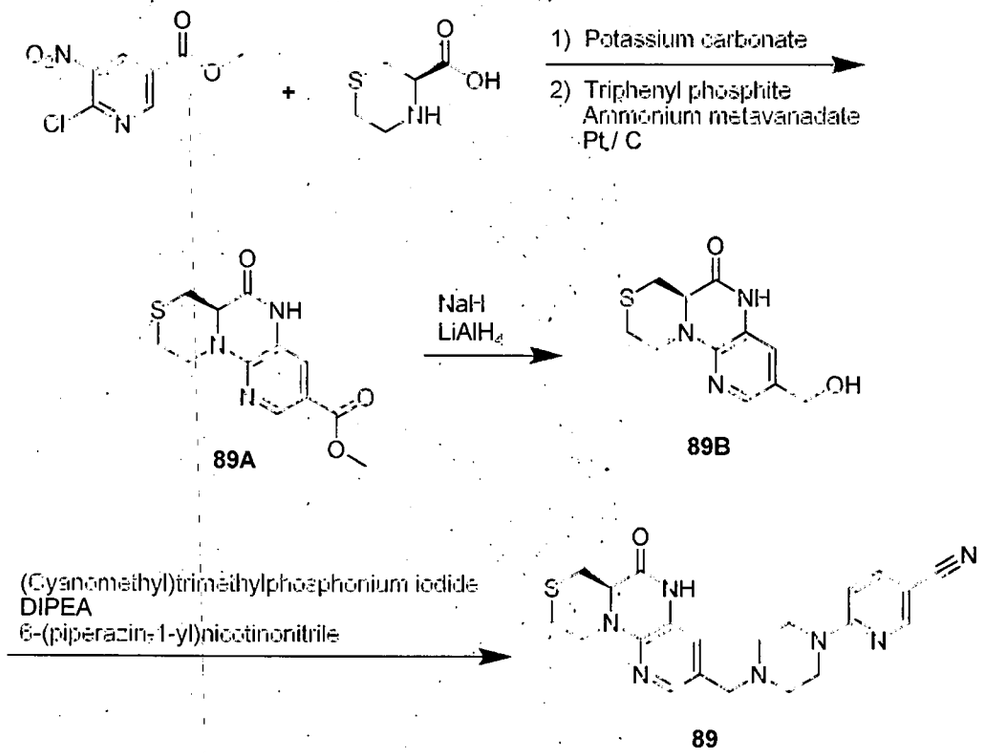
[0512] 3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (Compound 86C; 100 mg, 0.36 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (130 ul, 1.03 mmol). To the stirred mixture was then added 1-(4-chlorophenyl)piperazine hydrochloride (104.9 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The solids were collected to afford the title compound (36.1 mg, 56%) as a white solid. ^{1}H NMR (DMSO-d_6) δ: 10.66 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.16 - 7.26 (m, 2H), 7.00 (d, J = 2.0 Hz, 1H), 6.86 - 6.96 (m, 2H), 4.33 (dt, J = 13.6, 2.7 Hz, 1H), 4.26 (dd, J = 10.7, 2.9 Hz, 1H), 3.34 - 3.42 (m, 2H), 3.07 - 3.16 (m, 4H), 3.02 (td, J = 12.8, 2.3 Hz, 1H), 2.65 - 2.83 (m, 3H), 2.43 - 2.48 (m, 5H). [M+H] calc'd for C21H24ClN5OS, 430; found, 430.

Compound 88: 3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one



[0513] 3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (Compound 86C; 100 mg, 0.36 mmol) was suspended in propionitrile (1 mL) and (cyanomethyl)trimethylphosphonium iodide (123.0 mg, 0.51 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (130 ul, 1.03 mmol). To the stirred mixture was then added 4-(4-chlorophenyl)piperidine hydrochloride (104.5 mg, 0.45 mmol). The reaction was heated to 90°C with stirring for 2 h. The reaction was then cooled to room temperature and diluted with water (3 mL) and filtered. The solids were collected and refluxed in ethanol (5 mL) for 1 h. The suspension was cooled back to room temperature and filtered. The precipitate was filtered off and dried in vacuum to afford the title compound (86.1 mg, 56%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.44 - 10.83 (m, 1H), 7.63 (d, J = 1.8 Hz, 1H), 7.30 - 7.38 (m, 2H), 7.23 - 7.29 (m, 2H), 6.99 (d, J = 2.0 Hz, 1H), 4.83 - 4.91 (m, 1H), 4.22 - 4.29 (m, 1H), 3.33 (s, 3H), 2.96 - 3.07 (m, 1H), 2.83 - 2.94 (m, 2H), 2.65 - 2.83 (m, 3H), 2.39 - 2.48 (m, 1H), 1.91 - 2.06 (m, 2H), 1.66 - 1.78 (m, 2H), 1.49 - 1.66 (m, 2H) [M+H] calc'd for C22H25ClN4OS, 429; found, 429.

Compound 89: (R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile



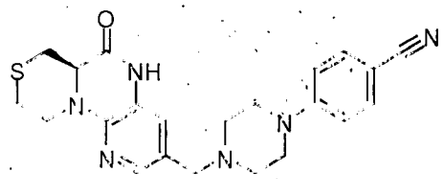
[0514] Compound 89A: (R)-methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate: To a suspension of (R)-thiomorpholine-3-carboxylic acid (1.009 g, 6.86 mmol) in THF was added methyl 6-chloro-5-nitronicotinate (1.35 g, 6.23 mmol) and potassium carbonate (2.58 g, 18.70 mmol). The suspension was heated to reflux for 3 hours. The crude orange solution was allowed to cool to RT and filtered through a pad of celite which was washed with DCM (50 mL), and transferred to a bomb hydroginator. To the solution was added triphenyl phosphite (0.019 ml, 0.061 mmol), platinum (0.238 g, 0.061 mmol), and ammonium metavanadate. The vessel was sealed and pressurized to 140 psi with stirring for 24 h at room temperature. The vessel was depressurized and the mixture was diluted with DCM (100 mL) and refluxed for 30 minutes. The hot mixture was filtered through celite and concentrated to yield 337 mg (52%) of the product as a white solid. [M+H] calc'd for C12H13N3O3S, 280; found, 280.

[0515] Compound 89B: (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one: (R)-methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate (837 mg, 3.18 mmol) was taken up in tetrahydrofuran (40 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (191 mg, 4.76 mmol, 60% dispersion in mineral oil) and stirred 30 minutes. The reaction was then cooled to -45 °C and lithium aluminum hydride (4.76 mL, 2M in THF) was added. The reaction was stirred at a temperature between -20 and -10 °C for 1 hour. The reaction was then cooled back to -78 °C and methanol (5 ml) followed by water (1 ml) was added. The reaction was allowed to stir at ambient temperature for 2 hours and then poured into ethyl acetate (400 ml) and water (100 ml). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The filtrate was collected. The layers were separated and the aqueous phase was extracted with ethyl acetate (1 x 100 ml). The organic layers were combined, washed with brine (100 ml), and concentrated to yield 710.8 mg (89%) of the title compound as a white solid. [M+H] calc'd for C11H13N3O2S, 252; found, 252.

[0516] Compound 89: (R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile: (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (80.0 mg, 0.318 mmol) was suspended in propionitrile (0.8 mL) and (cyanomethyl)trimethylphosphonium iodide (93.0 mg, 0.382 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (167 ul, 0.955 mmol). To the stirred mixture was then added 6-(piperazin-1-yl)nicotinonitrile (59.9 mg, 0.318 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was cooled to room temperature and left to sit 48 h. The

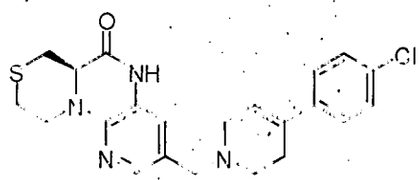
precipitate was filtered off, washed with ethanol (5 mL) and dried in vacuum to afford the title compound (53.9 mg, 40.2%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.41 (d, J = 1.8 Hz, 1H), 7.78 (d, J = 1.8 Hz, 2H), 7.62 (dd, J = 8.8, 2.3 Hz, 1H), 6.95 (br. s., 1H), 6.60 (d, J = 8.8 Hz, 1H), 5.06 (dt, J = 13.6, 2.8 Hz, 1H), 4.43 (dd, J = 10.4, 3.3 Hz, 1H), 3.70 (br. s., 4H), 3.45 (br. s., 2H), 3.15 (td, J = 12.9, 2.3 Hz, 1H), 3.00 (td, J = 12.8, 2.8 Hz, 1H), 2.78 - 2.94 (m, 2H), 2.54 (br. s., 4H), 2.40 (dd, J = 13.6, 1.5 Hz, 1H). [M+H] calc'd for C21H23N7OS, 422; found, 422.

Compound 90: (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



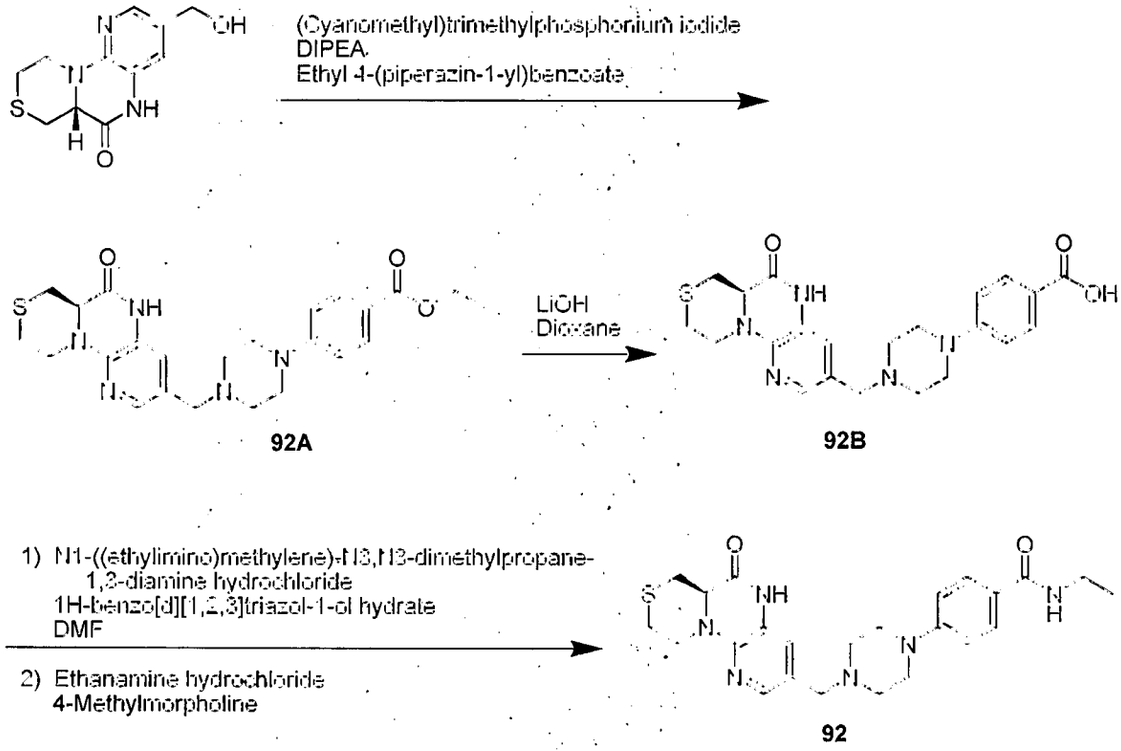
[0517] (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (80.0 mg, 0.318 mmol) was suspended in propionitrile (0.8 mL) and (cyanomethyl)trimethylphosphonium iodide (93.0 mg, 0.382 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (167 ul, 0.955 mmol). To the stirred mixture was then added 4-(piperazin-1-yl)benzonitrile (59.6 mg, 0.318 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was cooled to room temperature and left to sit 48 h. The precipitate was filtered off, washed with ethanol (5 mL) and dried in vacuum to afford the title compound (36.0 mg, 26.9%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 8.26 (br. s., 1H), 7.79 (d, J = 1.8 Hz, 1H), 7.44 - 7.60 (m, 2H), 6.96 (br. s., 1H), 6.76 - 6.91 (m, 2H), 5.05 (dt, J = 13.6, 2.7 Hz, 1H), 4.43 (dd, J = 10.7, 3.2 Hz, 1H), 3.27 - 3.63 (m, 6H), 3.15 (td, J = 12.8, 2.3 Hz, 1H), 3.00 (td, J = 12.8, 2.7 Hz, 1H), 2.77 - 2.93 (m, 2H), 2.59 (br. s., 4H), 2.34 - 2.45 (m, 1H). [M+H] calc'd for C22H24N6OS, 421; found, 421.

Compound 91: (R)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one



[0518] To a suspension of (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (70 mg, 0.279 mmol) in propiononitrile (Volume: 696 µl) was added (cyanomethyl)trimethylphosphonium iodide (81 mg, 0.334 mmol), DIEA (146 µl, 0.836 mmol) and finally 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (64.1 mg, 0.279 mmol). The vial was heated to 90 °C for 12 hours. Cooled to rt and concentrated to a brown residue which was treated with MeOH (5 mL). The precipitate was filtered, the solids were collected, taken up in EtOH (15mL) and refluxed 2 hours. Let sit at RT ON. Filtered, dried in vacuum and retrieved 75.6 mg (63.6%) of the title compound as a white solid. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.80 (d, J = 1.8 Hz, 1H), 7.66 (br. s., 1H), 7.30 (d, J = 3.3 Hz, 5H), 7.04 (br. s., 1H), 6.02 - 6.09 (m, 1H), 5.06 (ddd, J = 13.5, 2.8, 2.7 Hz, 1H), 4.42 (dd, J = 10.5, 3.2 Hz, 1H), 3.54 (br. s., 2H), 3.10 - 3.26 (m, 3H), 3.00 (td, J = 12.8, 2.7 Hz, 1H), 2.85 - 2.92 (m, 1H), 2.75 (br. s., 2H), 2.56 (br. s., 2H), 2.35 - 2.44 (m, 1H). [M+H] calc'd for C22H23ClN4OS, 427; found, 427.

Compound 92: (R)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



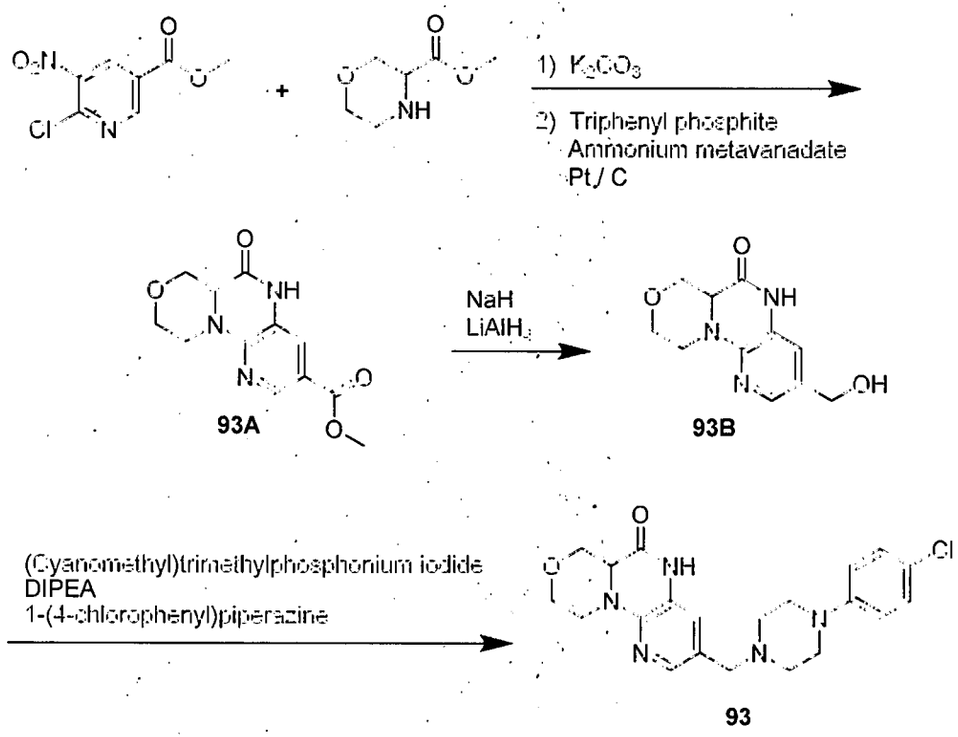
[0519] **Compound 92A: (R)-ethyl 4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate:** To a suspension of (R)-

3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (333 mg, 1.325 mmol) in propiononitrile (3313 µl) was added (cyanomethyl)trimethylphosphonium iodide (336 mg, 1.590 mmol) and DIPEA (694 µl, 3.98 mmol) and finally ethyl 4-(piperazin-1-yl)benzoate (310 mg, 1.325 mmol). The vial was heated to 90 °C for 12 hours. The reaction was then cooled to room temperature, diluted with EtOH (8 ml) and water (1 mL), then filtered. The precipitate was filtered off and dried in vacuum to afford the title compound 508 mg, 82%) as a white solid. [M+H] calc'd for C24H29N5O3S, 468; found, 468.

[0520] Compound 92B: (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid: (R)-ethyl 4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate (130 mg, 0.335 mmol) was taken up in dioxane (2081 µl) and LiOH (1N, 2310 µl, 2.310 mmol) was added. The reaction was stirred 16h at room temperature. The reaction was concentrated in-vacuo and the residue was taken up in water (5 mL) and acidified (4.5N HCl) to pH 4. A tan precipitate formed which was filtered and the solids were collected, dried and determined to be the product (166 mg, 93%) as a tan solid. [M+H] calc'd for C22H25N5O3S, 440; found, 440.

[0521] Compound 92: (R)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (50 mg, 0.114 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (32.7 mg, 0.171 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hydrate (26.1 mg, 0.171 mmol), and DMF (Volume: 0.5mL) were stirred together to give a yellow solution. Ethanamine hydrochloride (9.28 mg, 0.114 mmol) and 4-methylmorpholine (0.065 mL, 0.593 mmol) were added. The reaction was stirred at room temperature for 4 hours. The crude reaction was purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (12.0 mg, 22.6%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.79 (s, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.53 (s, 1H), 6.85 - 7.00 (m, 3H), 5.96 (br. s., 1H), 5.06 (d, J = 13.4 Hz, 1H), 4.43 (dd, J = 10.5, 3.4 Hz, 1H), 3.39 - 3.54 (m, 4H), 3.30 (br. s., 4H), 3.15 (td, J = 12.9, 2.3 Hz, 1H), 3.00 (br. s., 1H), 2.87 (d, J = 10.4 Hz, 2H), 2.60 (br. s., 4H), 2.42 (d, J = 1.5 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H). [M+H] calc'd for C24H30N6O2S, 467; found, 467. MP: 288.9 °C

Compound 93: 3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one



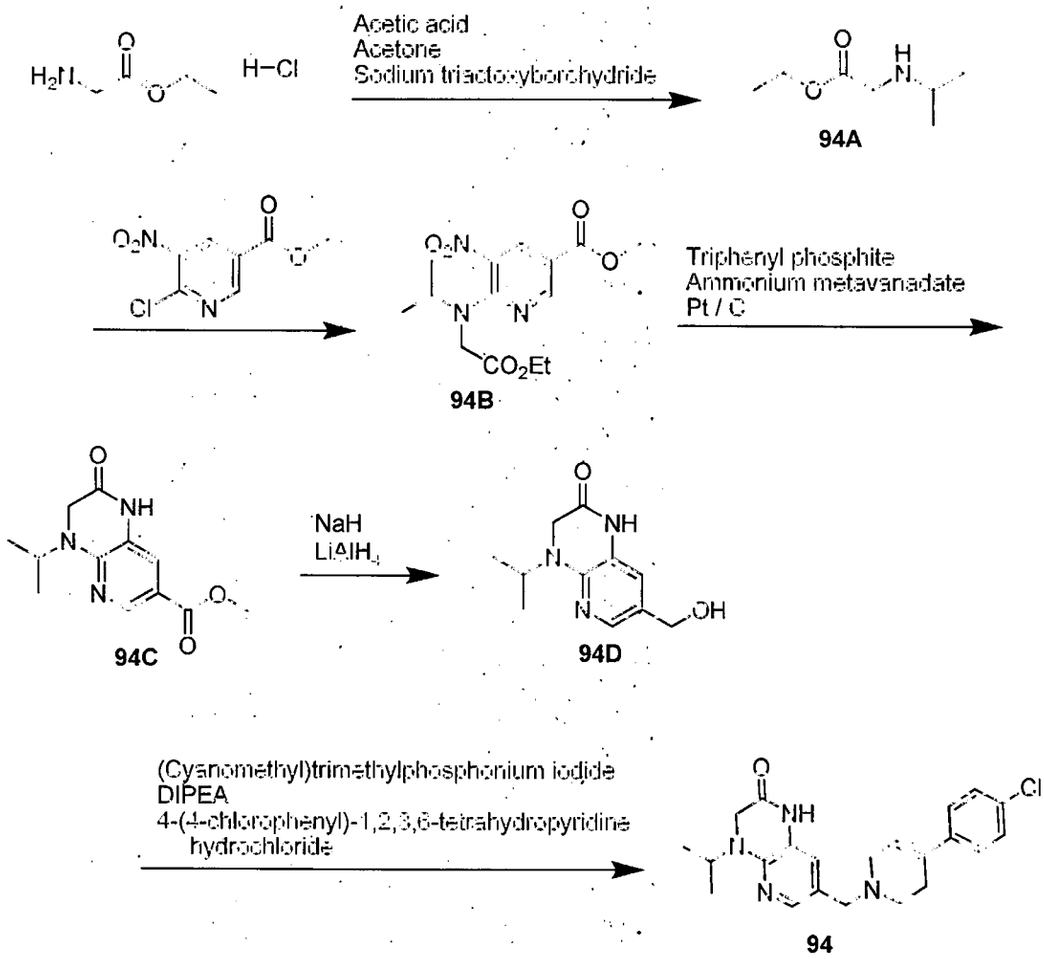
[0522] Compound 93A: methyl 6-oxo-5,6,6a,7,9,10-hexahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazine-3-carboxylate: To a suspension of methyl morpholine-3-carboxylate (2.0 g, 13.73 mmol) in THF was added methyl methyl 6-chloro-5-nitronicotinate (2.71 g, 12.53 mmol) and potassium carbonate (5.19 g, 37.6 mmol). The suspension was heated to reflux for 3 hours. The crude orange solution was allowed to cool to RT and filtered through a pad of celite which was washed with DCM (50 mL) and transferred to a bomb hydroginator. To the solution was added triphenyl phosphite (0.039 ml, 0.125 mmol), platinum (5%, 0.489 g, 0.125 mmol), and ammonium metavanadate (0.117 g, 1.0 mmol). The vessel was sealed and pressurized to 140 psi with stirring for 24 h at room temperature. The vessel was depressurized and the mixture was diluted with DCM (100 mL) and refluxed for 30 minutes. The hot mixture was filtered through celite and concentrated to yield 1.98 g (60%) of the product as a white solid. [M+H] calc'd for C12H13N3O4, 264; found, 264.

[0523] Compound 93B: 3-(hydroxymethyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one: Methyl 6-oxo-5,6,6a,7,9,10-hexahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazine-3-carboxylate (1000 mg, 3.80 mmol) was taken up in tetrahydrofuran (47 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (228 mg, 5.70 mmol, 60% dispersion in mineral oil) and stirred 30 minutes. The reaction

was then cooled to -45 °C and lithium aluminum hydride (11.4 mL, 1M in THF) was added. The reaction was stirred at a temperature between -20 and -10 °C for 1 hour. The reaction was then cooled back to -73 °C and methanol (3 ml) followed by water (1 ml) was added. The reaction was allowed to stir at ambient temperature for 2 hours and then poured into ethyl acetate (400 ml) and water (100 ml). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The filtrate was collected. The layers were separated and the aqueous phase was extracted with ethyl acetate (1 x 100 ml). The organic layers were combined, washed with brine (100 ml), and concentrated to yield 657 mg (73.5%) of the title compound as a white solid. [M+H] calc'd for C11H13N3O3, 236; found, 236.

[0524] Compound 93: 3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one: To a suspension of 3-(hydroxymethyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one (73.2 mg, 0.311 mmol) in propiononitrile (778 µl) was added (cyanomethyl)trimethylphosphonium iodide (91 mg, 0.373 mmol) and DIPEA (163 µl, 0.934 mmol) and finally 1-(4-chlorophenyl)piperazine (61.2 mg, 0.311 mmol). The mixture was heated to 90 °C for 4 hours. The crude product was cooled to RT and left to sit 16 hours, then treated with MeOH (5 mL). The precipitate was collected and refluxed in EtOH (15mL) 2 hours. The suspension was cooled to room temperature and filtered to retrieve the title compound (75.6 mg, 58.7%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ (ppm): 7.82 (d, J = 1.8 Hz, 1H), 7.72 (br. s., 1H), 7.16 - 7.24 (m, 2H), 6.99 (br. s., 1H), 6.77 - 6.89 (m, 2H), 4.41 (dd, J = 11.5, 3.7 Hz, 1H), 4.26 (dd, J = 13.3, 1.6 Hz, 1H), 3.95 - 4.12 (m, 2H), 3.59 - 3.75 (m, 2H), 3.46 (br. s., 2H), 3.16 (br. s., 4H), 2.94 - 3.06 (m, 1H), 2.60 (br. s., 4H). [M+H] calc'd for C21H24ClN5O2, 414; found, 414.

Compound 94: 7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one.



[0525] Compound 94A: Ethyl 2-(isopropylamino)acetate: To a suspension of ethyl 2-aminoacetate hydrochloride (20 g, 143.28 mmol) in THF (400 mL) was added glacial acetic acid (20 mL) followed by acetone (11.59 mL, 151.62 mmol). The reaction was stirred 30 min at room temperature. Sodium triacetoxyborohydride (60.73 g, 286.56 mmol) was added over the course of one hour. The reaction was poured slowly into a vigorously stirred biphasic mixture of water (300 mL) and ethyl acetate (300 mL). The aqueous layer was adjusted to pH 13 using a solution of 50% (weight) NaOH. The mixture was stirred 30 min and poured into a separatory funnel. The organic layer was collected and the aqueous layer was back extracted with ethyl acetate (3 x 200 mL). The organic layers were combined, washed with brine (300 mL), dried with sodium sulfate, and concentrated to yield the title compound (17.6 g, 85%) as a translucent oil which was used in the next step without further purification. [M+H] calc'd for C7H15NO2, 146; found, 146.

[0526] Compound 94B: Methyl 6-((2-ethoxy-2-oxoethyl)(isopropyl)amino)-5-nitronicotinate: Methyl 6-chloro-5-nitronicotinate (2 g, 9.23 mmol) was added to ethyl 2-(isopropylamino) acetate (5.0 g, 34.5 mmol) neat while stirring at room temperature. The viscous yellow reaction was heated to 90°C for one h and then allowed to cool back to room temperature. The reaction was diluted with dichloromethane (20 mL) and purified via column chromatography (220 g SiO2, 20-30% gradient, ethyl acetate in hexanes) to yield the title compound (2.39 g, 83%) as a yellow oil. [M+H] calc'd for C14H19N3O6, 326; found, 326.

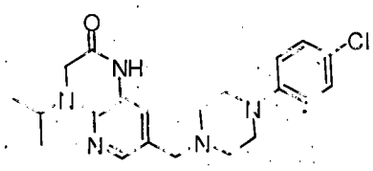
[0527] Compound 94C: Methyl 4-isopropyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate: Methyl 6-((2-ethoxy-2-oxoethyl)(isopropyl)amino)-5-nitronicotinate (2.39 g, 7.35 mmol) was dissolved in dichloromethane (10 mL). To the yellow solution was added ammonium metavanadate (15.0 mg, 1.13 mmol), triphenyl phosphite (aprox 10 ul, 0.032 mmol), and Pt/C (240 mg, 5% w/w). The reaction mixture was pressurized with hydrogen gas (110 psi) and stirred at room temperature for 16 h. The reaction was then depressurized and diluted with dichloromethane (80 mL) which was then refluxed for 30 min. The hot solution was filtered through a pad of celite and washed with hot dichloromethane (3 x 20 mL). The filtrate was concentrated to yield the title compound (1.70 g, 93%) as a white solid. [M+H] calc'd for C12H15N3O3, 250; found, 250..

[0528] Compound 94D: 7-(hydroxymethyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: Methyl 4-isopropyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate (1.3 g, 5.45 mmol) was suspended in tetrahydrofuran (68 mL). The white suspension was cooled to 0 °C and NaH (60% dispersion in mineral oil, 0.327 g, 8.17 mmol) was added. The reaction was removed from the ice bath and allowed to stir at RT for 0.5 h. The solution was then cooled to -78°C and $LiAlH_4$ was added over two min. A temperature between -30 and -20°C was maintained. The reaction was cooled to -78°C and MeOH (2 mL) was added. The reaction was stirred at room temperature 30 min. The reaction was poured into ethyl acetate (400 mL) and water (100 mL), and stirred for 1 hr. The mixture was filtered through medium frit to remove tan solids. The aqueous layer was extracted with ethyl acetate (1X100mL). The organic fractions were combined, washed once with brine (100 mL), dried with sodium sulfate and concentrated to the title compound (1.10 g, 91%) as a white solid. [M+H] calc'd for C11H15N3O2, 222; found, 222.

[0529] Compound 94:-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one: 7-(hydroxymethyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.452 mmol) was taken up as a suspension in propiononitrile (1 mL). Next was added (cyanomethyl)trimethylphosphonium iodide (132 mg,

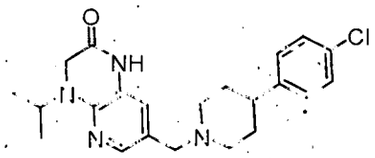
0.542 mmol) followed by DIPEA (0.237 mL, 1.356 mmol). To the stirred white suspension was then added the 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (114 mg, 0.50 mmol). The reaction was heated to 90°C and stirred overnight. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in 3mL DMSO and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (46.9 mg, 26%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.50 (s, 1H), 7.65 (d, J = 1.8 Hz, 1H), 7.40 - 7.46 (m, 2H), 7.34 - 7.39 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.18 (br. s., 1H), 4.76 - 4.87 (m, 1H), 3.31 (s, 2H), 3.40 (s, 2H), 3.01 (d, J = 2.8 Hz, 2H), 2.60 (t, J = 5.6 Hz, 2H), 2.43 (br. s., 2H), 1.12 (d, J = 6.8 Hz, 6H). [M+H] calc'd for C22H25ClN4O, 397; found, 397.

Compound 95: 7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one.



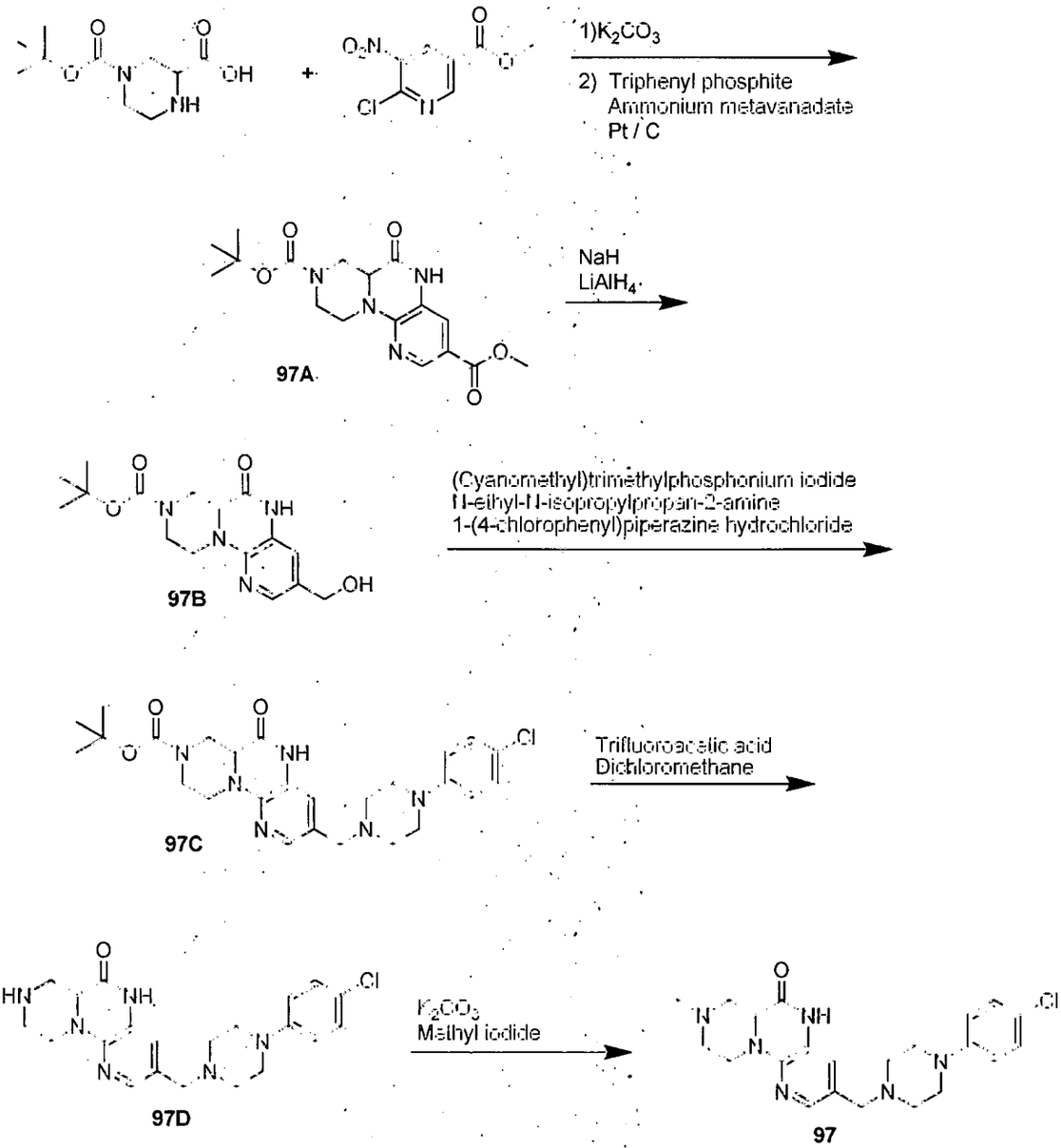
[0530] The 7-(hydroxymethyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.452 mmol) was weighed into a vial and taken up as a suspension in propiononitrile (1 mL). Next was added (cyanomethyl)trimethylphosphonium iodide (132 mg, 0.542 mmol) followed by DIEA (0.237 mL, 1.356 mmol). To the stirred white suspension was then added the 1-(4-chlorophenyl)piperazine hydrochloride (116 mg, 0.50 mmol). The reaction was stirred overnight at 90°C. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in DMSO (3 mL) and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (46.6 mg, 26%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.49 (s, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 9.1 Hz, 2H), 6.97 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 4.74 - 4.87 (m, 1H), 3.31 (s, 2H), 3.33 (d, J = 2.0 Hz, 2H), 3.01 - 3.15 (m, 4H), 2.41 - 2.48 (m, 4H), 1.12 (d, J = 6.8 Hz, 6H). [M+H] calc'd for C21H26ClN5O, 400; found, 400.

Compound 96: 7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one.



[0531] The 7-(hydroxymethyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one (100 mg, 0.452 mmol) suspended in propionitrile (1 mL). To this was added (cyanomethyl)trimethylphosphonium iodide (132 mg, 0.542 mmol) followed by DIEA (0.237 mL, 1.356 mmol) and 4-(4-chlorophenyl)piperidine hydrochloride (115 mg, 0.50 mmol). The reaction was stirred at 90°C overnight. The crude reaction was cooled to room temperature and concentrated to a residue, then taken up in DMSO (3 mL) and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered and dried in vacuum to afford the title compound (28.3 mg, 16%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.49 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.29 - 7.37 (m, 2H), 7.18 - 7.29 (m, 2H), 6.96 (d, J = 2.0 Hz, 1H), 4.75 - 4.87 (m, 1H), 3.81 (s, 2H), 3.32 (d, J = 12.9 Hz, 3H), 2.88 (d, J = 11.1 Hz, 2H), 1.87 - 2.07 (m, 2H), 1.65 - 1.77 (m, 2H), 1.57 (dd, J = 12.4, 3.3 Hz, 2H), 1.10 (d, 6H). [M+H] calc'd for C22H27ClN4O, 399; found, 399.

Compound 97: 7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-2-methyl-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one



[0532] Compound 97A: 10-Oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2,7-dicarboxylic acid 2-tert-butyl ester 7-methyl ester: To a suspension of 4-(tert-butoxycarbonyl)piperazine-2-carboxylic acid (1169 mg, 5.08 mmol) in THF (46 mL) was added methyl 6-chloro-5-nitronicotinate (1000 mg, 4.62 mmol) and K_2CO_3 (638 mg, 4.62 mmol). The suspension was heated to reflux for 2 hours, cooled to room temperature, and filtered through a pad of celite. The celite was washed with DCM (50 mL) and the organic portions were combined. The solution was charged into a bomb hydroginator, then treated

with triphenyl phosphite (0.015 ml, 0.043 mmol), ammonium vanadate (44 mg, 0.330 mmol), and platinum (1.853 g, 0.475 mmol). The reaction was sealed and pressurized with hydrogen gas (150 psi) overnight. The reaction was then diluted with DCM (100 mL) and heated to reflux for 1 hr. The hot mixture was filtered through celite, washed with DCM (50 mL), and concentrated to 1.65 g (96%) of the title compound as an off-white solid. [M+H] calc'd for C17H22N4O5, 363; found, 363.

[0533] Compound 97B: 7-Hydroxymethyl-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester: 10-Oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2,7-dicarboxylic acid 2-tert-butyl ester 7-methyl ester (545 mg, 1.504 mmol) was taken up in tetrahydrofuran (18 mL) in an inert environment. To the stirred suspension at room temperature was added NaH (90 mg, 2.26 mmol, 60% dispersion in mineral oil) and stirred 30 minutes. The reaction was then cooled to -45 °C and lithium aluminum hydride (2.26 ml, 2M in THF) was added. The reaction was stirred at a temperature between -20 and -10 °C for 1 hour. The reaction was then cooled back to -60 °C and MeOH (5 ml) followed by water (1 ml) was added. The reaction was allowed to stir at ambient temperature for 2 hours and then poured into ethyl acetate (400 ml) and water (100 ml). The biphasic mixture was stirred vigorously and then filtered through a medium frit. The filtrate was collected. The layers were separated and the aqueous phase was extracted with ethyl acetate (1 x 100 ml). The organic layers were combined, washed with brine (100 ml), and concentrated to 429.4 mg (96%) of the title compound as an off-white solid. [M+H] calc'd for C16H22N4O4, 335; found, 335

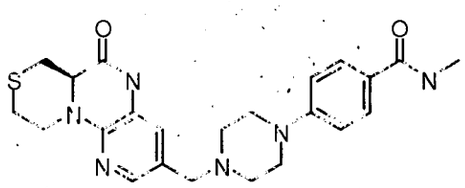
[0534] Compound 97C: 7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester: 7-Hydroxymethyl-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester (22.0 mg, 0.593 mmol) was suspended in propionitrile (1.5 mL) and (cyanomethyl)trimethylphosphonium iodide (174.0 mg, 0.718 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (313 ul, 1.794 mmol). To the stirred mixture was then added 1-(4-chlorophenyl)piperazine hydrochloride (139 mg, 0.598 mmol). The reaction was heated to 90°C with stirring for 16 h. The crude reaction was cooled to room temperature and purified on silica coulumn (24 g, 25% THF in ethyl acetate). The fractions were combined and concentrated to afford 250.9 mg (32%) of the title compound as a brown solid in 30% purity. [M+H] calc'd for C26H33ClN6O3, 513; found, 513.

[0535] Compound 97D: 7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one: 7-[4-(4-Chloro-phenyl)-

piperazin-1-ylmethyl]-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester (250 mg, 0.487 mmol) was dissolved in dichloromethane (5 mL) and trifluroacetic acid (3 mL) was added while stirring at room temperature. The reaction was stirred for 16 h and concentrated to a residue. The residue was dissolved in DMF and purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (17.8 mg, 8.8%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.68 (s, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.14 - 7.30 (m, 2H), 7.03 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 4.33 (d, J = 11.4 Hz, 1H), 3.97 (dd, J = 11.0, 3.4 Hz, 1H), 3.45 (dd, J = 12.5, 2.9 Hz, 4H), 3.32 - 3.36 (m, 4H), 3.16 (d, J = 9.6 Hz, 1H), 3.06 - 3.13 (m, 4H), 2.72 - 2.87 (m, 3H). [M+H] calc'd for C26H33ClN6O3, 413; found, 413.

[0536] Compound 97: 7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-2-methyl-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one: To a solution of 7-[4-(4-Chloro-phenyl)-piperazin-1-ylmethyl]-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one (139 mg, 0.337 mmol) in DMF (3.4 mL) cooled to 0 °C was added potassium carbonate (233 mg, 1.683 mmol) and methyl iodide (2 M in THF, 0.168 mL). The reaction was stirred 1 h at 0 °C and filtered through celite. The filtrate was purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were combined and concentrated until a white solid precipitated. The precipitate was filtered off and dried in vacuum to afford the title compound (4.6 mg, 3.2%) as a white solid. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.59 (s, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.15 - 7.28 (m, 2H), 7.01 (d, J = 2.0 Hz, 1H), 6.85 - 6.97 (m, 2H), 4.17 - 4.30 (m, 1H), 3.88 (dd, J = 10.6, 3.3 Hz, 1H), 3.37 (s, 2H), 3.14 - 3.20 (m, 1H), 3.06 - 3.14 (m, 4H), 2.84 (d, J = 11.6 Hz, 1H), 2.74 (td, J = 12.4, 3.0 Hz, 1H), 2.44 - 2.48 (m, 4H), 2.26 (s, 3H), 1.91 - 2.02 (m, 2H). [M+H] calc'd for C22H27ClN6O, 427; found, 427.

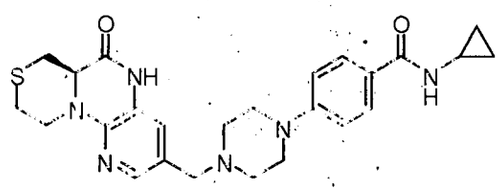
Compound 98: (R)-N-methyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0537] In a vial equipped with a stir bar was charged (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid

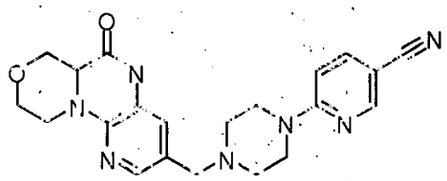
(50 mg, 0.114 mmol) was taken up in DMF (1.14 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (59 µl, 0.34 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (64.9 mg, 0.171 mmol), and methanamine hydrochloride (8.45 mg, 0.125 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer). The fractions were collected and lyophilized to yield 25.1 mg (49%) of the product as a white solid. ^{1}H NMR (CHLOROFORM-d) δ: 8.37 (br. s., 1H), 7.58 - 7.89 (m, 3H), 7.15 (br. s., 1H), 6.87 (d, J = 8.8 Hz, 2H), 6.07 (d, J = 4.5 Hz, 1H), 5.06 (dt, J = 13.6, 2.5 Hz, 1H), 4.42 (dd, J = 10.1, 3.8 Hz, 1H), 3.55 (br. s., 2H), 3.36 (br. s., 4H), 3.08 - 3.24 (m, 1H), 2.56 - 3.08 (m, 8H), 2.40 (dd, J = 13.5, 1.1 Hz, 1H), 1.74 (br. s., 2H). [M+H] calc'd for C23H28N6O2S, 453; found, 453.

Compound 99: (R)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



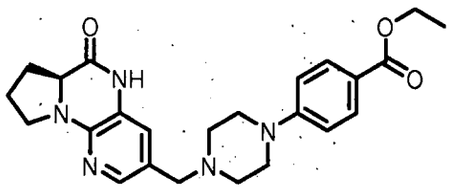
[0538] In a vial equipped with a stir bar was charged (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (50 mg, 0.114 mmol) was taken up in DMF (1.14 mL). To the mixture was added N-ethyl-N-isopropylpropan-2-amine (59 µl, 0.34 mmol), O-(7-Azabenzotriazole-1-yl)-N, N,N'N'-tetramethyluronium hexafluorophosphate (64.9 mg, 0.171 mmol), and cyclopropanamine (9.16uL, 0.125 mmol). The reaction was stirred at room temperature overnight. The reaction was purified via HPLC (55-90% acetonitrile in water, ammonium bicarbonate buffer).The fractions were collected and lyophilized to yield 25.1 mg (49%) of the product as a white solid^{1}H NMR (CHLOROFORM-d) δ: 8.42 (br. s., 1H), 7.78 (d, J = 1.5 Hz, 1H), 7.65 (d, J = 8.8 Hz, 2H), 7.13 (br. s., 1H), 6.85 (d, J = 9.1 Hz, 2H), 6.17 (d, J = 2.3 Hz, 1H), 5.05 (ddd, J = 13.5, 2.7, 2.5 Hz, 1H), 4.42 (dd; J = 10.4, 3.5 Hz, 1H), 3.53 (br. s., 2H), 3.34 (br. s., 4H), 3.14 (td, J = 12.9, 2.3 Hz, 1H), 2.99 (td, J = 12.8, 2.7 Hz, 1H), 2.78 - 2.93 (m, 3H), 2.68 (br. s., 4H), 2.39 (dd, J = 13.6, 1.3 Hz, 1H), 0.80 - 0.90 (m, 2H), 0.54 - 0.67 (m, 2H). [M+H] calc'd for C23H28N6O2S, 479; found, 479.

Compound 100: 6-(4-((6-oxo-5,6,6a,7,9,10-hexahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile



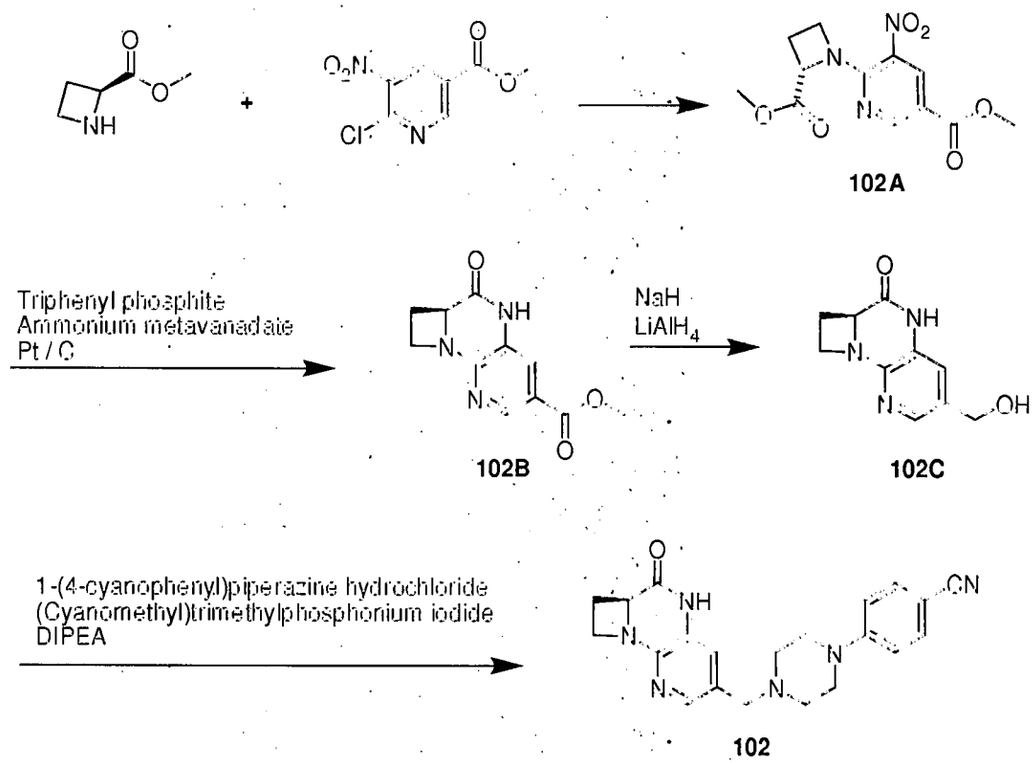
[0539] 3-(hydroxymethyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one (70.0 mg, 0.298 mmol) was suspended in propionitrile (0.74 mL) and (cyanomethyl)trimethylphosphonium iodide (37.0 mg, 0.357 mmol) was added followed by N-ethyl-N-isopropylpropan-2-amine (115 ul, 0.893 mmol). To the stirred mixture was then added 6-(piperazin-1-yl)nicotinonitrile (56.0 mg, 0.298 mmol). The reaction was heated to 90°C with stirring for 16 h. The reaction was cooled to room temperature and left to sit 48 h. The precipitate was filtered off, washed with methanol (5 mL) and dried in vacuum to afford the title compound (72.5 mg, 60.1%) as a white solid. ^{1}H NMR (CHLOROFORM-d) δ: 8.41 (d, J = 1.8 Hz, 1H), 8.20 (br. s., 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 9.0, 2.4 Hz, 1H), 6.99 (br. s., 1H), 6.59 (d, J = 9.1 Hz, 1H), 4.42 (dd, J = 11.5, 3.7 Hz, 1H), 4.26 (dd, J = 13.3, 1.6 Hz, 1H), 3.95 - 4.12 (m, 2H), 3.58 - 3.80 (m, 6H), 3.45 (s, 2H), 2.92 - 3.08 (m, 1H), 2.53 (br. s., 4H). [M+H] calc'd for C21H23N7O2, 406; found, 406.

Compound 101: (S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate



[0540] Compound 101 was prepared using a procedure analogous to that described in connection with compound 23. [M+H] calc'd for $C_{24}H_{29}N_5O_3$ 436; found, 436.1.

Compound 102: (S)-4-(4-((6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0541] Compound 102A: (S)-methyl 6-(2-(methoxycarbonyl)azetidin-1-yl)-5-nitronicotinate: (S)-methyl azetidine-2-carboxylate hydrochloride (1 g, 6.60 mmol) was diluted with Tetrahydrofuran (Volume: 20 ml) and treated with TRIETHYLAMINE (0.919 ml, 6.60 mmol). The reaction mixture was stirred vigorously and sonicated periodically, until a fine suspension resulted. This was stirred for 1 h and filtered through a small plug of celite. The plug was washed well with THF (20 mL) and the combined filtrate and washes were treated with methyl 6-chloro-5-nitronicotinate (0.714 g, 3.30 mmol). The reaction mixture was concentrated in vacuo and heated briefly (5 min) to 80 °C. LCMS showed complete conversion. The reaction mixture was diluted with DCM (10 mL) and purified using flash column chromatography on silica gel (80 g SiO2, 20-30% ethyl acetate in hexanes) to afford the title compound (S)-methyl 6-(2-(methoxycarbonyl)azetidin-1-yl)-5-nitronicotinate (0.90 g, 3.05 mmol, 92 % yield) as a yellow oil. [M+H] calc'd for $C_{12}H_{15}N_3O_6$, 295; found, 295.

[0542] Compound 102B: (S)-methyl 6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate: (S)-methyl 6-(2-(methoxycarbonyl)azetidin-1-yl)-5-nitronicotinate (0.90 g, 3.05 mmol) was dissolved in dichloromethane (Volume: 15.24 ml) and

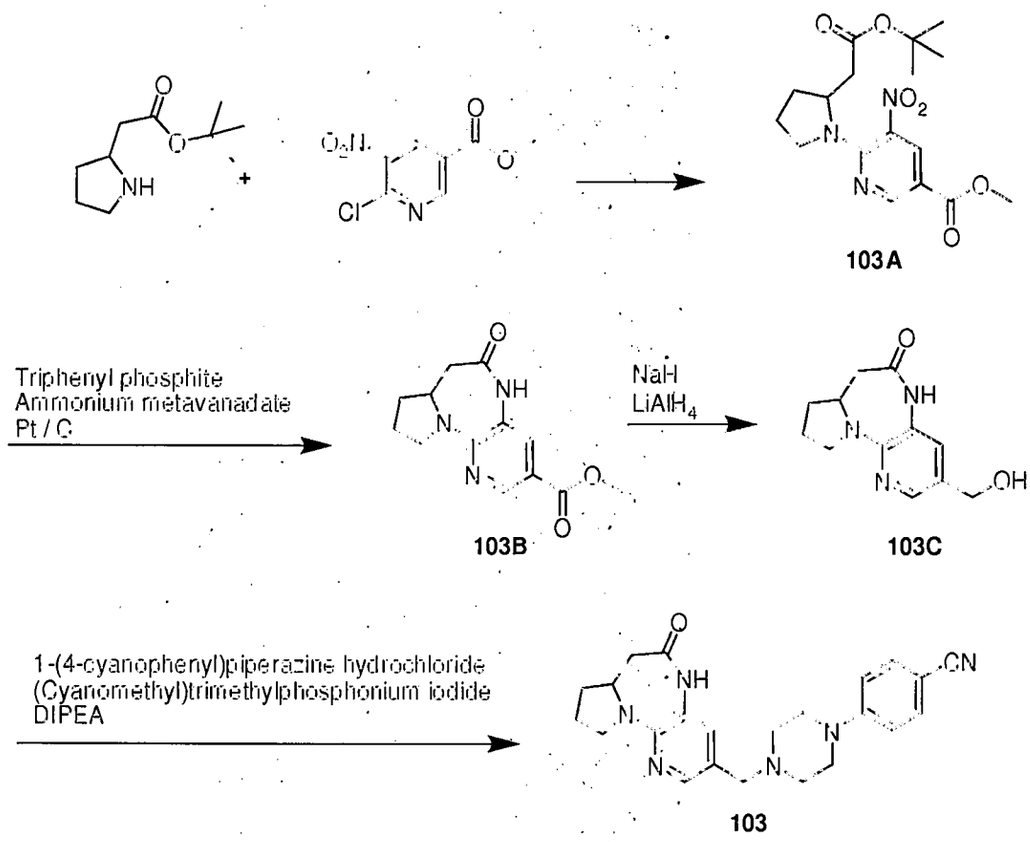
to this solution was added triphenyl phosphite (9.46 mg, 0.030 mmol), ammonium metavanadate (0.021 g, 0.183 mmol) and Pt/C (5% wt.) (0.119 g, 0.030 mmol). The reaction mixture was hydrogenated at 100 psi at 25 °C for 2h. LCMS showed complete conversion of the starting material to the corresponding amine, but no cyclization product was observed. The reaction mixture was filtered through a short plug of celite and the plug and precipitate were washed well with dichloromethane (30 mL) and methanol (20 mL). The combined filtrates were concentrated in vacuo (LC: CR1) and dissolved in AcOH (5 mL) (LC: AA-rt). This solution was heated to 80 °C for 5 min (LCMS - AA-90C-5min - complete conversion to the desired product) and concentrated in vacuo. The residue was crystallized with ethyl ether (20 mL) and sonicated until a fine suspension was obtained The precipitate was filtered off and dried in vacuum to afford (S)-methyl 6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate (0.5840, 2.504 mmol, 82 % yield) as a light pink solid. [M+H] calc'd for $C_{11}H_{11}N_3O_3$, 234; found, 234.

[0543] Compound 102C: (S)-3-(hydroxymethyl)-7,8-dihydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-6(6aH)-one: (S)-methyl 6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate (0.570 g, 2.444 mmol) was suspended in Tetrahydrofuran (Volume: 8.15 ml) under nitrogen atmosphere and NaH (196 mg, 4.9 mmol) was added in several portions over 2 min. The reaction mixture was stirred at room temperature for 10 min and cooled to below -50 °C. lithium aluminum hydride (2.200 ml, 4.40 mmol) was added over the period of 5 min and the reaction was kept at a temperature between -30 and -20 °C for 1 h (LCMS: >95% conversion). The mixture was cooled to below -50 °C and MeOH (4 mL) was added. Water (1 mL) was added and the reaction mixture was stirred at rt for 10 min. Rochelle salt (20% solution) was added (10 mL) and the mixture was extracted with EtOAc (3x30 mL) and THF (3X100 mL). The combined organic extracts were dried (Na2SO4 and MgSO4), filtered and concentrated in vacuo. The residue was suspended in THF/Ethyl ether (1:1, 20 mL), filtered off and dried in vacuum to afford (S)-3-(hydroxymethyl)-7,8-dihydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-6(6aH)-one (0.332 g, 1.613 mmol, 66.2 % yield) as a light tan solid. [M+H] calc'd for $C_{10}H_{11}N_3O_2$, 205; found, 205.

[0544] Compound 102: (S)-4-(4-((6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile: (S)-3-(hydroxymethyl)-7,8-dihydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-6(6aH)-one (103 mg, 0.5 mmol), 4-(piperazin-1-yl)benzonitrile (108 mg, 0.575 mmol), (cyanomethyl)trimethylphosphonium iodide (207 mg, 0.850 mmol) and N,N-diisopropylethylamine (0.437 ml, 2.500 mmol) were suspended in Propiononitrile (Volume: 1.502 ml) and heated in a closed vial at 90 °C for 23h. The reaction

mixture was cooled, diluted with MeOH (2 mL) and purified using preparative HPLC (basic phase). The fractions containing product were concentrated in vacuo and crystallized from water-methanol (3 mL, ~5:1) The precipitate was filtered and dried in vacuum to afford (S)-4-(4-((6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile (11.7 mg, 0.031 mmol, 6.25 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 2.37 - 2.47 (m, 4 H) 2.68 - 2.80 (m, 1 H) 2.94 (tt, *J*=10.67, 7.26 Hz, 1 H) 3.30 (d, *J*=4.80 Hz, 4 H) 3.36 (s, 2 H) 3.87 - 4.00 (m, 1 H) 4.21 (q, *J*=7.66 Hz, 1 H) 4.93 (t, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.00 (d, *J*=9.09 Hz, 2 H) 7.57 (d, *J*=9.09 Hz, 2 H) 7.65 (d, *J*=1.77 Hz, 1 H) 10.34 (s, 1 H). [M+H] calc'd for $C_{21}H_{22}N_6O$, 374; found, 374.

Compound 103: 4-(4-((6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0545] Compound 103A: Methyl 6-(2-(2-tert-butoxy-2-oxoethyl)pyrrolidin-1-yl)-5-nitronicotinate: Tert-butyl 2-(pyrrolidin-2-yl)acetate (1.00 g, 5.40 mmol) was added to a solution of methyl 6-chloro-5-nitronicotinate (1.169 g, 5.40 mmol) in THF (Volume: 10 ml). The reaction mixture was stirred at rt for 1h and K_2CO_3 (0.760 g, 5.50 mmol) was added. The reaction mixture was stirred for 2h and triethylamine (0.379 ml, 2.70 mmol) was added. The

mixture was stirred for 1h, filtered and concentrated in vacuo. Flash column chromatography on silica gel (120 g SiO2, hexanes : ethyl acetate 9:1) afforded methyl 6-(2-(2-tert-butoxy-2-oxoethyl)pyrrolidin-1-yl)-5-nitronicotinate (1.79 g, 4.90 mmol, 91 % yield) as a yellow oil. [M+H] calc'd for $C_{17}H_{22}N_3O_6$, 365; found, 365.

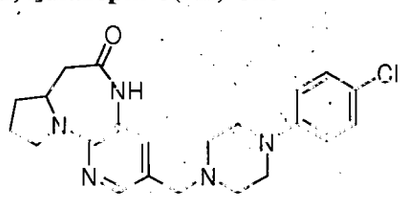
[0546] Compound 103B: Methyl 6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepine-3-carboxylate: Methyl 6-(2-(2-tert-butoxy-2-oxoethyl)pyrrolidin-1-yl)-5-nitronicotinate (1.79 g, 4.90 mmol) was dissolved in dichloromethane (Volume: 24.49 ml) and to this solution was added triphenyl phosphite (0.015 g, 0.049 mmol), ammonium metavanadate (0.034 g, 0.294 mmol) and Pt/C (5% wt.) (0.191 g, 0.049 mmol). The reaction mixture was hydrogenated at 100 psi at 25 °C for 3h. The reaction mixture was filtered through a short plug of celite and the plug and precipitate were washed well with dichloromethane (30 mL). The combined filtrates were concentrated in vacuo and dissolved in AcOH (7 mL). This solution was heated to 90 °C for 10 min and concentrated in vacuo. The residue was crystallized with ethyl ether (20 mL) and sonicated until a fine suspension was obtained The precipitate was filtered off and dried in vacuum to afford methyl 6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepine-3-carboxylate (0.927 g, 3.55 mmol, 72.4 % yield) as a light pink solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.55 - 1.71 (m, 1 H) 1.74 - 1.89 (m, 1 H) 1.89 - 1.99 (m, 1 H) 2.19 (d, *J*=5.81 Hz, 1 H) 2.59 (dd, *J*=14.78, 1.64 Hz, 1 H) 2.77 (dd, *J*=14.78, 9.98 Hz, 1 H) 3.56 - 3.67 (m, 1 H) 3.67 - 3.76 (m, 1 H) 3.78 (s, 3 H) 3.99 (td, *J*=9.85, 5.56 Hz, 1 H) 7.64 (d, *J*=2.02 Hz, 1 H) 8.40 (d, *J*=2.02 Hz, 1 H) 9.73 (d, 1 H) [M+H] calc'd for $C_{15}H_{15}N_3O_3$, 261; found, 261.

[0547] Compound 103C: 3-(Hydroxymethyl)-7a,8,9,10-tetrahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one: Methyl 6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepine-3-carboxylate (0.900 g, 3.44 mmol) was suspended in THF (Volume: 11.48 ml) under nitrogen atmosphere and NaH (276 mg, 6.9 mmol) was added in several portions over 2 min. The reaction mixture was stirred at room temperature for 10 min and cooled to below -50 °C. aluminum(III) lithium hydride (3.10 ml, 6.20 mmol) was added over the period of 5 min and the reaction was kept at a temperature between -30 and -20 °C for 1 h (LCMS: >95% conversion). The mixture was cooled to below -50 °C and MeOH (4 mL) was added. Water (1 mL) was added and the reaction mixture was stirred at rt for 10 min. Rochelle salt (20% solution) was added (10 mL) and the mixture was extracted with THF (4X10 mL). The combined organic extracts were dried (Na2SO4 and MgSO4), filtered and concentrated in vacuo. The residue was recrystallized from THF/Ethyl ether (1:1, 20 mL). The solid was filtered off and dried in vacuum to afford 3-(hydroxymethyl)-7a,8,9,10-tetrahydro-

5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one (0.654 g, 2.80 mmol, 81 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.53 (m, *J*=11.62, 11.62, 9.73, 6.69 Hz, 1 H) 1.74 - 1.85 (m, 1 H) 1.86 - 1.96 (m, 1 H) 2.14 (m, *J*=11.91, 5.98, 5.98, 1.89 Hz, 1 H) 2.52 - 2.53 (m, 1 H) 2.58 - 2.67 (m, 1 H) 3.49 (ddd, *J*=10.93, 8.15, 2.15 Hz, 1 H) 3.66 (td, *J*=10.61, 6.82 Hz, 1 H) 3.81 - 3.93 (m, 1 H) 4.31 (d, *J*=5.31 Hz, 2 H) 5.01 (t, *J*=5.43 Hz, 1 H) 7.14 (d, *J*=2.02 Hz, 1 H) 7.77 (d, *J*=2.02 Hz, 1 H) 9.60 (d, 1 H). [M+H] calc'd for $C_{12}H_{15}N_3O_2$, 233; found, 233.

[0548] Compound 103: 4-(4-((6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-3-yl)methyl)piperazin-1-yl)benzonitrile: 4-(4-((6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-3-yl)methyl)piperazin-1-yl)benzonitrile: 3-(hydroxymethyl)-7a,8,9,10-tetrahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one (100 mg, 0.429 mmol), 4-(piperazin-1-yl)benzonitrile (96 mg, 0.514 mmol), (cyanomethyl)trimethylphosphonium iodide (167 mg, 0.685 mmol) and N,N-diisopropylethylamine (0.374 mL, 2.141 mmol) were suspended in propionitrile (Volume: 2 mL) and heated in a closed vial at 90 °C for 5h. The reaction mixture was cooled, diluted with DMSO (2 mL) and purified using preparative HPLC (basic phase, 25-95% ACN). The fractions containing product were concentrated in vacuo and crystallized from water (5 mL). The precipitate was filtered and dried in vacuum to afford 4-(4-((6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-3-yl)methyl)piperazin-1-yl)benzonitrile (124.2 mg, 0.309 mmol, 72.1 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.51 - 1.65 (m, 1 H) 1.72 - 1.86 (m, 1 H) 1.87 - 1.97 (m, 1 H) 2.14 (qd, *J*=5.81, 4.04 Hz, 1 H) 2.40 - 2.48 (m, 4 H) 2.52 - 2.59 (m, 1 H) 2.66 (dd, 1 H) 3.30 (br. s., 4 H) 3.33 - 3.40 (m, 2 H) 3.45 - 3.54 (m, 1 H) 3.66 (td, *J*=10.61, 6.82 Hz, 1 H) 3.88 (td, *J*=9.47, 6.06 Hz, 1 H) 7.00 (d, *J*=9.35 Hz, 2 H) 7.14 (d, *J*=2.02 Hz, 1 H) 7.57 (d, *J*=9.09 Hz, 2 H) 7.75 (d, *J*=2.02 Hz, 1 H) 9.56 (d, 1 H). [M+H] calc'd for $C_{23}H_{26}N_6O$, 402; found, 402.

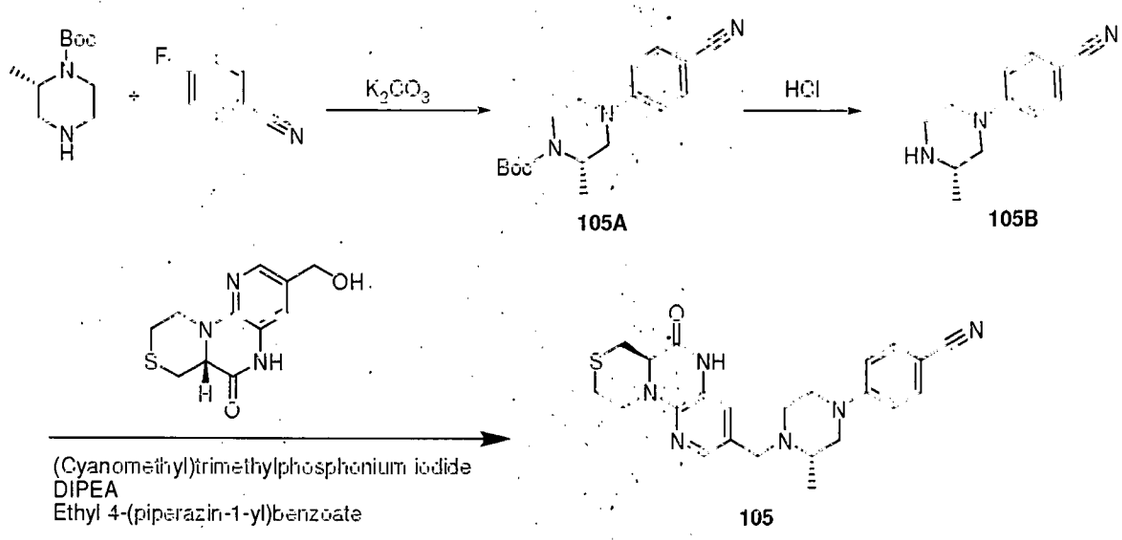
Compound 104: 3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7a,8,9,10-tetrahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one



[0549] Compound 104 was prepared using a procedure analogous to that described in connection with compound 103, except that 1-(4-chlorophenyl)piperazine hydrochloride was

used instead of 1-(4-cyanophenyl)piperazine hydrochloride. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.51 - 1.65 (m, 1 H) 1.70 - 1.87 (m, 1 H) 1.87 - 1.98 (m, 1 H) 2.09 - 2.21 (m, 1 H) 2.40 - 2.48 (m, 4 H) 2.55 (d, 1 H) 2.66 (dd, 1 H) 3.04 - 3.15 (m, 4 H) 3.34 (dd, 2 H) 3.46 - 3.55 (m, 1 H) 3.66 (td, *J*=10.55, 6.69 Hz, 1 H) 3.83 (td, *J*=9.35, 6.06 Hz, 1 H) 6.92 (d, *J*=9.09 Hz, 2 H) 7.14 (d, *J*=1.77 Hz, 1 H) 7.21 (d, *J*=9.09 Hz, 2 H) 7.76 (d, *J*=1.77 Hz, 1 H) 9.55 (br. s., 1 H). [M+H] calc'd for $C_{23}H_{26}ClN_5O$, 411; found, 411.

Compound 105: 4-((S)-3-methyl-4-(((R)-6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile

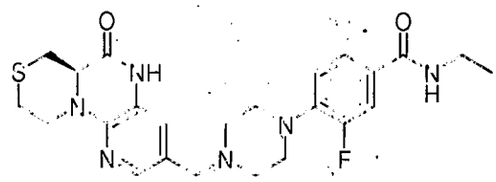


[0550] Compound 105A: (S)-tert-butyl 4-(4-cyanophenyl)-2-methylpiperazine-1-carboxylate: (S)-tert-butyl 2-methylpiperazine-1-carboxylate (1g, 4.99 mmol), 4-fluorobenzonitrile (0.605 g, 4.99 mmol), and K_2CO_3 (0.897 g, 6.49 mmol) were combined into a vial equipped with a stir bar. The reaction was heated to 110 °C for 48 h. Cooled to RT, diluted with EA and filtered. Concentrated to a clear oil and purified on silica gel (80 g, 10-20% EA in Hex) to give a clear oil (450 mg, 30% yield) which became a crystalline solid upon sitting. [M+H] calc'd for $C_{17}H_{23}N_3O_2$, 301; found, 301.

[0551] Compound 105B: (S)-4-(3-methylpiperazin-1-yl)benzonitrile hydrochloride: (S)-tert-butyl 4-(4-cyanophenyl)-2-methylpiperazine-1-carboxylate (0.404 g, 1.340 mmol) was diluted with 4.0M HCl in dioxane (3 mL) and stirred for 30 min. The thick white precipitate that formed was diluted with ethyl ether (10 mL) and stirred until a fine suspension resulted. The precipitate was filtered under nitrogen and dried in vacuum to afford a white solid (300 mg, 94%). [M+H] calc'd for $C_{12}H_{15}N_3$, 201; found, 201.

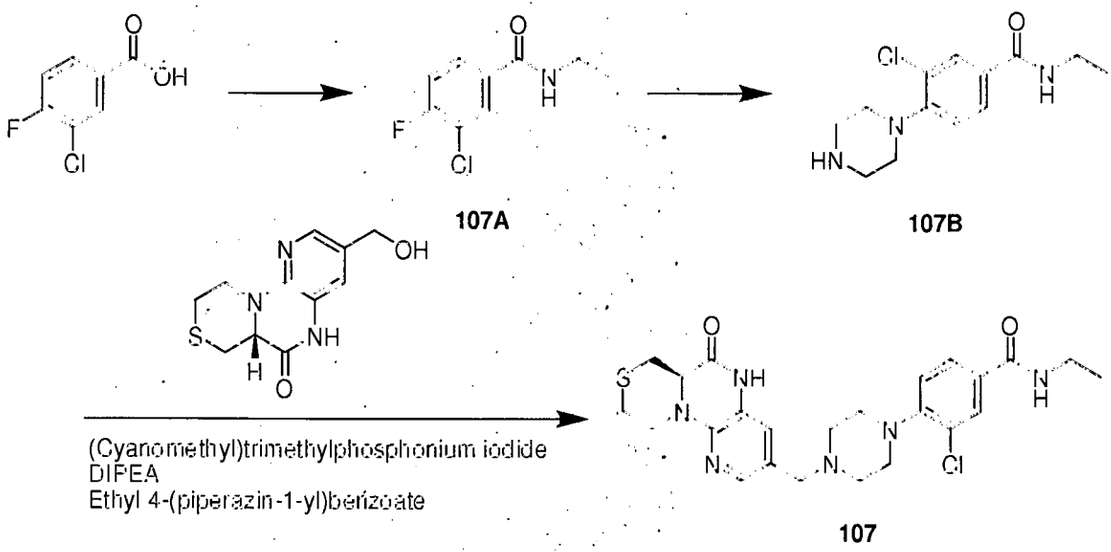
[0552] Compound 105: 4-((S)-3-methyl-4-(((R)-6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile: To a suspension of (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (100 mg, 0.617 mmol) in propiononitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (180 mg, 0.74 mmol) and DIEA (0.323 ml, 1.80 mmol) and finally (S)-4-(3-methylpiperazin-1-yl)benzonitrile hydrochloride (0.147 g, 0.617 mmol). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic) to give the product as a tan solid (53 mg, 22% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.62 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 9.1 Hz, 2H), 6.92 - 7.11 (m, 3H), 4.37 (dt, J = 13.6, 2.7 Hz, 1H), 4.25 (dd, J = 10.9, 3.0 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.66 (d, J = 10.6 Hz, 1H), 3.53 (d, J = 12.6 Hz, 1H), 2.87 - 3.12 (m, 3H), 2.64 - 2.83 (m, 5H), 2.39 - 2.48 (m, 2H), 2.06 - 2.19 (m, 1H), 1.14 (d, J = 6.1 Hz, 3H). [M+H] calc'd for $C_{23}H_{26}N_6OS$, 434; found, 434.

Compound 106: (R)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0553] To a suspension of (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (146 mg, 0.581 mmol) in propiononitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (169 mg, 0.697 mmol) and N-ethyl-3-fluoro-4-(piperazin-1-yl)benzamide hydrochloride (167 mg, 0.581 mmol) and DIEA (304 µl, 1.743 mmol)). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (97 mg, 34% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.66 (s, 1H), 8.35 (t, J = 5.6 Hz, 1H), 7.69 (d, J = 1.3 Hz, 1H), 7.55 - 7.65 (m, 2H), 6.97 - 7.08 (m, 2H), 4.38 (dt, J = 13.6, 2.7 Hz, 1H), 4.27 (dd, J = 10.9, 3.0 Hz, 1H), 3.38 (d, J = 2.0 Hz, 2H), 3.20 - 3.30 (m, 2H), 2.95 - 3.15 (m, 5H), 2.65 - 2.87 (m, 3H), 2.51 (br. s., 4H), 2.45 (dd, J = 13.4, 1.8 Hz, 1H), 1.09 (t, J = 7.2 Hz, 3H). [M+H] calc'd for $C_{24}H_{29}FN_6O_2S$, 484; found, 484.

Compound 107: (R)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



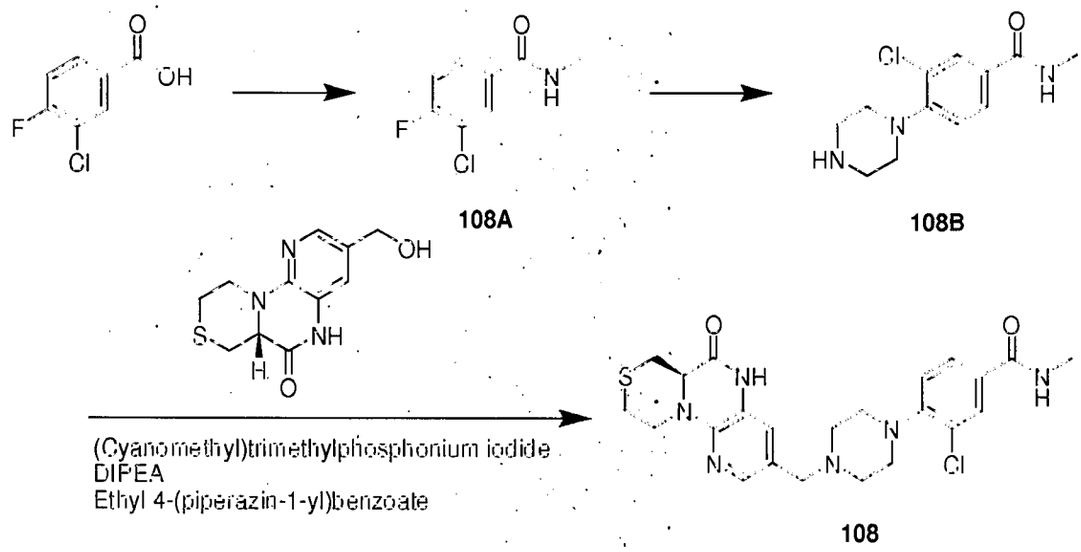
[0554] **Compound 107A:** 3-chloro-4-fluoro-N-ethylbenzamide: Using ethanamine hydrochloride and 3-chloro-4-fluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (77% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, J=7.20 Hz, 3 H) 3.28 (qd, J=7.16, 5.56 Hz, 2 H) 7.53 (t, J=8.84 Hz, 1 H) 7.87 (ddd, J=8.72, 4.80, 2.15 Hz, 1 H) 8.06 (dd, J=7.33, 2.27 Hz, 1 H) 8.61 (t, J=4.67 Hz, 1 H). ESI-MS: m/z 202.0 $(M+H)^+$. mp = 101.7-101.8°C.

[0555] **Compound 107B:** 3-chloro-N-ethyl-4-(piperazin-1-yl)benzamide: Using 3-chloro-4-fluoro-N-ethylbenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (74% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, J=7.20 Hz, 3 H) 2.24 (br. s., 1 H) 2.81 - 2.87 (m, 4 H) 2.90 - 2.98 (m, 4 H) 3.26 (qd, J=7.24, 5.56 Hz, 2 H) 7.15 (d, J=8.59 Hz, 1 H) 7.77 (dd, J=8.34, 2.02 Hz, 1 H) 7.87 (d, J=2.27 Hz, 1 H) 8.43 (t, J=5.56 Hz, 1 H). ESI-MS. m/z 268.2 $(M+H)^+$. mp = 117.3-118.7 °C.

[0556] **Compound 107**: (R)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: To a suspension of (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (154 mg, 0.613 mmol) in propionontrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (179 mg, 0.735 mmol) and 3-chloro-N-ethyl-4-(piperazin-1-yl)benzamide hydrochloride (186 mg, 0.613 mmol) and DIEA (321 µl, 1.838 mmol). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1

ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (80 mg, 26% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.67 (s, 1H), 8.43 (t, J = 5.6 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.76 (dd, J = 8.6, 2.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.17 (d, J = 8.3 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 4.33 (dt, J = 13.6, 2.7 Hz, 1H), 4.27 (dd, J = 10.7, 3.2 Hz, 1H), 3.40 (s, 2H), 3.18 - 3.30 (m, 2H), 2.90 - 3.16 (m, 5H), 2.67 - 2.85 (m, 3H), 2.52 (br. s., 4H), 2.45 (dd, J = 13.5, 1.6 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H). [M+H] calc'd for $C_{24}H_{29}ClN_6O_2S$, 501; found, 501.

Compound 108: (R)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



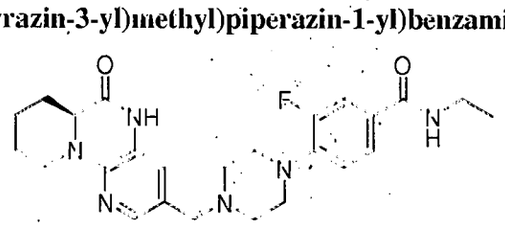
[0557] Compound 108A: 3-chloro-4-fluoro-N-methylbenzamide: To a suspension of 3-chloro-4-fluorobenzoic acid (25.0 g, 143 mmol), Methylamine hydrochloride (11.60 g, 172 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (41.2 g, 215 mmol), and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (32.9 g, 215 mmol) in DMF (Volume: 150 mL) was added 4-methylmorpholine (79 mL, 716 mmol) at 23 °C. The reaction was stirred at 23 °C for 3 hr. The reaction mixture was diluted with water (500 mL) to furnish a yellow-orange solution. The solution was stirred overnight at 23 °C affording a suspension. The suspension was filtered, washed with H2O (3 x 100 mL), and the resulting solid was dried *in vacuo* at 30 °C to provide 3-chloro-4-fluoro-N-methylbenzamide (14.24g, 76 mmol, 53.0 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.73 (d, *J*=4.55 Hz, 3 H)

7.53 (t, *J*=8.97 Hz, 1 H) 7.86 (ddd, *J*=8.59, 4.30, 2.27 Hz, 1 H) 8.04 (dd, *J*=7.20, 2.15 Hz, 1 H) 8.51 - 8.65 (m, 1 H). ESI-MS: m/z 133.0 $(M+H)^+$. Mp = 108.3-110.0 °C.

[0558] **Compound 108B: 3-chloro-N-methyl-4-(piperazin-1-yl)benzamide:** Using 3-chloro-4-fluoro-N-methylbenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (29% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.59 - 2.70 (m, 2 H) 2.73 - 2.79 (m, 3 H) 2.87 - 2.93 (m, 2 H) 2.95 - 3.01 (m, 2 H) 3.03 - 3.11 (m, 2 H) 3.23 - 4.03 (m, 1 H) 7.14 - 7.23 (m, 1 H) 7.77 (dd, *J*=8.46, 2.15 Hz, 1 H) 7.85 - 7.90 (m, 1 H) 8.38 - 8.48 (m, 1 H). ESI-MS: m/z 254.2 $(M+H)^+$. mp=176.4-189.1°C.

[0559] **Compound 108:** (R)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: To a suspension of (R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one (97 mg, 0.386 mmol) in propiononitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (113 mg, 0.463 mmol) and 3-chloro-N-methyl-4-(piperazin-1-yl)benzamide hydrochloride (112 mg, 0.386 mmol) and DIEA (202 µl, 1.158 mmol). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (21 mg, 11% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.67 (s, 1H), 8.41 (d, J = 4.5 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 8.6, 2.0 Hz, 1H), 7.70 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 7.00 (d, J = 2.0 Hz, 1H), 4.88 (ddd, J = 13.5, 2.7, 2.5 Hz, 1H), 4.27 (dd, J = 10.6, 3.0 Hz, 1H), 3.40 (s, 2H), 2.92 - 3.14 (m, 5H), 2.64 - 2.85 (m, 6H), 2.51 - 2.64 (m, 3H), 2.45 (dd, J = 13.4, 1.5 Hz, 2H). [M+H] calc'd for $C_{23}H_{27}ClN_6O_2S$, 487; found, 487.

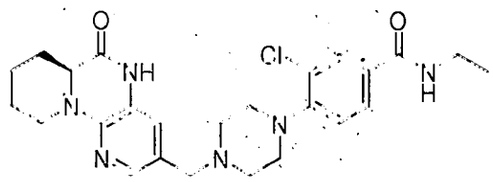
Compound 109: (S)-N-ethyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0560] To a suspension of(S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (83 mg, 0.355 mmol) in propiononitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (104 mg, 0.426 mmol) and DIEA (0.186 ml, 1.066

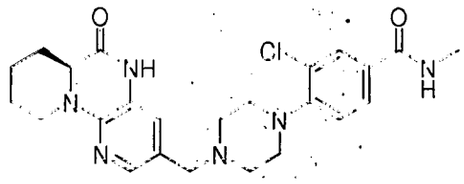
mmol) and finally N-ethyl-3-fluoro-4-(piperazin-1-yl)benzamide (102 mg, 0.355 mmol) . The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (50 mg, 30% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.48 (s, 1H), 8.35 (t, J = 5.4 Hz, 1H), 7.49 - 7.72 (m, 3H), 6.87 - 7.15 (m, 2H), 4.50 (d, J = 12.9 Hz, 1H), 3.84 (dd, J = 11.4, 2.8 Hz, 1H), 3.40 (d, J = 2.8 Hz, 2H), 3.18 - 3.30 (m, 2H), 3.08 (br. s., 4H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.49 (br. s., 4H), 2.03 (d, J = 12.9 Hz, 1H), 1.77 - 1.91 (m, 1H), 1.64 (d, J = 12.9 Hz, 1H), 1.32 - 1.57 (m, 3H), 1.09 (t, J = 7.2 Hz, 3H). [M+H] calc'd for $C_{25}H_{31}FN_6O_2$, 467; found, 467.

Compound 110: (S)-3-chloro-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



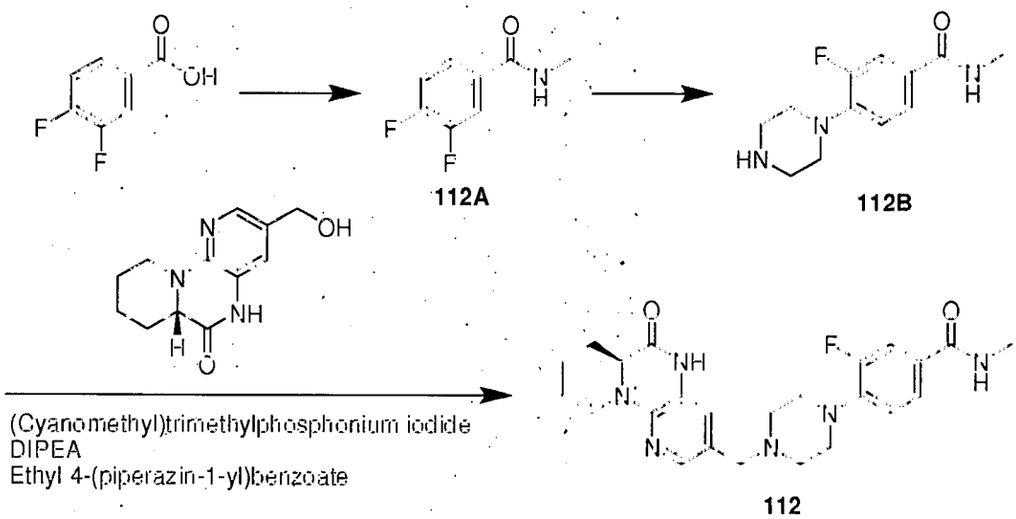
[0561] To a suspension of (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (81 mg, 0.347 mmol) in propionitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (101 mg, 0.417 mmol) and DIEA (182 µl, 1.042 mmol) and finally 3-chloro-N-ethyl-4-(piperazin-1-yl)benzamide hydrochloride (106 mg, 0.347 mmol). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (70 mg, 20% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.48 (s, 1H), 8.43 (t, J = 5.4 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 8.3, 2.0 Hz, 1H), 7.66 (d, J = 1.8 Hz, 1H), 7.17 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 4.50 (d, J = 12.9 Hz, 1H), 3.84 (dd, J = 11.4, 2.8 Hz, 1H), 3.38 (s, 2H), 3.18 - 3.31 (m, 2H), 3.03 (br. s., 4H), 2.60 (td, J = 12.7, 2.7 Hz, 1H), 2.51 (br. s., 4H), 2.04 (d, J = 12.9 Hz, 1H), 1.85 (d, J = 12.1 Hz, 1H), 1.64 (d, J = 12.6 Hz, 1H), 1.32 - 1.58 (m, 3H), 1.10 (t, J = 7.1 Hz, 3H). [M+H] calc'd for $C_{25}H_{31}ClN_6O_2$, 483; found, 483.

Compound 111: (S)-3-chloro-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0562] To a suspension of (S)-3-((S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (111 mg, 0.476 mmol) in propiononitrile (1.2 mL) was added (cyanomethyl)trimethylphosphonium iodide (139 mg, 0.571 mmol) and DIEA (249 µl, 1.428 mmol) and finally 3-chloro-N-methyl-4-(piperazin-1-yl)benzamide hydrochloride (138 mg, 0.476 mmol). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (64 mg, 29% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10.52 (br. s., 1H), 8.43 (d, J = 4.3 Hz, 1H), 7.87 (s, 1H), 7.76 (dd, J = 8.3, 1.5 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 7.54 - 7.74 (m, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.99 (br. s., 1H), 4.52 (d, J = 12.6 Hz, 1H), 3.85 (br. s., 1H), 3.44 (br. s., 2H), 2.92 (d, J = 4.5 Hz, 4H), 2.75 (d, J = 4.5 Hz, 4H), 2.52 - 2.69 (m, 3H), 1.99 - 2.09 (m, 1H), 1.85 (d, J = 12.4 Hz, 1H), 1.64 (d, J = 12.4 Hz, 1H), 1.32 - 1.58 (m, 3H). [M+H] calc'd for $C_{24}H_{29}ClN_6O_2$, 469; found, 469.

Compound 112: (S)-3-fluoro-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

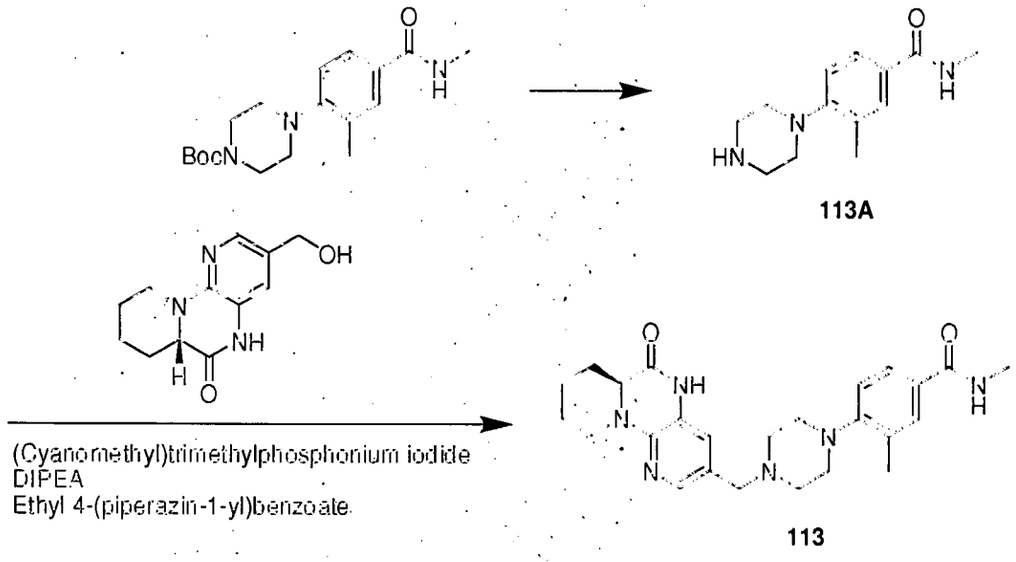


[0563] **Compound 112A: 3,4-difluoro-N-methylbenzamide:** Using methanamine hydrochloride and 3,4-difluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (75% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (d, *J*=4.55 Hz, 3 H) 7.55 (dt, *J*=10.61, 8.34 Hz, 1 H) 7.72 (dddd, *J*=8.59, 4.55, 2.15, 1.39 Hz, 1 H) 7.86 (ddd, *J*=11.68, 7.89, 2.15 Hz, 1 H) 8.48 - 8.59 (m, 1 H). ESI-MS: m/z 172.1 $(M+H)^+$. mp=142.7-145.0 °C.

[0564] **Compound 112B: 3-fluoro-N-methyl-4-(piperazin-1-yl)benzamide:** Using 3,4-difluoro-N-methylbenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (43% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (br. s., 1 H) 2.57 - 2.66 (m, 1 H) 2.72 - 2.79 (m, 3 H) 2.80 - 2.88 (m, 3 H) 2.95 - 3.04 (m, 3 H) 3.07 - 3.16 (m, 1 H) 6.99 - 7.11 (m, 1 H) 7.52 - 7.65 (m, 2 H) 8.29 - 8.38 (m, 1 H). ESI-MS: m/z 238.2 $(M+H)^+$. mp = 174.1-192.9°C.

[0565] **Compound 112: (S)-3-fluoro-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide**: To a suspension of (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (129 mg, 0.553 mmol) in propionitrile (1.2 mL) was added ((cyanomethyl)trimethylphosphonium iodide (161 mg, 0.664 mmol)) and 3-fluoro-N-methyl-4-(piperazin-1-yl)benzamide hydrochloride (151 mg, 0.553 mmol) and DIEA (290 µl, 1.659 mmol)). The vial was heated to 90 °C for 16 hours. The crude rxn was cooled to RT, DMSO (1 ml) was added, and purified via HPLC (55-90, basic). The fractions were collected, concentrated until a precipitate was visible and filtered. The solids were washed with water and collected to retrieve the product as a white solid (83 mg, 33% yield). ^{1}H NMR (400 MHz, DMSO-$d6$) δ ppm 10.43 (s, 1H), 8.33 (d, J = 4.5 Hz, 1H), 7.45 - 7.70 (m, 3H), 6.88 - 7.10 (m, 2H), 4.50 (d, J = 12.9 Hz, 1H), 3.83 (dd, J = 11.1, 2.5 Hz, 1H), 3.36 (s, 2H), 3.08 (br. s., 4H), 2.75 (d, J = 4.5 Hz, 3H), 2.56 - 2.64 (m, 1H), 2.50 (br. s., 4H), 1.97 - 2.12 (m, 1H), 1.85 (d, J = 11.1 Hz, 1H), 1.63 (d, J = 11.9 Hz, 1H), 1.29 - 1.57 (m, 3H). [M+H] calc'd for $C_{24}H_{29}FN_6O_2$, 453; found, 453.

Compound 113: (S)-N,3-dimethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide

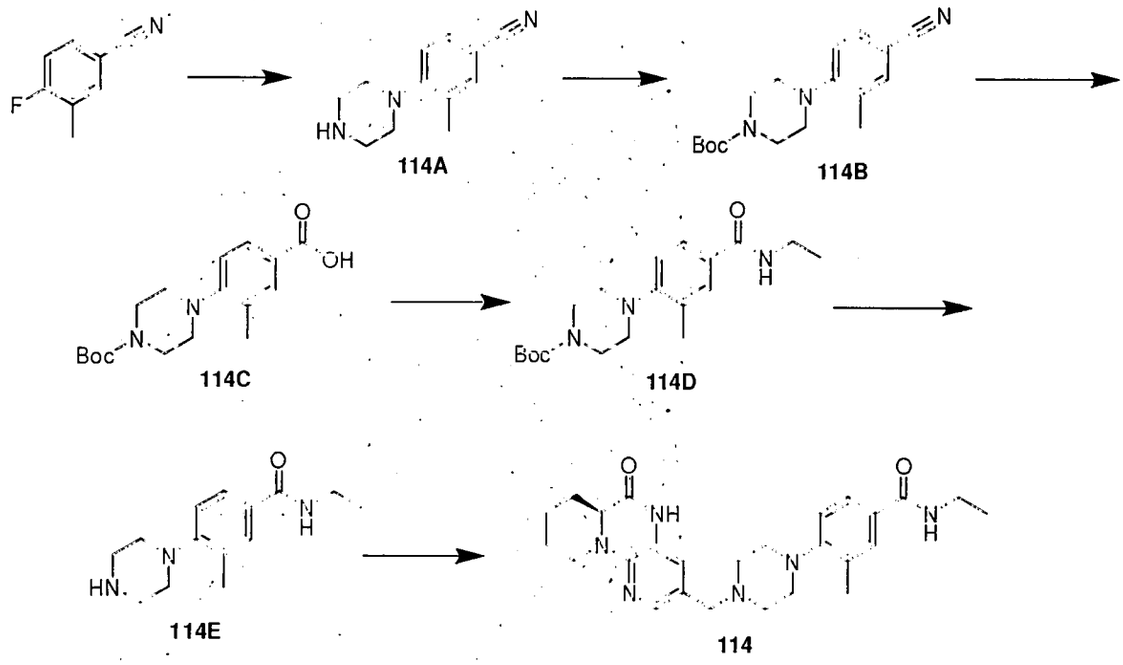


[0566] Compound 113A: N,3-dimethyl-4-(piperazin-1-yl)benzamide: To tert-butyl 4-(2-methyl-4-(methylcarbamoyl)phenyl)piperazine-1-carboxylate (1.90 g, 5.70 mmol) was added Hydrochloric acid solution (17.10 ml, 68.4 mmol) in dioxane at 23 °C. The reaction was stirred at 23 °C for 30 min. The resulting suspension was diluted with Et2O (20 mL), filtered, rinsed with Et2O (3 x 10 mL), and the resulting solid was dried *in vacuo* to provide N,3-dimethyl-4-(piperazin-1-yl)benzamide dihydrochloride (1.70 g, 5.55 mmol, 97 % yield) as an off-white, hygroscopic solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.28 (s, 3 H) 2.72 - 2.79 (m, 3 H) 3.05 - 3.14 (m, 4 H) 3.17 - 3.28 (m, 4 H) 7.06 (d, *J*=8.34 Hz, 1 H) 7.64 - 7.68 (m, 1 H) 7.68 - 7.70 (m, 1 H) 8.29 - 8.39 (m, 1 H) 9.36 (br. s., 2 H). ESI-MS: m/z 234.2 (M+H)$^+$.

[0567] Compound 113: (S)-N,3-dimethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol), N,3-dimethyl-4-(piperazin-1-yl)benzamide dihydrochloride (131 mg, 0.429 mmol), (cyanomethyl)trimethylphosphonium iodide (167 mg, 0.686 mmol) and N,N-diisopropylethylamine (374 µl, 2.143 mmol) were suspended in propiononitrile (Volume: 1287 µl) and heated in a closed vial at 90 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature and purified using HPLC (NH4HCO3 buffered, 20-70% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from MeCN (5 mL), filtered off, washed with water (2 mL) and dried in vacuum to afford (S)-N,3-dimethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-

e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (27.4 mg, 0.061 mmol, 14.25 % yield) as a light beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.31 - 1.57 (m, 3 H) 1.64 (d, *J*=11.37 Hz, 1 H) 1.85 (d, *J*=11.37 Hz, 1 H) 2.04 (d, *J*=11.37 Hz, 1 H) 2.25 (s, 3 H) 2.51 - 2.70 (m, 5 H) 2.56 - 2.70 (m, 2 H) 2.74 (d, *J*=4.29 Hz, 3 H) 2.87 (br. s., 4 H) 3.37 - 3.45 (m, 2 H) 3.84 (dd, *J*=11.24, 2.40 Hz, 1 H) 4.50 (d, *J*=13.14 Hz, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.01 (d, *J*=8.34 Hz, 1 H) 7.61 (dd, *J*=8.46, 1.64 Hz, 1 H) 7.65 (dd, *J*=12.25, 1.64 Hz, 2 H) 8.23 (q, *J*=4.13 Hz, 1 H) 10.48 (s, 1 H); [M+H] calc'd for $C_{25}H_{32}N_6O_2$, 449; found, 449.

Compound 114: (S)-N-ethyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0568] Compound 114A: 3-methyl-4-(piperazin-1-yl)benzonitrile: To a solution of 4-fluoro-3-methylbenzonitrile (2.5 g, 18.50 mmol) in DMSO (Volume: 10.0 mL) was added piperazine (7.97 g, 92 mmol) at 23 °C. The reaction was stirred at 140 °C for 16 hr. The reaction mixture was poured into H2O (100 mL) and the reaction vessel was rinsed with H2O (~50 mL). The resulting suspension was filtered, rinsed with H20 (3 x 10 mL) and the resulting solid was dried *in vacuo* to provide 3-methyl-4-(piperazin-1-yl)benzonitrile (2.593g, 12.88 mmol, 69.6 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 - 2.30 (m, 3 H) 2.57 - 2.70 (m, 1 H) 2.83 (s, 8 H) 7.03 - 7.09 (m, 1 H) 7.55 - 7.62 (m, 2 H). ESI-MS: m/z 202.1 $(M+H)^+$.

[0569] Compound 114B: tert-butyl 4-(4-cyano-2-methylphenyl)piperazine-1-carboxylate: To a solution of 3-methyl-4-(piperazin-1-yl)benzonitrile (2.533 g, 12.59 mmol) in THF (Ratio: 1.000, Volume: 25 mL) and MeOH (Ratio: 1.000, Volume: 25 mL) was added Di-tert-butyl dicarbonate (3.09 mL, 13.47 mmol) at 10 °C. The reaction was stirred at 10 °C for 15 min warmed to 23 °C and stirred at for 18 hr. The resulting suspension was filtered, rinsed with THF (3 x 5 mL) and the filtrate was concentrated *in vacuo*. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 (s, 9 H) 2.23 (s, 3 H) 2.83 - 2.92 (m, 4 H) 3.42 - 3.52 (m, 4 H) 7.08 - 7.13 (m, 1 H) 7.57 - 7.65 (m, 2 H). ESI-MS: m/z 302.1 $(M+H)^+$.

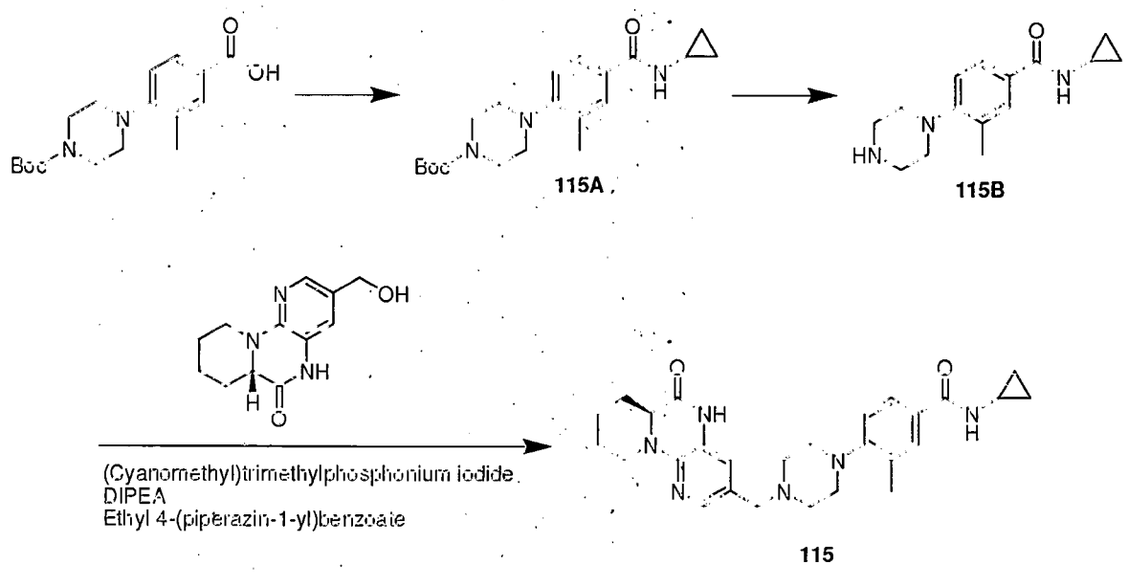
[0570] Compound 114C: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-methylbenzoic acid: To a suspension of tert-butyl 4-(4-cyano-2-methylphenyl)piperazine-1-carboxylate (3.685 g, 12.23 mmol) in EtOH (Ratio: 1.000, Volume: 50 mL) and Water (Ratio: 1.000, Volume: 10 mL) was added Sodium hydroxide solution (8.48 mL, 162 mmol) at 23 °C. Rinsed sodium hydroxide forward with Water (Ratio: 1.000, Volume: 2.5 mL) The reaction was stirred at 90 °C for 10 hr. The reaction mixture was cooled to 23 °C, neutralized with 3N HCl (52 mL), filtered, rinsed with H2O (3 x 10 mL), and the resulting solid was dried in vacuo to provide 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-methylbenzoic acid (3.588 g, 11.20 mmol, 92 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.42 (s, 9 H) 2.29 (s, 3 H) 2.81 - 2.90 (m, 4 H) 3.42 - 3.53 (m, 4 H) 7.05 (d, *J*=8.08 Hz, 1 H) 7.70 - 7.77 (m, 2 H) 12.61 (br. s., 1 H). ESI-MS: m/z 321.2 $(M+H)^+$.

[0571] Compound 114D: tert-butyl 4-(4-(ethylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-methylbenzoic acid (0.866 g, 2.70 mmol), ethanamine hydrochloride (0.264 g, 3.24 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.777 g, 4.05 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (0.621 g, 4.05 mmol) were suspended in DMF (Volume: 3.68 ml) and 4-methylmorpholine (1.486 ml, 13.52 mmol) was added. The reaction mixture was stirred at ambient temperature for 2h. It was diluted with water (50 mL) and extracted with ethyl acetate (3X75 mL). The combined organic extracts were washed with 1N HCl (aq., 25 mL), NaHCO3 (sat. aq., 25 mL), water (25 mL), brine (25 mL), dried (MgSO4), concentrated in vacuo and dried under vacuum to afford tert-butyl 4-(4-(ethylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate (0.9327 g, 2.68 mmol, 99 % yield) as a white solid. ^{1}H NMR (DMSO-d_6 ,400MHz): δ = 8.24 (t, *J*=5.4 Hz, 1 H), 7.66 (d, *J*=1.8 Hz, 2 H), 7.03 (d, *J*=8.3 Hz, 1 H), 3.42 - 3.52 (m, 4 H), 3.20 - 3.27 (m, 2 H), 2.73 - 2.87 (m, 4 H), 2.28 (s, 3 H), 1.43 (s, 9 H), 1.10 ppm (t, *J*=7.2 Hz, 3 H). ESI-MS: m/z 348.4 $(M+H)^+$.

[0572] Compound 114E: N-ethyl-3-methyl-4-(piperazin-1-yl)benzamide: Tert-butyl 4-(4-(ethylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate (0.9323 g, 2.68 mmol) was diluted with 4.0M HCl in dioxane (8 mL) and stirred for 30 min. The thick white precipitate that formed was diluted with ethyl ether (10 mL) and stirred until a fine suspension resulted. The precipitate was filtered under nitrogen, washed with ether (5mL) and dried in vacuum to afford N-ethyl-3-methyl-4-(piperazin-1-yl)benzamide hydrochloride (0.7528 g, 2.65 mmol, 99 % yield) as a white solid. 1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.10 (t, *J*=7.20 Hz, 3 H) 2.29 (s, 3 H) 3.00 - 3.14 (m, 4 H) 3.16 - 3.32 (m, 6 H) 7.07 (d, *J*=8.34 Hz, 1 H) 7.62 - 7.71 (m, 2 H) 8.34 (t, *J*=5.43 Hz, 1 H) 9.17 (br. s., 2 H). ESI-MS: m/z 248.2 $(M+H)^+$.

[0573] Compound 114: (S)-N-ethyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol), N-ethyl-3-methyl-4-(piperazin-1-yl)benzamide hydrochloride (133 mg, 0.469 mmol), (cyanomethyl)trimethylphosphonium iodide (167 mg, 0.636 mmol) and N,N-diisopropylethylamine (374 µl, 2.143 mmol) were suspended in Propiononitrile (Volume: 1287 µl) and heated in a closed vial at 90 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature and purified using HPLC (NH4HCO3 buffered, 20-70% ACN in water). The fractions were concentrated in vacuo and the resulting solid was slurried with hot MeCN (5 mL), cooled to ambient temperature, filtered off, washed with water (2 mL) and dried in vacuum to afford (S)-N-ethyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (70.3 mg, 0.152 mmol, 35.4 % yield) as a light beige solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.09 (t, *J*=7.20 Hz, 3 H) 1.33 - 1.57 (m, 3 H) 1.64 (d, *J*=12.13 Hz, 1 H) 1.85 (d, *J*=11.37 Hz, 1 H) 2.04 (d, *J*=12.13 Hz, 1 H) 2.26 (s, 3 H) 2.52 - 2.70 (m, 5 H) 2.87 (br. s., 4 H) 3.19 - 3.29 (m, 2 H) 3.37 - 3.43 (m, 2 H) 3.84 (dd, *J*=11.49, 2.65 Hz, 1 H) 4.50 (d, *J*=12.88 Hz, 1 H) 6.98 (d, *J*=1.52 Hz, 1 H) 7.01 (d, *J*=8.34 Hz, 1 H) 7.62 (d, *J*=8.59 Hz, 1 H) 7.65 (dd, *J*=9.35, 1.26 Hz, 2 H) 8.26 (t, *J*=5.43 Hz, 1 H) 10.49 (s, 1 H); [M+H] calc'd for $C_{26}H_{34}N_6O_2$, 463; found, 463.

Compound 115: (S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



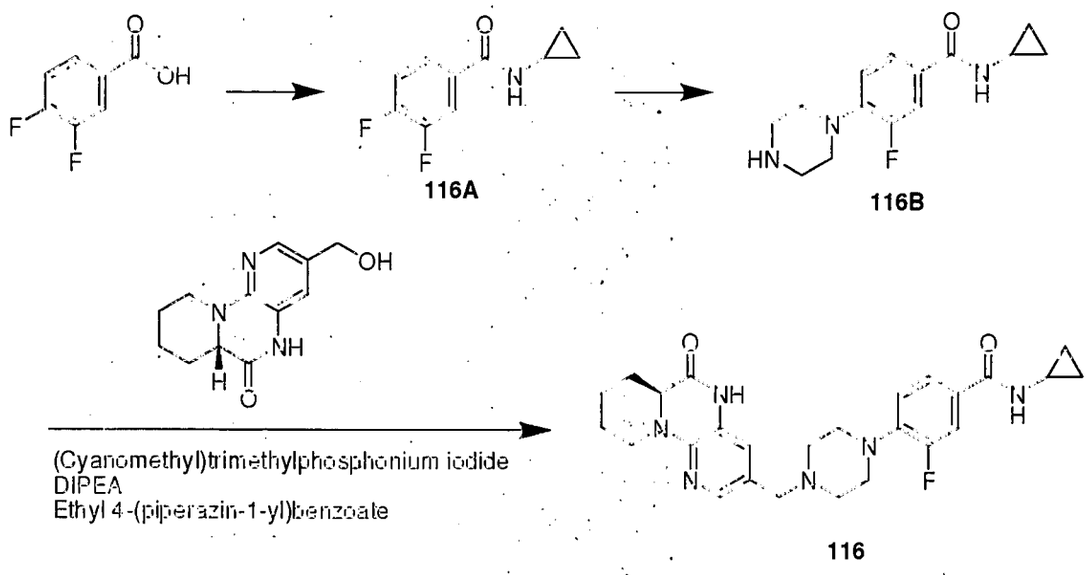
[0574] Compound 115A: tert-butyl 4-(4-(cyclopropylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate: Cyclopropylamine (0.389 mL, 5.62 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (1.346 g, 7.02 mmol), and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (1.075 g, 7.02 mmol) in DMF (Volume: 6.4 mL) was added 4-methylmorpholine (2.57 mL, 23.41 mmol) at 23 °C. The reaction was stirred at 23 °C for 2 hr. The reaction mixture was diluted with water (50 mL) and the product was extracted with EtOAc (3 x 50 mL). The organic extracts were combined, washed with 1N HCl (25 mL), saturated NaHCO3 (25 mL), H2O (25 mL), brine (25 mL), dried over MgSO4, filtered, rinsed with EtOAc, and dried *in vacuo* to provide tert-butyl 4-(4-(cyclopropylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate (1.53 g, 4.26 mmol, 91 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.51 - 0.60 (m, 2 H) 0.60 - 0.70 (m, 2 H) 1.42 (s, 9 H) 2.28 (s, 3 H) 2.77 - 2.87 (m, 5 H) 3.41 - 3.53 (m, 4 H) 7.02 (d, *J*=8.08 Hz, 1 H) 7.61 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.64 (d, *J*=1.77 Hz, 1 H) 8.25 (d, *J*=4.29 Hz, 1 H). ESI-MS:m/z 360.3 $(M+H)^+$. mp=111.0-115.4 °C.

[0575] Compound 115B: N-cyclopropyl-3-methyl-4-(piperazin-1-yl)benzamide: To tert-butyl 4-(4-(cyclopropylcarbamoyl)-2-methylphenyl)piperazine-1-carboxylate (1.490 g, 4.15 mmol) was added Hydrochloric acid solution (8.72 mL, 34.9 mmol) in dioxane at 23 °C. The reaction was stirred at 23 °C for 30 min. The resulting suspension was diluted with Et2O (10 mL), filtered, rinsed with Et2O (3 x 5 mL), and the resulting solid was dried *in vacuo* to provide N-cyclopropyl-3-methyl-4-(piperazin-1-yl)benzamide dihydrochloride (1.37 g, 4.15

mmol, 100 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.51 - 0.61 (m, 2 H) 0.61 - 0.70 (m, 2 H) 2.28 (s, 3 H) 2.82 (tq, *J*=7.41, 3.99 Hz, 1 H) 3.02 - 3.13 (m, 4 H) 3.14 - 3.29 (m, 4 H) 7.05 (d, *J*=8.34 Hz, 1 H) 7.62 - 7.69 (m, 2 H) 8.32 (d, *J*=4.29 Hz, 1 H) 9.38 (br. s., 2 H). ESI-MS : m/z 260.2 $(M+H)^+$. mp=171.5-172.8 °C.

[0576] Compound 115: (S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (100 mg, 0.429 mmol), N-cyclopropyl-3-methyl-4-(piperazin-1-yl)benzamide dihydrochloride (143 mg, 0.430 mmol), (cyanomethyl)trimethylphosphonium iodide (167 mg, 0.686 mmol) and N,N-diisopropylethylamine (374 µl, 2.143 mmol) were suspended in Propiononitrile (Volume: 1287 µl) and heated in a closed vial at 90 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature and purified using HPLC (NH4HCO3 buffered, 20-70% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from MeCN (20 mL), filtered off, washed with water (2 mL) and dried in vacuum to afford (S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (50.7 mg, 0.107 mmol, 24.92 % yield) as a light brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.49 - 0.59 (m, 2 H) 0.60 - 0.71 (m, 2 H) 1.33 - 1.57 (m, 3 H) 1.64 (d, *J*=12.88 Hz, 1 H) 1.85 (d, *J*=12.63 Hz, 1 H) 2.04 (d, *J*=12.88 Hz, 1 H) 2.25 (s, 3 H) 2.42 - 2.56 (m, 4 H) 2.60 (td, *J*=12.63, 2.78 Hz, 1 H) 2.76 - 2.93 (m, 5 H) 3.38 (s, 2 H) 3.84 (dd, *J*=11.37, 2.78 Hz, 1 H) 4.50 (d, *J*=13.14 Hz, 1 H) 6.98 (d, *J*=2.02 Hz, 1 H) 7.00 (d, *J*=8.34 Hz, 1 H) 7.56 - 7.63 (m, 2 H) 7.66 (d, *J*=2.02 Hz, 1 H) 8.22 (d, *J*=4.29 Hz, 1 H) 10.49 (s, 1 H); [M+H] calc'd for $C_{27}H_{34}N_6O_2$, 475; found, 475.

Compound 116: (S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



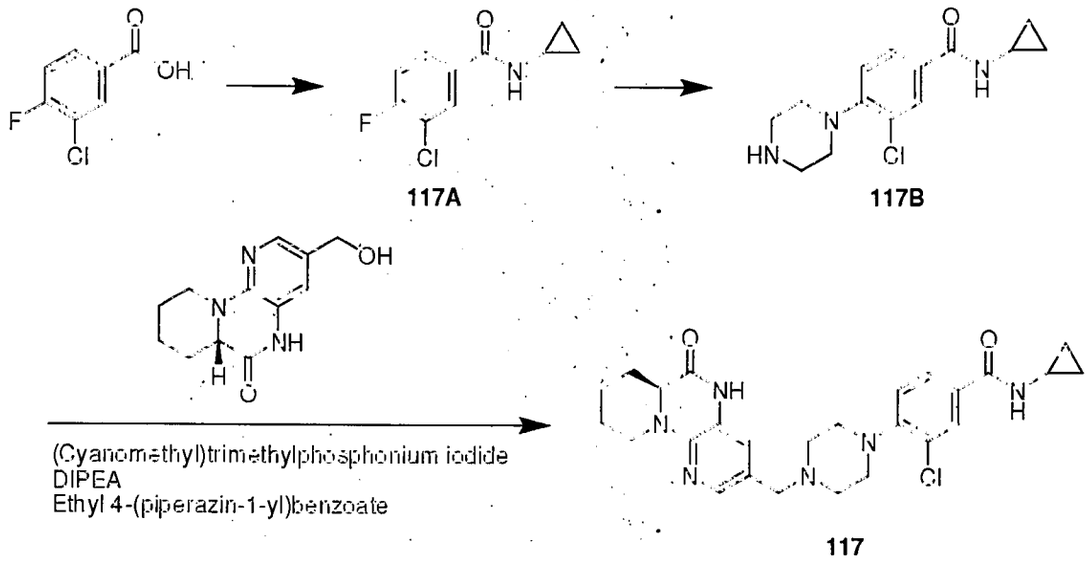
[0577] Compound 116A: N-cyclopropyl-3,4-difluorobenzamide: Using cyclopropylamine and 3,4-difluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (89% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.52 - 0.63 (m, 2 H) 0.63 - 0.74 (m, 2 H) 2.83 (tq, *J*=7.42, 3.98 Hz, 1 H) 7.52 (dt, *J*=10.55, 8.37 Hz, 1 H) 7.66 - 7.75 (m, 1 H) 7.85 (ddd, *J*=11.68, 7.89, 2.15 Hz, 1 H) 8.42 - 8.60 (m, 1 H). ESI-MS:m/z 198.1 $(M+H)^+$. mp = 104.1-108.4 °C.

[0578] Compound 116B: N-cyclopropyl-3-fluoro-4-(piperazin-1-yl)benzamide: Using N-cyclopropyl-3,4-difluorobenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (33% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.51 - 0.61 (m, 2 H) 0.61 - 0.71 (m, 2 H) 2.55 - 2.68 (m, 1 H) 2.71 - 2.91 (m, 5 H) 2.92 - 3.09 (m, 4 H) 6.97 - 7.09 (m, 1 H) 7.51 - 7.65 (m, 2 H) 8.27 (d, *J*=4.04 Hz, 1 H). ESI-MS:m/z 264.2 $(M+H)^+$. mp = 140.9-143.1 °C.

[0579] Compound 116: (S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (150 mg, 0.643 mmol), N-cyclopropyl-3-fluoro-4-(piperazin-1-yl)benzamide (203 mg, 0.772 mmol), (cyanomethyl)trimethylphosphonium iodide (250 mg, 1.029 mmol) and N,N-diisopropylethylamine (562 µl, 3.22 mmol) were suspended in Propiononitrile (Volume: 1931 µl) and heated in a closed vial at 100 °C for 4h. The reaction mixture became a dark brown solution with precipitate. It was cooled to room temperature and the precipitate was filtered off,

washed with MeCN (2 mL) and suspended in MeCN with heating and sonication. The suspension was cooled to ambient temperature, and the precipitate was filtered off, washed with MeCN (2 mL) and dried in vacuum to afford (S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (265 mg, 0.554 mmol, 36 % yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 8.31 (d, J = 4.3 Hz, 1H), 7.53 - 7.69 (m, 4H), 7.02 (t, J = 8.8 Hz, 1H), 6.97 (d, J = 2.0 Hz, 1H), 4.50 (br. d, J = 12.9 Hz, 1H), 3.84 (dd, J = 11.2, 2.7 Hz, 1H), 3.37 (s, 2H), 3.01 - 3.13 (m, 4H), 2.80 (tq, J = 7.4, 3.9 Hz, 1H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.44 - 2.51 (m, 4H), 2.04 (br. d, J = 12.9 Hz, 1H), 1.85 (br. d, J = 12.4 Hz, 1H), 1.64 (br. d, J = 12.6 Hz, 1H), 1.33 - 1.56 (m, 3H), 0.61 - 0.71 (m, 2H), 0.50 - 0.60 (m, 2H); [M+H] calc'd for $C_{26}H_{31}FN_6O_2$, 479; found, 479.

Compound 117: (S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



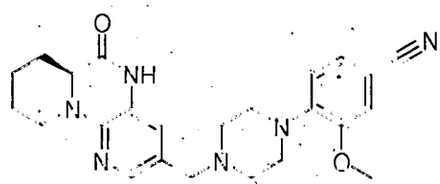
[0580] Compound 117A: 3-chloro-N-cyclopropyl-4-fluorobenzamide: Using cyclopropylamine and 3-chloro-4-fluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (89% yield) as a white solid. ^{1}H NMR (DMSO-d_6 ,400MHz): δ = 8.56 (d, *J*=3.5 Hz, 1 H), 8.03 (dd, *J*=7.3, 2.3 Hz, 1 H), 7.85 (ddd, *J*=8.6, 4.8, 2.3 Hz, 1 H), 7.52 (t, *J*=9.0 Hz, 1 H), 2.83 (tq, *J*=7.4, 3.9 Hz, 1 H), 0.66 - 0.75 (m, 2 H), 0.53 - 0.61 ppm (m, 2 H). ESI-MS: m/z 214.0 $(M+H)^+$.

[0581] Compound 117B: 3-chloro-N-cyclopropyl-4-(piperazin-1-yl)benzamide: Using 3-chloro-N-cyclopropyl-4-fluorobenzamide in the general procedure for nucleophilic aromatic

substitution reactions, the title compound was obtained (77% yield) as a white solid. ESI-MS: m/z 280.2 $(M+H)^+$.

[0582] Compound 117: (S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (150 mg, 0.643 mmol), 3-chloro-N-cyclopropyl-4-(piperazin-1-yl)benzamide (216 mg, 0.772 mmol), (cyanomethyl)trimethylphosphonium iodide (250 mg, 1.029 mmol) and N,N-diisopropylethylamine (562 µl, 3.22 mmol) were suspended in Propiononitrile (Volume: 1931 µl) and heated in a closed vial at 100 °C for 4h. The reaction mixture became a dark brown solution with a precipitate. It was cooled to room temperature and the precipitate was filtered off, washed with MeCN (2 mL) and suspended in MeCN (15 mL) with heating and sonication. It was then cooled to ambient temperature, the precipitate was filtered off, washed with MeCN (2 mL) and dried in vacuum to afford (S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (272.4 mg, 0.550 mmol, 86 % yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.49 (s, 1H), 8.39 (d, J = 4.3 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.75 (dd, J = 8.3, 2.0 Hz, 1H), 7.66 (s, 1H), 7.16 (d, J = 8.6 Hz, 1H), 6.97 (d, J = 1.8 Hz, 1H), 4.50 (d, J = 12.9 Hz, 1H), 3.84 (dd, J = 11.4, 2.8 Hz, 1H), 3.38 (s, 2H), 3.02 (br. s., 4H), 2.77 - 2.88 (m, J = 0.8 Hz, 1H), 2.60 (td, J = 12.6, 2.5 Hz, 1H), 2.49 - 2.55 (m, J = 3.5, 1.8, 1.8 Hz, 4H), 2.04 (br. d, J = 12.6 Hz, 1H), 1.86 - 1.87 (m, 0H), 1.84 (br. s., 1H), 1.64 (br. d, J = 12.6 Hz, 1H), 1.32 - 1.57 (m, 3H), 0.61 - 0.72 (m, 2H), 0.51 - 0.61 (m, 2H); [M+H] calc'd for $C_{26}H_{31}ClN_6O_2$, 495; found, 495.

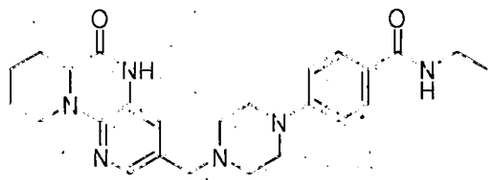
Compound 118: (S)-3-methoxy-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0583] (S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (150 mg, 0.643 mmol), 3-methoxy-4-(piperazin-1-yl)benzonitrile hydrochloride (163 mg, 0.643 mmol), (cyanomethyl)trimethylphosphonium iodide (250 mg, 1.029 mmol) and N,N-diisopropylethylamine (562 µl, 3.22 mmol) were suspended in Propiononitrile (Volume: 1931 µl) and heated in a closed vial at 100 °C for 2h. The reaction mixture became a dark brown solution. It was diluted with MeCN (4 mL) and concentrated in vacuo to about 3 mL.

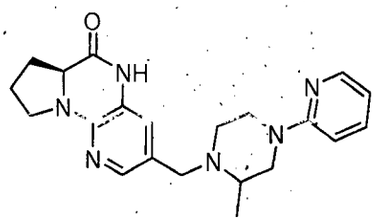
The resulting precipitate was filtered, recrystallized from MeCN (5 mL)and dried in vacuum to afford (S)-3-methoxy-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile (125 mg, 0.289 mmol, 44.9 % yield) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 10.48 (s, 1H), 7.65 (d, J = 2.0 Hz, 1H), 7.30 - 7.36 (m, 2H), 6.93 - 6.98 (m, 2H), 4.50 (d, J = 12.9 Hz, 1H), 3.79 - 3.87 (m, 4H), 3.34 - 3.40 (m, 2H), 3.07 (br. s., 4H), 2.60 (td, J = 12.7, 2.7 Hz, 1H), 2.47 (br. s., 4H), 2.02 (br. s., 1H), 1.85 (d, J = 12.1 Hz, 1H), 1.64 (d, J = 12.4 Hz, 1H), 1.32 - 1.57 (m, 3H); [M+H] calc'd for $C_{24}H_{28}N_6O_2$, 433; found, 433.

Compound 119: N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



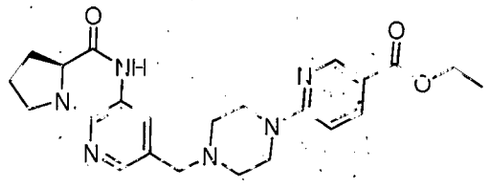
[0584] 3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (50 mg, 0.214 mmol), N-ethyl-4-(piperazin-1-yl)benzamide (55.0 mg, 0.236 mmol), (cyanomethyl)trimethylphosphonium iodide (67.7 mg, 0.279 mmol) and N,N-diisopropylethylamine (187 µl, 1.072 mmol) were suspended in Propionitrile (Volume: 644 µl) and heated in a closed vial at 90 °C for 1h. It was cooled to ambient temperature, the resulting precipitate was filtered, washed with MeCN (5 mL) and dried in vacuum to afford N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (56 mg, 0.125 mmol, 58.2 % yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ 10.43 (s, 1H), 8.12 (t, J = 5.6 Hz, 1H), 7.70 (d, J = 9.1 Hz, 2H), 7.66 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 9.1 Hz, 2H), 4.47 - 4.55 (m, 1H), 3.83 (dd, J = 11.4, 2.3 Hz, 1H), 3.32 - 3.40 (m, 2H), 3.18 - 3.28 (m, 6H), 2.61 (td, J = 12.6, 2.5 Hz, 1H), 2.43 - 2.49 (m, 4H), 2.04 (d, J = 13.1 Hz, 1H), 1.80 - 1.91 (m, 2H), 1.64 (d, J = 12.6 Hz, 2H), 1.33 - 1.58 (m, 3H), 1.09 (d, J = 14.4 Hz, 3H); [M+H] calc'd for $C_{25}H_{32}N_6O_2$, 449; found, 449.

Compound 120: (6aS)-3-((2-methyl-4-(pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



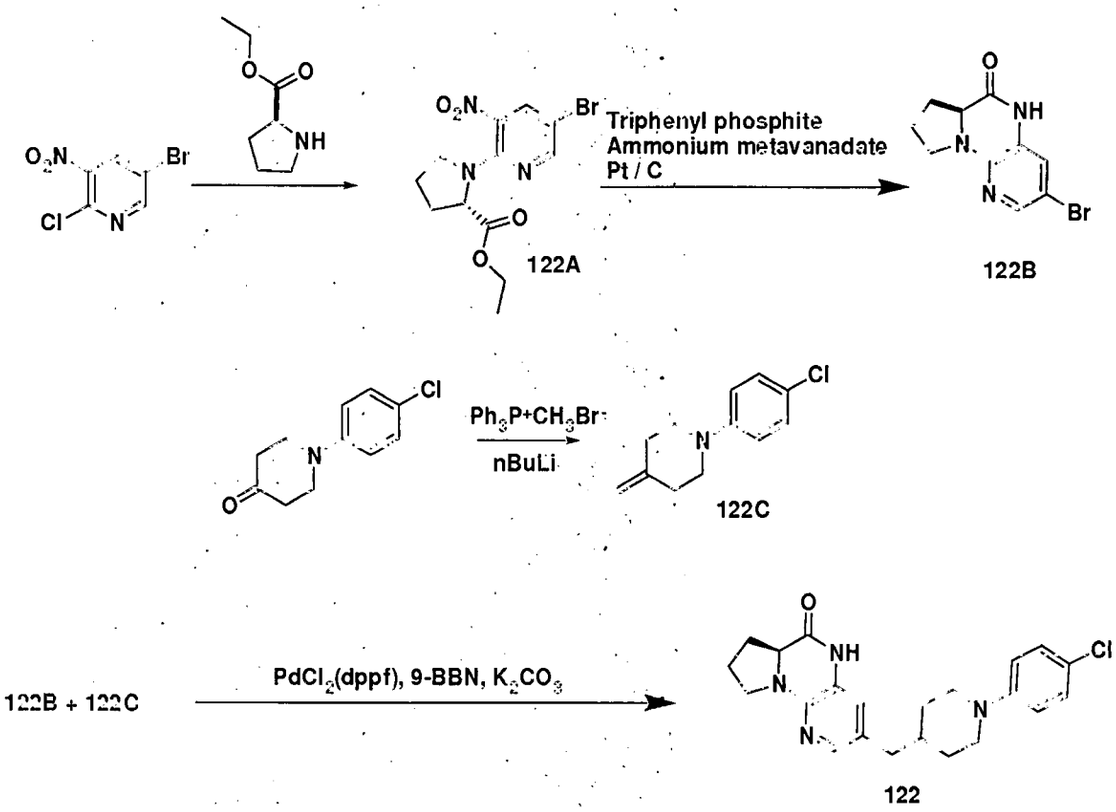
[0585] Compound 120 was prepared using a procedure analogous to that described in connection with compound 1, except that 3-methyl-1-(pyridin-2-yl)piperazine was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. [M+H] calc'd for $C_{21}H_{26}N_6O$, 379; found, 379.

Compound 121: (S)-ethyl 6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate



[0586] Compound 121 was prepared using a procedure analogous to that described in connection with compound 1, except that ethyl 6-(piperazin-1-yl)nicotinate was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. [M+H] calc'd for $C_{23}H_{28}N_6O_3$, 437; found, 437.

Compound 122: (S)-3-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



[0587] Compound 122A: (S)-ethyl 1-(5-bromo-3-nitropyridin-2-yl)pyrrolidine-2-carboxylate: 5-bromo-2-chloro-3-nitropyridine (5.94 g, 25 mmol) and (S)-ethyl pyrrolidine-2-carboxylate (7.52 g, 52.5 mmol) were combined and stirred at 90 °C for 10 min in a closed vial The crude material was purified by flash column chromatography (20-30% EtOAc in hexanes to afford (S)-ethyl 1-(5-bromo-3-nitropyridin-2-yl)pyrrolidine-2-carboxylate (8.43 g, 24.49 mmol, 98 % yield) as a yellow viscous oil. [M+H] calc'd for $C_{12}H_{14}BrN_3O_4$, 344; found, 344.

[0588] Compound 122B: (S)-3-bromo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: (S)-ethyl 1-(5-bromo-3-nitropyridin-2-yl)pyrrolidine-2-carboxylate (8.6 g, 24.99 mmol) was dissolved in dichloromethane (Volume: 125 ml) and to this solution was added triphenyl phosphite (0.078 g, 0.250 mmol), ammonium metavanadate (0.175 g, 1.499 mmol) and Pt/C (5% wt.) (0.975 g, 0.250 mmol). The reaction mixture was hydrogenated at 80 psi at 25 °C for 4h. The reaction mixture was filtered through celite using DCM and MeOH to complete the transfer and wash the celite plug. The combined filtrates and washes were concentrated in vacuo and crystallized with ethyl ether (75 mL). The precipitate was filtered

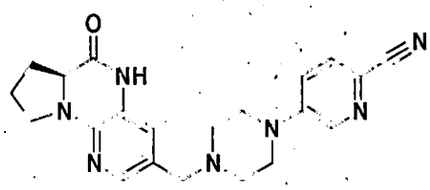
and dried in vacuum to afford (S)-3-bromo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (2.37 g, 10.70 mmol, 42.3 % yield) as a pale beige solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.82 - 2.03 (m, 3 H) 2.11 - 2.26 (m, 1 H) 3.27 - 3.47 (m, 1 H) 3.49 - 3.63 (m, 1 H) 4.01 - 4.11 (m, 1 H) 7.06
(d, *J*=2.27 Hz, 1 H) 7.77 (d, *J*=2.02 Hz, 1 H) 10.57 (s, 1 H). [M+H] calc'd for $C_{10}H_{10}BrN_3O$, 268; found, 268.

[0589] Compound 122C: 1-(4-chlorophenyl)-4-methylenepiperidine:
Methyltriphenylphosphonium bromide (1.429 g, 4.00 mmol) was suspended in THF (Ratio: 1.667, Volume: 2.5 ml) and cooled to -78°C. n-butyllithium (0.960 ml, 2.400 mmol) was added dropwise over 3 min and the resulting yellow suspension was stirred at -78°C for 10 min. A solution of 1-(4-chlorophenyl)piperidin-4-one (0.419 g, 2 mmol) in THF (Ratio: 1.000, Volume: 1.5 ml) was added dropwise over 3 min and the dark red suspension was stirred at -78°C for 10 min and then allowed to slowly warm to 5 °C over 1h. The reaction was stirred at 5 °C for 4h and was quenched with water (4 mL). This was extracted with ethyl ether (2 X 5 mL) and the extracts were washed with water (4 X 5 mL). The combined water washes were back-extracted with ethyl ether (5 mL) and the combined organic extracts were washed with brine (5 ml), dried (MgSO4), filtered and concentrated in vacuo. Flash column chromatography (40 g SiO_2, hexanes : ethyl acetate 9:1) afforded 1-(4-chlorophenyl)-4-methylenepiperidine (0.196 g, 0.944 mmol, 47.2 % yield) as a clear yellow oil. [M+H] calc'd for $C_{12}H_{14}Cl$, 208; found, 208.

[0590] Compound 122: (S)-3-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: 1-(4-chlorophenyl)-4-methylenepiperidine (70 mg, 0.337 mmol) was diluted with 0.5M THF solution of 9-BBN (0.674 mL, 0.337 mmol) under nitrogen and stirred at 75 °C for 1h. The reaction mixture was then added to a suspension of (S)-3-bromo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (90 mg, 0.337 mmol), PdCl2(dppf)-CH2Cl2 adduct (8.26 mg, 10.11 µmol) and potassium carbonate (93 mg, 0.674 mmol) in DMF (1.0 mL) and water (0.1 mL) and stirred at 60 °C for 4h.
The mixture was cooled, diluted with water (10 mL) and the resulting red material was separated off, washed with water, dissolved in ethyl acetate (10 mL), dried (MgSO4), filtered and concentrated in vacuo. Flash column chromatography (12 g SiO2, ethyl acetate) provided the desired product as a yellow solid. It was suspended in MeOH (5 mL) and the precipitate was filtered and dried in vacuo to give the product as a white solid (16 mg, 12% yield). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.11 - 1.30 (m, 2 H) 1.43 - 1.58 (m, 0 H) 1.63 (d, *J*=12.13

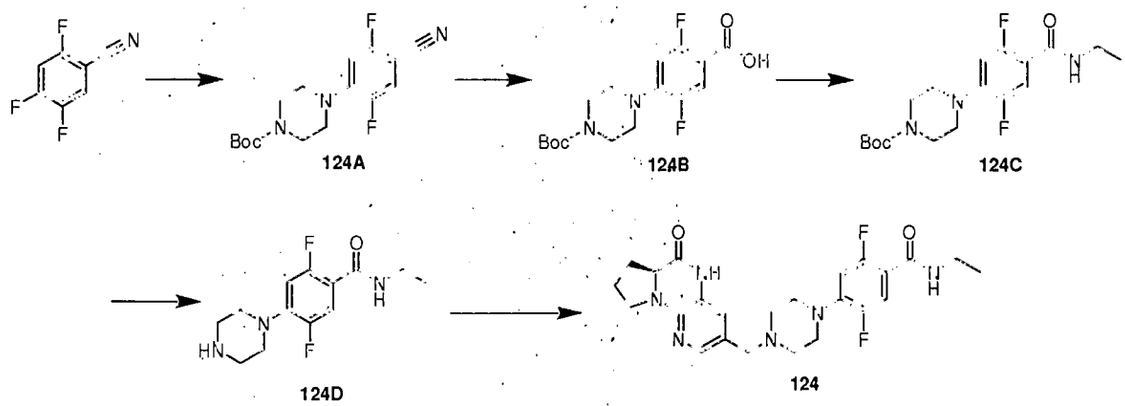
Hz, 1 H) 1.80 - 2.03 (m, 2 H) 2.06 - 2.25 (m, 1 H) 2.29 - 2.44 (m, 2 H) 2.53 - 2.64 (m, 2 H) 3.35 - 3.44 (m, 1 H) 3.51 - 3.62 (m, 1 H) 3.65 (d, *J*=12.13 Hz, 2 H) 3.87 - 3.98 (m, 1 H) 6.82 (d, *J*=1.77 Hz, 1 H) 6.91 (d, *J*=9.09 Hz, 2 H) 7.19 (d, *J*=9.09 Hz, 2 H) 7.54 (d, *J*=1.77 Hz, 1 H) 10.40 (s, 1 H). [M+H] calc'd for $C_{22}H_{25}ClN_4O$, 397; found, 397.

Compound 123: (S)-5-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)picolinonitrile



[0591] Compound 123 was prepared using a procedure analogous to that described in connection with compound 1, except that 5-(piperazin-1-yl)picolinonitrile was used instead of 1-(4-chlorophenyl)piperazine hydrochloride. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.84 - 2.02 (m, 3 H) 2.09 - 2.24 (m, 1 H) 2.39 - 2.48 (m, 4 H) 3.34 - 3.43 (m, 7 H) 3.53 - 3.64 (m, 1 H) 3.94 - 4.03 (m, 1 H) 6.97 (d, *J*=1.77 Hz, 1 H) 7.34 (dd, *J*=8.97, 2.91 Hz, 1 H) 7.61 (d, *J*=1.52 Hz, 1 H) 7.74 (d, *J*=8.84 Hz, 1 H) 8.40 (d, *J*=2.78 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{21}H_{23}N_7O$, 390; found, 390.

Compound 124: (S)-N-ethyl-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0592] Compound 124A: tert-butyl 4-(4-cyano-2,5-difluorophenyl)piperazine-1-carboxylate: Tert-butyl piperazine-1-carboxylate (0.931 g, 5 mmol) and 2,4,6-trifluorobenzonitrile (0.785 g, 5.00 mmol) were combined, potassium carbonate (0.898 g, 6.50 mmol) was added and the reaction mixture was stirred at 90 °C for 1 d. The mixture was

triturated with ethyl acetate (3 X 5 mL) and the combined organic extracts were filtered. This was concentrated down to about 5-10 mL and subjected to flash column chromatography on silica gel (120 g SiO_2, hexanes : ethyl acetate 1:0 to 4:1) to afford tert-butyl 4-(4-cyano-2,5-difluorophenyl)piperazine-1-carboxylate (1.363 g, 4.22 mmol, 84 % yield) as a white solid. ^1H NMR (400 MHz, DMSO-*d6*) δ ppm 1.41 (s, 9 H) 3.12 - 3.27 (m, 4 H) 3.45 (d, *J*=4.80 Hz, 4 H) 7.12 (dd, *J*=11.87, 7.07 Hz, 1 H) 7.80 (dd, *J*=12.88, 6.32 Hz, 1 H).

[0593] Compound 124B: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2,5-difluorobenzoic acid: Tert-butyl 4-(4-cyano-2,5-difluorophenyl)piperazine-1-carboxylate (20 mg, 0.062 mmol) was dissolved in ethanol (1 mL) and treated with water (0.2 mL) and 50% NaOH (0.2 mL, 2.500 mmol). The reaction mixture was stirred at 90 °C for 1h, diluted with water (2 mL) and acidified with 1N HCl to pH<4. The solid was filtered, washed with water and dried in vacuum to afford 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2,5-difluorobenzoic acid (21.0 mg, 0.061 mmol, 99 % yield) as a white solid. ESI-MS : m/z 343 $(M+H)^+$.

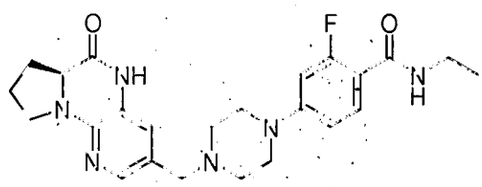
[0594] Compound 124C: tert-butyl 4-(4-(ethylcarbamoyl)-2,5-difluorophenyl)piperazine-1-carboxylate: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2,5-difluorobenzoic acid (0.021 g, 0.061 mmol) and ethylamine hydrochloride (7.50 mg, 0.092 mmol) were suspended in DMF (Volume: 0.7 mL) and treated with DIPEA (0.054 mL, 0.307 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (0.047 g, 0.123 mmol). The reaction mixture was stirred at room temperature for 15 min and diluted with water. The precipitate was filtered, washed with water and dried in vacuum to afford tert-butyl 4-(4-(ethylcarbamoyl)-2,5-difluorophenyl)piperazine-1-carboxylate (20.1 mg, 0.054 mmol, 89 % yield). ESI-MS : m/z 370 $(M+H)^+$.

[0595] Compound 124D: N-ethyl-2,5-difluoro-4-(piperazin-1-yl)benzamide: tert-butyl 4-(4-(ethylcarbamoyl)-2,5-difluorophenyl)piperazine-1-carboxylate (0.020 g, 0.054 mmol) was diluted with 4.0M HCl in dioxane (3 mL) and stirred for 30 min. The thick white precipitate that formed was diluted with ethyl ether (10 mL) and stirred until a fine suspension resulted. The precipitate was filtered under nitrogen and dried in vacuum to afford N-ethyl-2,5-difluoro-4-(piperazin-1-yl)benzamide hydrochloride (16.2 mg, 0.053 mmol, 98 % yield) as a white solid. ESI-MS : m/z 270 $(M+H)^+$.

[0596] Compound 124: (S)-N-ethyl-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (10.76 mg, 0.049 mmol), N-ethyl-2,5-difluoro-4-(piperazin-1-yl)benzamide hydrochloride (15 mg,

0.049 mmol), (cyanomethyl)trimethylphosphonium iodide (17.38 mg, 0.074 mmol) and N,N-diisopropylethylamine (0.043 mL, 0.245 mmol) were suspended in propionontrile (Volume: 0.2 mL) and heated in a closed vial at 90 °C for 2h. The reaction mixture became a dark brown solution. It was cooled to room temperature, diluted with dichloromethane (2 mL) and methanol (0.3 mL), and purified using flash column chromatography on silica gel (12 g SiO_2, dichloromethane - methanol 100:0 - 90:10). The resulting solid was suspended in ether (1 mL), stirred until a fine suspension resulted, filtered and the solid was recrystallized from MeOH-water (1:7, 4 mL) and dried in vacuum to afford (S)-N-ethyl-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (8.5 mg, 0.018 mmol, 36.8 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.20 Hz, 3 H) 1.76 - 1.97 (m, 3 H) 2.11 (m, *J*=6.44, 4.17 Hz, 1 H) 2.36 - 2.42 (m, 4 H) 3.03 (br. s., 4 H) 3.12 - 3.22 (m, 2 H) 3.28 - 3.37 (m, 3 H) 3.46 - 3.59 (m, 1 H) 3.86 - 3.97 (m, 1 H) 6.81 (dd, *J*=12.63, 7.07 Hz, 1 H) 6.91 (d, *J*=1.77 Hz, 1 H) 7.30 (dd, *J*=13.64, 6.82 Hz, 1 H) 7.55 (d, *J*=1.52 Hz, 1 H) 7.95 - 8.04 (m, 1 H) 10.38 (s, 1 H). [M+H] calc'd for $C_{24}H_{28}F_2N_6O_2$, 471; found, 471.

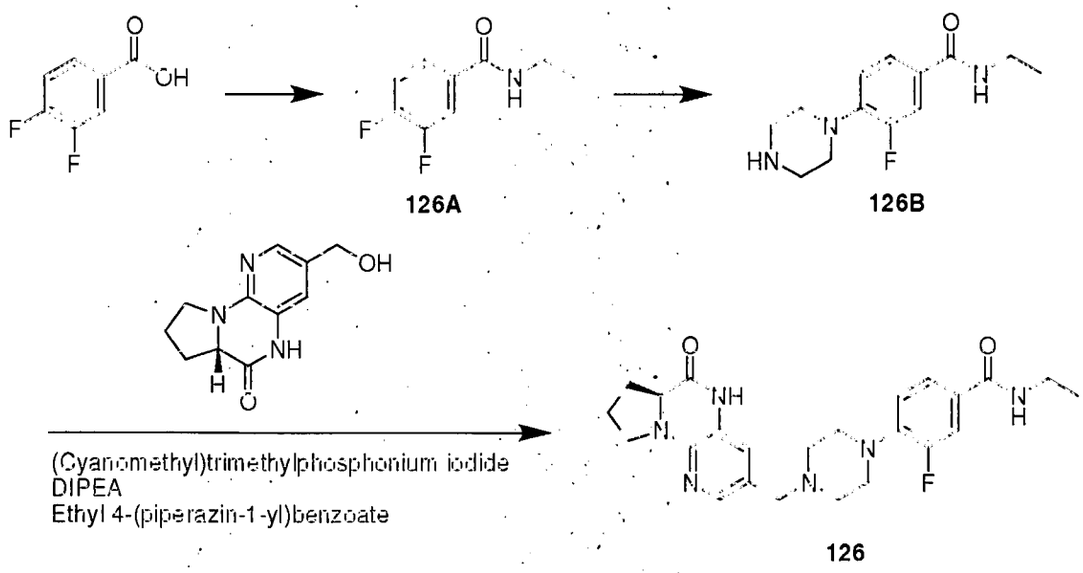
Compound 125: (S)-N-ethyl-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0597] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (76 mg, 0.348 mmol), N-ethyl-2-fluoro-4-(piperazin-1-yl)benzamide hydrochloride (100 mg, 0.348 mmol), (cyanomethyl)trimethylphosphonium iodide (127 mg, 0.521 mmol) and N,N-diisopropylethylamine (0.303 ml, 1.738 mmol) were suspended in propionontrile (Volume: 1.370 ml) and heated in a closed vial at 120 °C for 3h. The reaction mixture became a dark brown suspension. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 10-95% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-methanol (5:1, 6 mL) and dried in vacuum to afford (S)-N-ethyl-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (23.5 mg, 0.063 mmol, 18.12 % yield) as a brownish solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.13 (t, *J*=7.20 Hz, 3 H) 1.83 - 2.02 (m, 3 H) 2.18 (dd, *J*=6.44, 4.17 Hz, 1 H) 2.44 - 2.49 (m, 4 H)

2.81 - 3.01 (m, 4 H) 3.23 - 3.32 (m, 2 H) 3.34 - 3.44 (m, 3 H) 3.52 - 3.64 (m, 1 H) 3.93 - 4.01 (m, 1 H) 6.91 (td, *J*=8.21, 2.53 Hz, 1 H) 6.97 (d, *J*=1.77 Hz, 1 H) 7.00 (dd, *J*=11.37, 2.53 Hz, 1 H) 7.62 (d, *J*=1.52 Hz, 1 H) 7.67 (dd, *J*=8.46, 7.20 Hz, 1 H) 8.86 (t, *J*=5.43 Hz, 1 H) 10.45 (s, 1 H). [M+H] calc'd for $C_{24}H_{29}FN_6O_2$, 453; found, 453.

Compound 126: (S)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



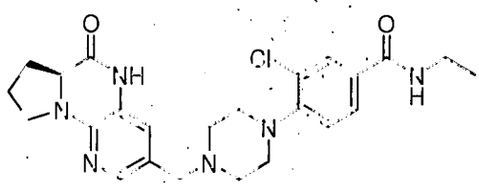
[0598] Compound 126A: 3,4-difluoro-N-ethylbenzamide: Using ethanamine hydrochloride and 3,4-difluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (56% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.12 (t, *J*=7.20 Hz, 3 H) 3.28 (qd, *J*=7.24, 5.56 Hz, 2 H) 7.55 (dt, *J*=10.48, 8.40 Hz, 1 H) 7.73 (m, *J*=7.33, 4.74, 2.08, 1.14, 1.14 Hz, 1 H) 7.88 (ddd, *J*=11.75, 7.83, 2.15 Hz, 1 H) 8.58 (t, *J*=4.93 Hz, 1 H). ESI-MS: m/z 186.1 $(M+H)^+$. mp=94.1-96.2°C.

[0599] Compound 126B: 3-fluoro-N-ethyl-4-(piperazin-1-yl)benzamide: Using 3,4-difluoro-N-ethylbenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (80% yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.20 Hz, 3 H) 2.31 (br. s., 1 H) 2.79 - 2.87 (m, 4 H) 2.95 - 3.03 (m, 4 H) 3.26 (qd, *J*=7.20, 5.68 Hz, 2 H) 7.03 (t, *J*=8.59 Hz, 1 H) 7.55 - 7.65 (m, 2 H) 8.35 (t, *J*=5.43 Hz, 1 H). ESI-MS: m/z 252.2 $(M+H)^+$. mp = 142.4-144.9°C.

[0600] Compound 126: (S)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (126): (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one

(100 mg, 0.456 mmol), N-ethyl-3-fluoro-4-(piperazin-1-yl)benzamide hydrochloride (131 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 10-95% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-methanol (5:1, 6mL) and dried in vacuum to afford (S)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (32.3 mg, 0.182 mmol, 39.9 % yield) as a yellow-green solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 0.98 - 1.08 (m, 3 H) 1.77 - 1.96 (m, 3 H) 2.04 - 2.18 (m, 1 H) 2.35 - 2.43 (m, 4 H) 2.93 - 3.07 (m, 4 H) 3.13 - 3.23 (m, 2 H) 3.28 - 3.38 (m, 3 H) 3.47 - 3.57 (m, 1 H) 3.88 - 3.95 (m, 1 H) 6.92 (d, *J*=2.02 Hz, 1 H) 6.97 (t, *J*=8.84 Hz, 1 H) 7.47 - 7.57 (m, 3 H) 8.28 (t, *J*=5.56 Hz, 1 H) 10.37 (s, 1 H). [M+H] calc'd for $C_{24}H_{29}FN_6O_2$, 453; found, 453.

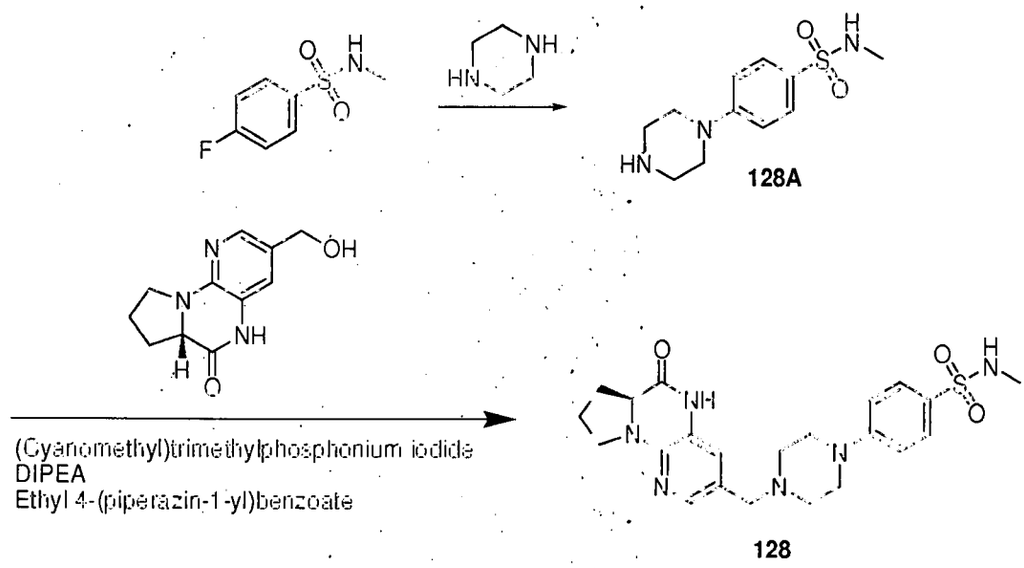
Compound 127: (S)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0601] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-chloro-N-ethyl-4-(piperazin-1-yl)benzamide hydrochloride (139 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 10-95% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-methanol (5:1, 6mL) and dried in vacuum to afford (S)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (75.6 mg, 0.161 mmol, 35.3 % yield) as a tan solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.03 (t, *J*=7.20 Hz, 3 H) 1.76 - 1.93 (m, 3 H) 2.06 - 2.17 (m, 1 H) 2.44 - 2.51 (m, 4 H) 2.96 (br. s., 4 H) 3.14 - 3.23 (m, 2 H) 3.28 - 3.38 (m, 3 H) 3.46 -

3.53 (m, 1 H) 3.83 - 3.97 (m, 1 H) 6.92 (d, *J*=2.02 Hz, 1 H) 7.10 (d, *J*=8.34 Hz, 1 H) 7.56 (d, *J*=1.77 Hz, 1 H) 7.70 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.81 (d, *J*=2.27 Hz, 1 H) 8.37 (t, *J*=5.43 Hz, 1 H) 10.38 (s, 1 H). [M+H] calc'd for $C_{24}H_{29}ClN_6O_2$, 469; found, 469.

Compound 128: (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzenesulfonamide

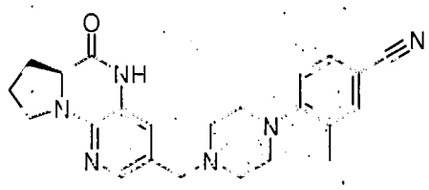


[0602] Compound 128A: N-methyl-4-(piperazin-1-yl)benzenesulfonamide: 4-fluoro-N-methylbenzenesulfonamide (189 mg, 0.999 mmol) and piperazine (430 mg, 4.99 mmol) were combined and the reaction mixture was stirred at 120 °C for 2h. It was diluted with water (5 mL) and stirred until a fine suspension resulted. The precipitate was filtered, washed with water (5x3 mL) and dried in vacuum to afford N-methyl-4-(piperazin-1-yl)benzenesulfonamide (222 mg, 0.869 mmol, 87 % yield) as a white solid. ESI-MS : m/z 256 $(M+H)^+$.

[0603] Compound 128: (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzenesulfonamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), N-methyl-4-(piperazin-1-yl)benzenesulfonamide (116 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propionitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 10-95% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-methanol (2:1,

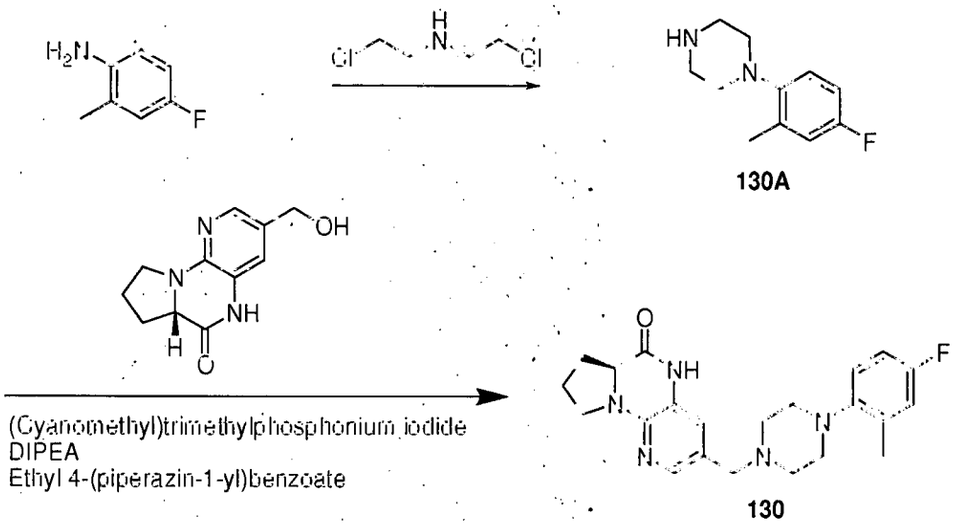
6mL) and dried in vacuum to afford (S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzenesulfonamide (110 mg, 0.241 mmol, 52.8 % yield) as a tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.38 - 2.04 (m, 3 H) 2.15 - 2.27 (m, 1 H) 2.38 (d, *J*=4.80 Hz, 3 H) 2.51 (d, *J*=4.29 Hz, 4 H) 3.32 (br. s., 4 H) 3.38 - 3.49 (m, 3 H) 3.57 - 3.69 (m, 1 H) 3.97 - 4.07 (m, 1 H) 7.02 (d, *J*=1.52 Hz, 1 H) 7.07 (d, *J*=9.09 Hz, 2 H) 7.15 (q, *J*=4.72 Hz, 1 H) 7.59 (d, *J*=8.84 Hz, 2 H) 7.66 (d, *J*=1.77 Hz, 1 H) 10.48 (s, 1 H). [M+H] calc'd for $C_{24}H_{29}ClN_6O_2$, 457; found, 457.

Compound 129: (S)-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile



[0604] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-methyl-4-(piperazin-1-yl)benzonitrile (92 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propionitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HFLC (basic, 10-95% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water (6 mL) and dried in vacuum to afford (S)-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile (90.1 mg, 0.224 mmol, 49.1 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.85 - 2.01 (m, 3 H) 2.12 - 2.21 (m, 1 H) 2.24 (s, 3 H) 2.43 - 2.55 (m, 4 H) 2.85 - 2.97 (m, 4 H) 3.35 - 3.44 (m, 3 H) 3.53 - 3.63 (m, 1 H) 3.95 - 4.03 (m, 1 H) 6.98 (d, J=2.02 Hz, 1 H) 7.05 - 7.12 (m, 1 H) 7.54 - 7.60 (m, 2 H) 7.62 (d, J=1.77 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{23}H_{26}N_6O$, 403; found, 403.

Compound 130: (S)-3-((4-(4-fluoro-2-methylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one

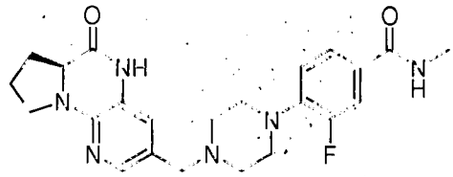


[0605] Compound 130A: 1-(4-fluoro-2-methylphenyl)piperazine: Bis(2-chloroethyl)amine hydrochloride (1.79 g, 10.03 mmol) and 4-fluoro-2-methylaniline (1.26 g, 10.07 mmol) were dissolved in 2-propanol (Volume: 10 mL) and stirred in a closed vial at 100 °C overnight. The reaction mixture was diluted with i-PrOH (10 mL) and cooled to 10 °C. The resulting precipitate was filtered and purified using HPLC (10-30% ACN in water, TFA-buffered). The fractions were concentrated in vacuo, suspended in ether (3 mL) and treated with 4N HCl in dioxane (1 mL). The precipitate was filtered and dried in vacuum to afford 1-(4-fluoro-2-methylphenyl)piperazine dihydrochloride (150 mg, 0.561 mmol, 5.60 % yield). ESI-MS : m/z 195 $(M+H)^+$.

[0606] Compound 130: (S)-3-((4-(4-fluoro-2-methylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 1-(4-fluoro-2-methylphenyl)piperazine dihydrochloride (122 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.634 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford (S)-3-((4-(4-fluoro-2-methylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (102.3 mg, 0.259 mmol, 56.7

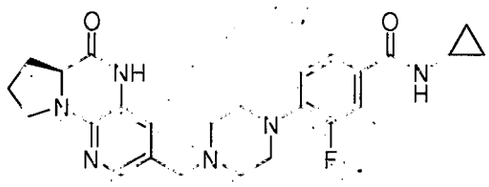
% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.80 - 2.02 (m, 3 H) 2.09 - 2.20 (m, 1 H) 2.23 (s, 3 H) 2.37 - 2.49 (m, 4 H) 2.77 (br. s., 4 H) 3.34 - 3.44 (m, 3 H) 3.52 - 3.65 (m, 1 H) 3.93 - 4.03 (m, 1 H) 6.88 - 7.07 (m, 4 H) 7.62 (s, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{22}H_{26}FN_5O$, 396; found, 396.

Compound 131: (S)-3-fluoro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



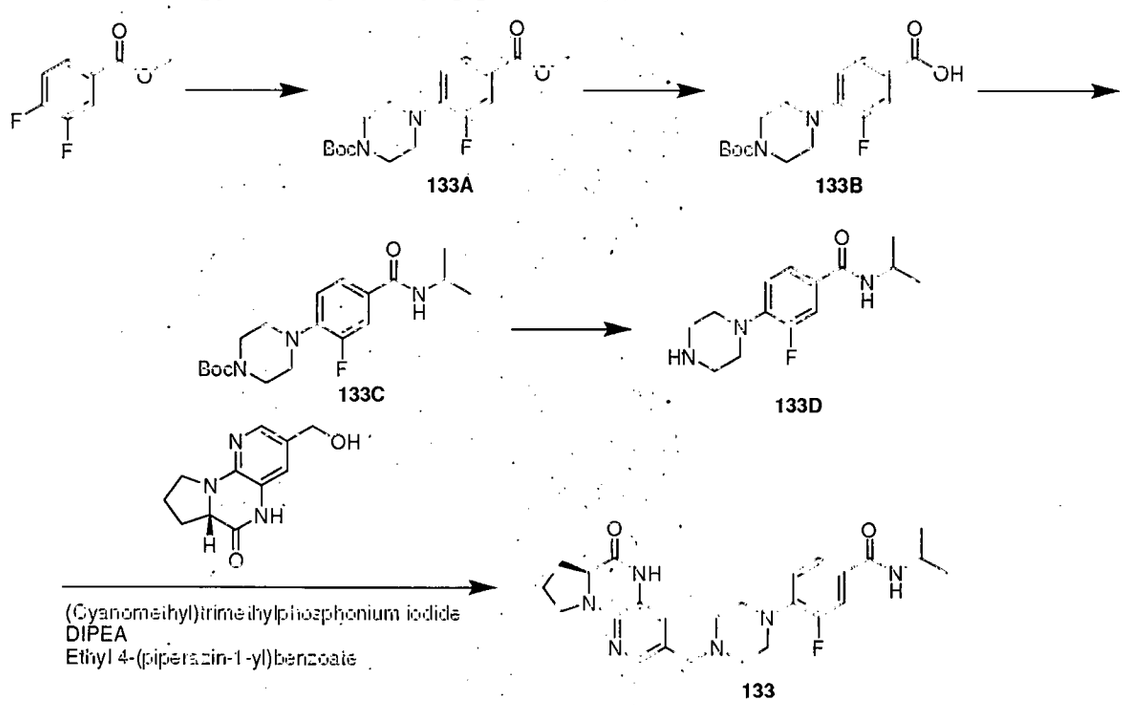
[0607] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-fluoro-N-methyl-4-(piperazin-1-yl)benzamide hydrochloride (125 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford (S)-3-fluoro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (128.5 mg, 0.293 mmol, 64.2 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 - 2.03 (m, 3 H) 2.09 - 2.25 (m, 1 H) 2.50 (m, 4 H) 2.75 (d, J=4.29 Hz, 3 H) 2.96 - 3.14 (m, 4 H) 3.35 - 3.45 (m, 3 H) 3.53 - 3.65 (m, 1 H) 3.93 - 4.05 (m, 1 H) 6.98 (d, J=1.77 Hz, 1 H) 7.04 (t, J=8.59 Hz, 1 H) 7.51 - 7.67 (m, 3 H) 8.27 - 8.38 (m, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{23}H_{27}FN_6O_2$, 439; found, 439.

Compound 132: (S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0608] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), N-cyclopropyl-3-fluoro-4-(piperazin-1-yl)benzamide hydrochloride (137 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propionontrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford (S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (35.3 mg, 0.184 mmol, 40.3 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.45 - 0.61 (m, 2 H) 0.61 - 0.76 (m, 2 H) 1.83 - 2.05 (m, 3 H) 2.08 - 2.25 (m, 1 H) 2.44 - 2.49 (m, 4 H) 2.80 (td, *J*=7.33, 3.79 Hz, 1 H) 3.08 (br. s., 4 H) 3.54 - 3.66 (m, 1 H) 3.91 - 4.06 (m, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.02 (t, *J*=8.84 Hz, 1 H) 7.49 - 7.69 (m, 3 H) 8.31 (d, *J*=4.04 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{25}H_{29}FN_6O_2$, 465; found, 465.

Compound 133: (S)-3-fluoro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0609] Compound 133A: tert-butyl 4-(2-fluoro-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate: Potassium carbonate (5.56 g, 40.3 mmol) and tert-butyl piperazine-1-carboxylate (6.92 g, 37.2 mmol) were combined, methyl 3,4-difluorobenzoate (5.33 g, 31.0 mmol) was added and the reaction mixture was stirred at 90 °C for 1 d. The mixture was triturated with ethyl acetate (3 X 5 mL) and the combined organic extracts were filtered. This was concentrated down to about 5-10 mL and subjected to flash column chromatography on silica gel (120 g SiO2, hexanes : ethyl acetate 1:0 to 4:1) to afford tert-butyl 4-(2-fluoro-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (4.702 g, 13.90 mmol, 44.9 % yield) as a white solid. ESI-MS : m/z 339 $(M+H)^+$.

[0610] Compound 133B: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-fluorobenzoic acid: Tert-butyl 4-(2-fluoro-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (4.6 g, 13.59 mmol) was suspended in 1,4-Dioxane (Volume: 68.0 ml) and treated with 1N LiOH (68.0 ml, 68.0 mmol). The reaction mixture was stirred at room temperature for 23 h. The reaction mixture was concentrated in vacuo until most of the dioxane was gone and acidified with HCl (4.5 N) until a thick precipitate resulted. It was filtered off, washed with water and dried in vacuum to afford 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-fluorobenzoic acid (4.40 g, 13.57 mmol, 100 % yield) as a brown solid. ESI-MS : m/z 325 $(M+H)^+$.

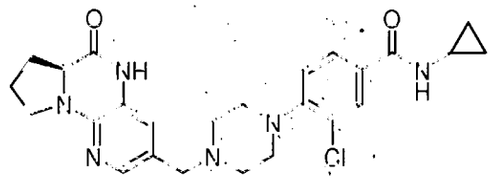
[0611] Compound 133C: tert-butyl 4-(2-fluoro-4-(isopropylcarbamoyl)phenyl)piperazine-1-carboxylate: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-3-fluorobenzoic acid (1.1 g, 3.39 mmol), propan-2-amine (0.241 g, 4.07 mmol), N1-((ethylimino)methylene)-N3,N3-dimethylpropane-1,3-diamine hydrochloride (0.975 g, 5.09 mmol) and 1H-benzo[d][1,2,3]triazol-1-ol hydrate (0.779 g, 5.09 mmol) were suspended in DMF (Volume: 13.57 ml) and 4-methylmorpholine (1.864 ml, 16.96 mmol) was added. The reaction mixture was stirred at ambient temperature for 2h. It was diluted with water (50 mL) and extracted with ethyl acetate (3X100 mL). The combined organic extracts were washed with brine (3x50 mL), dried (MgSO4) and concentrated in vacuo to afford tert-butyl 4-(2-fluoro-4-(isopropylcarbamoyl)phenyl)piperazine-1-carboxylate (1.11 g, 3.04 mmol, 89 % yield) as an off-white solid. ESI-MS : m/z 366 $(M+H)^+$.

[0612] Compound 133D: 3-fluoro-N-isopropyl-4-(piperazin-1-yl)benzamide (133D): Tert-butyl 4-(2-fluoro-4-(isopropylcarbamoyl)phenyl)piperazine-1-carboxylate (1.10 g, 3.01 mmol) was diluted with 4.0M HCl in dioxane (3 mL) and stirred for 30 min. The thick white precipitate that formed was diluted with ethyl ether (10 mL) and stirred until a fine suspension resulted. The precipitate was filtered under nitrogen and dried in vacuum to afford 3-fluoro-N-

isopropyl-4-(piperazin-1-yl)benzamide hydrochloride as a white solid. ESI-MS : m/z 302 $(M+H)^+$.

[0613] Compound 133: (S)-3-fluoro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-fluoro-N-isopropyl-4-(piperazin-1-yl)benzamide hydrochloride (133 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford (S)-3-fluoro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (71.4 mg, 0.153 mmol, 33.6 % yield) as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (d, J=6.57 Hz, 6 H) 1.82 - 2.01 (m, 3 H) 2.12 - 2.24 (m, 1 H) 2.46 - 2.50 (m, 4 H) 2.98 - 3.15 (m, 4 H) 3.35 - 3.44 (m, 3 H) 3.54 - 3.64 (m, 1 H) 3.92 - 4.14 (m, 2 H) 6.98 (d, J=1.77 Hz, 1 H) 7.03 (t, J=8.34 Hz, 1 H) 7.56 - 7.66 (m, 3 H) 8.09 (d, J=7.33 Hz, 1 H) 10.45 (s, 1 H). [M+H] calc'd for $C_{25}H_{31}FN_6O_2$; 467; found, 467.

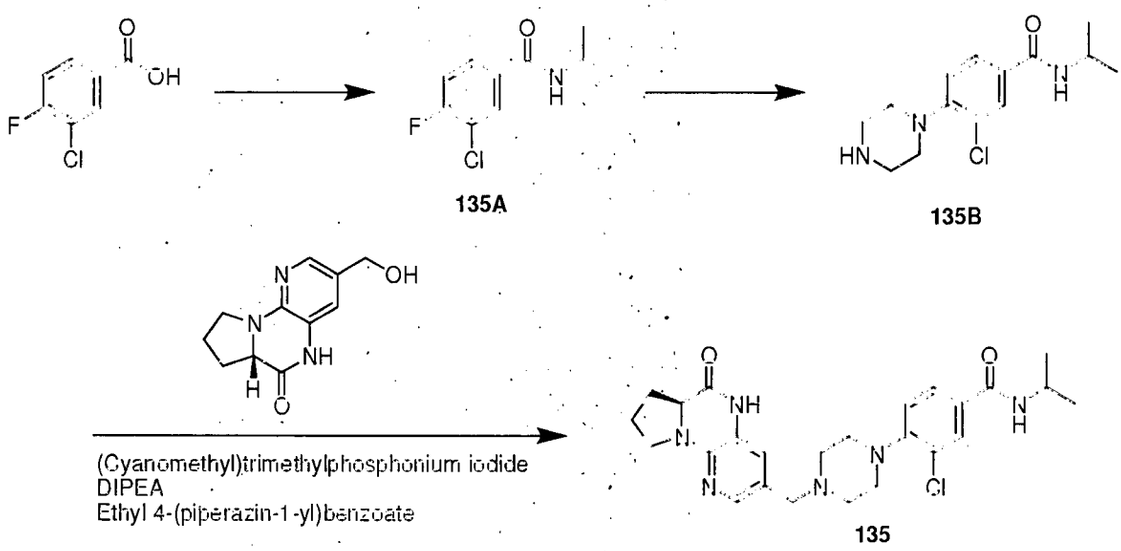
Compound 134: (S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0614] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-chloro-N-cyclopropyl-4-(piperazin-1-yl)benzamide (128 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0 684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 25-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-

MeOH (2:1, 15 mL) and dried in vacuum to afford(S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (120.4 mg, 0.250 mmol, 54.9 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.50 - 0.60 (m, 2 H) 0.61 - 0.72 (m, 2 H) 1.84 - 2.01 (m, 3 H) 2.12 - 2.23 (m, 1 H) 2.51 - 2.57 (m, 4 H) 2.77 - 2.86 (m, 1 H) 3.02 (br. s., 4 H) 3.35 - 3.46 (m, 3 H) 3.54 - 3.64 (m, 1 H) 3.95 - 4.03 (m, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.16 (d, *J*=8.34 Hz, 1 H) 7.63 (d, *J*=1.77 Hz, 1 H) 7.75 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.85 (d, *J*=2.02 Hz, 1 H) 8.39 (d, *J*=4.04 Hz, 1 H) 10.45 (s, 1 H). [M+H] calc'd for $C_{25}H_{29}ClN_6O_2$, 481; found, 481.

Compound 135: (S)-3-chloro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



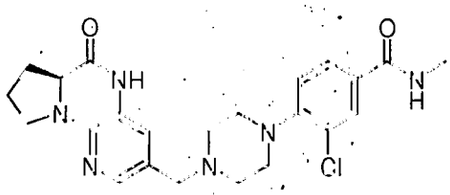
[0615] Compound 135A: 3-chloro-4-fluoro-N-isopropylbenzamide: Using isopropylamine hydrochloride and 3-chloro-4-fluorobenzoic acid in the general procedure for coupling of amines to carboxylic acids, the title compound was obtained (81% yield) as a white solid. ESI-MS: m/z 216 $(M+H)^+$.

[0616] Compound 135B: 3-chloro-N-isopropyl-4-(piperazin-1-yl)benzamide: Using 3-chloro-4-fluoro-N-isopropylbenzamide in the general procedure for nucleophilic aromatic substitution reactions, the title compound was obtained (51% yield) as an off-white solid. ESI-MS: m/z 282.2 $(M+H)^+$.

[0617] Compound 135: (S)-3-chloro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg,

0.456 mmol), 3-chloro-N-isopropyl-4-(piperazin-1-yl)benzamide (129 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.393 ml, 2.281 mmol) were suspended in propionontrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 25-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 15 mL) and dried in vacuum to afford (S)-3-chloro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (122.1 mg, 0.253 mmol, 55.4 % yield) as a light tan solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (d, *J*=6.57 Hz, 6 H) 1.84 - 2.03 (m, 3 H) 2.12 - 2.25 (m, 1 H) 2.50 - 2.59 (m, 4 H) 3.02 (br. s., 4 H) 3.35 - 3.45 (m, 3 H) 3.53 - 3.64 (m, 1 H) 3.94 - 4.09 (m, 2 H) 6.98 (d, *J*=1.52 Hz, 1 H) 7.17 (d, *J*=8.59 Hz, 1 H) 7.63 (d, *J*=1.77 Hz, 1 H) 7.77 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.89 (d, *J*=2.02 Hz, 1 H) 8.18 (d, *J*=7.58 Hz, 1 H) 10.45 (s, 1 H). [M+H] calc'd for $C_{25}H_{31}ClN_6O_2$, 483; found, 483.

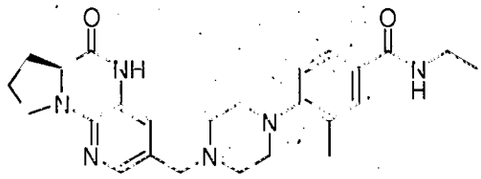
Compound 136: (S)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0618] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), 3-chloro-N-methyl-4-(piperazin-1-yl)benzamide hydrochloride (132 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.393 ml, 2.281 mmol) were suspended in propionontrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford (S)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (53.1 mg, 0.117 mmol, 25.6 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 - 2.02 (m, 3 H) 2.10 - 2.24 (m, 1 H) 2.51 (br.

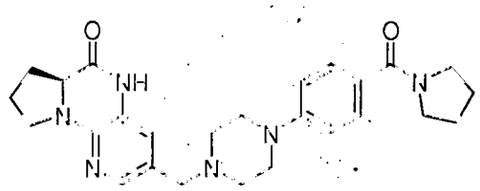
s., 4 H) 2.75 (d, *J*=4.55 Hz, 3 H) 3.03 (br. s., 4 H) 3.36 - 3.45 (m, 3 H) 3.52 - 3.65 (m, 1 H) 3.93 - 4.03 (m, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.17 (d, *J*=8.34 Hz, 1 H) 7.63 (d, *J*=1.77 Hz, 1 H) 7.75 (dd, *J*=8.34, 2.02 Hz, 1 H) 7.86 (d, *J*=2.02 Hz, 1 H) 8.41 (q, *J*=4.13 Hz, 1 H) 10.45 (s, 1 H). [M+H] calc'd for $C_{23}H_{27}ClN_6O_2$, 455; found, 455.

Compound 137: (S)-N-ethyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



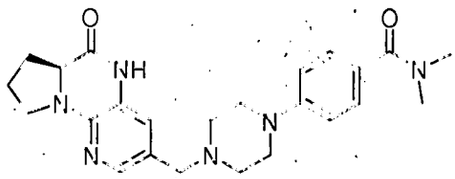
[0619] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.456 mmol), N-ethyl-3-methyl-4-(piperazin-1-yl)benzamide hydrochloride (129 mg, 0.456 mmol), (cyanomethyl)trimethylphosphonium iodide (166 mg, 0.684 mmol) and N,N-diisopropylethylamine (0.398 ml, 2.281 mmol) were suspended in propiononitrile (Volume: 1.370 ml) and heated in a closed vial at 90-120 °C for 4h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (basic, 45-95% ACN in water, basic). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (2:1, 6 mL) and dried in vacuum to afford(S)-N-ethyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (128.5 mg, 0.286 mmol, 62.8 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.83 - 2.03 (m, 3 H) 2.09 - 2.25 (m, 1 H) 2.50 (m, 4 H) 2.75 (d, *J*=4.29 Hz, 3 H) 2.96 - 3.14 (m, 4 H) 3.35 - 3.45 (m, 3 H) 3.53 - 3.65 (m, 1 H) 3.93 - 4.05 (m, 1 H) 6.98 (d, *J*=1.77 Hz, 1 H) 7.04 (t, *J*=8.59 Hz, 1 H) 7.51 - 7.67 (m, 3 H) 8.27 - 8.38 (m, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{25}H_{32}N_6O_2$, 449; found, 449.

Compound 138: (S)-3-((4-(4-(pyrrolidine-1-carbonyl)phenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one



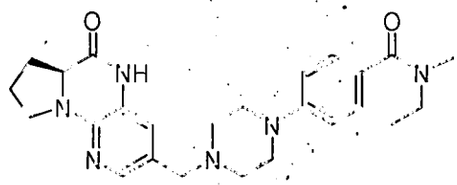
[0620] In a 1 dram vial, (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (100 mg, 0.245 mmol) was suspended in DMF (Volume: 1.227 mL) then added pyrrolidine (0.024 mL, 0.295 mmol), HATU (140 mg, 0.368 mmol) and N-methylmorpholine (0.108 mL, 0.982 mmol). The rxn was stirred at RT overnight. The mixture was purified by prep HPLC-MS (acidic mode, 15-35%). The pH of the combined fractions was adjusted to pH = 8-9 and extracted with EtOAc (3x30 ml), washed with brine, dried with $MgSO_4$, filtered and concentrated to dryness. The residue was taken up with water/ACN (1:1), and concentrated in vacuo to provide the title compound as a fluffy white solid (29 mg, 26% yield). m.p. = 121.3 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.73 - 1.87 (m, 4 H) 1.87 - 2.01 (m, 3 H) 2.14 - 2.21 (m, 1 H) 2.43 - 2.49 (m, 4 H) 3.15 - 3.23 (m, 4 H) 3.35 (br. s., 2 H) 3.37 - 3.49 (m, 5 H) 3.54 - 3.65 (m, 1 H) 3.95 - 4.04 (m, 1 H) 6.91 (d, *J*=9.09 Hz, 2 H) 6.99 (d, *J*=2.02 Hz, 1 H) 7.42 (d, *J*=8.84 Hz, 2H) 7.62 (d, *J*=1.77 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{26}H_{32}N_6O_2$, 461; found, 461.

Compound 139: (S)-N,N-dimethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



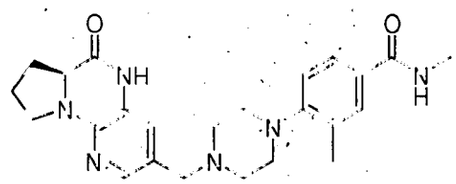
[0621] In a 1 dram vial, (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (100 mg, 0.245 mmol) was suspended in DMF (Volume: 1.227 mL) then added dimethylamine hydrochloride (24.02 mg, 0.295 mmol), HATU (140 mg, 0.368 mmol) and N-methylmorpholine (0.108 mL, 0.982 mmol). The reaction was stirred at RT overnight. The mixture was purified by prep HPLC-MS (acidic mode, 15-35%). The pH of the combined fractions was adjusted to pH = 8-9 and extracted with EtOAc (3x30 ml), washed with brine, dried with $MgSO_4$, filtered and concentrated to dryness. The residue was taken up with water/ACN (1:1), and concentrated in vacuo to provide the title compound as a fluffy white solid (21 mg, 19% yield). m.p. = 99.2 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.85 - 2.04 (m, 3 H) 2.12 - 2.21 (m, 1 H) 2.43 - 2.49 (m, 4 H) 2.94 (s, 6 H) 3.14 - 3.23 (m, 4 H) 3.35 - 3.43 (m, 3 H) 3.54 - 3.64 (m, 1 H) 3.94 - 4.03 (m, 1 H) 6.92 (d, *J*=9.09 Hz, 2 H) 6.99 (d, *J*=1.77 Hz, 1 H) 7.29 (d, *J*=8.84 Hz, 2 H) 7.62 (d, *J*=1.52 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{24}H_{30}N_6O_2$, 435; found, 435.

Compound 140: (S)-N-ethyl-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0622] In a 1 dram vial, (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid (100 mg, 0.245 mmol) was suspended in DMF (Volume: 1.227 mL) then added N-methylethanamine (0.025 mL, 0.295 mmol), HATU (140 mg, 0.368 mmol) and N-methylmorpholine (0.108 mL, 0.982 mmol). The reaction was stirred at RT overnight. The mixture was purified by prep HPLC-MS (acidic mode, 15-35%). The pH of the combined fractions was adjusted to pH = 8-9 and extracted with EtOAc (3x30 ml), washed with brine, dried with $MgSO_4$, filtered and concentrated to dryness. The residue was taken up with water/ACN (1:1), and concentrated in vacuo to provide the title compound as a fluffy white solid (13 mg, 17% yield). m.p. = 91.9 °C. ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1.09 (t, *J*=7.07 Hz, 3 H) 1.24 (br. s., 3 H) 1.85 - 2.04 (m, 3 H) 2.13 - 2.21 (m, 1 H) 2.43 - 2.48 (m, 3 H) 2.90 (s, 3 H) 3.14 - 3.22 (m, 4 H) 3.34 - 3.43 (m, 3 H) 3.54 - 3.64 (m, 1 H) 3.95 - 4.02 (m, 1 H) 6.92 (d, *J*=8.84 Hz, 2 H) 6.99 (d, *J*=2.02 Hz, 1 H) 7.25 (d, *J*=8.59 Hz, 2 H) 7.62 (d, *J*=1.77 Hz, 1 H) 10.44 (s, 1 H). [M+H] calc'd for $C_{25}H_{32}N_6O_2$, 449; found, 449.

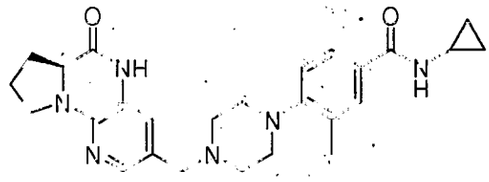
Compound 141: (S)-N,3-dimethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0623] (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (300 mg, 1.368 mmol), [Reactants], (cyanomethyl)trimethylphosphonium iodide (499 mg, 2.053 mmol) and N,N-diisopropylethylamine (1195 µl, 6.84 mmol) were suspended in propiononitrile (Volume: 4109 µl) and heated in a closed vial at 120 °C for 2h. The reaction mixture became a dark brown solution. It was cooled to room temperature, concentrated in vacuo, dissolved in DMSO (2 mL) and purified using HPLC (NH_4HCO_3 buffered, 20-70% ACN in water). The fractions were concentrated in vacuo and the resulting solid was recrystallized from water-MeOH (1:1, 5 mL), and then from ACN (30 mL), and dried in

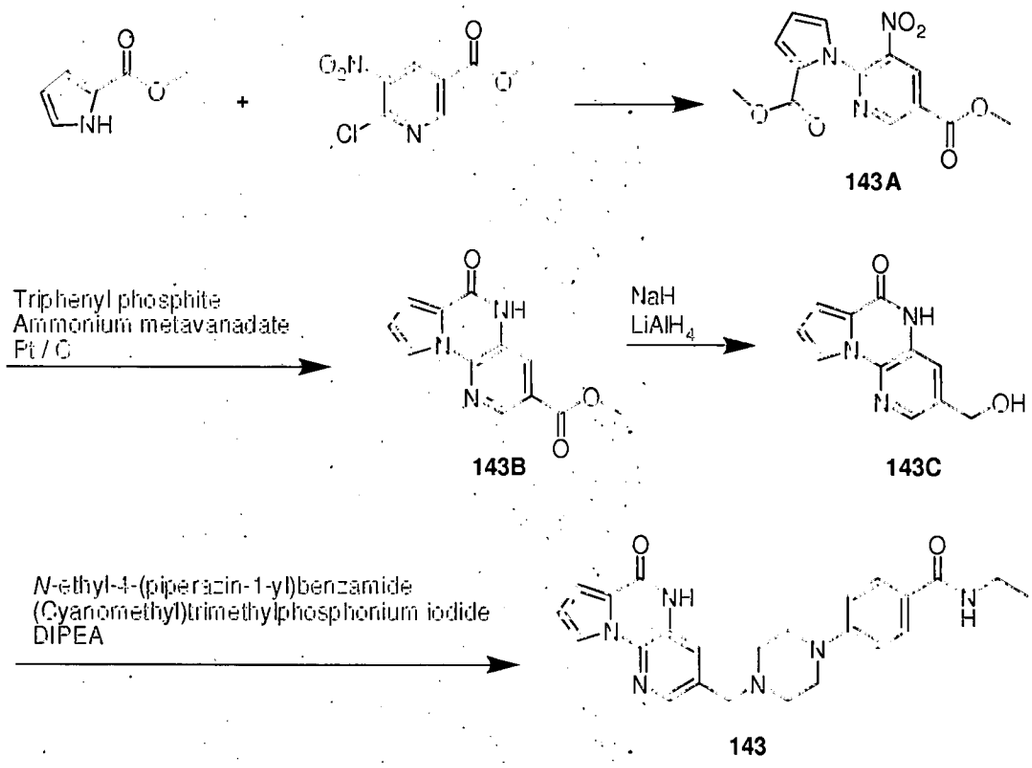
vacuum to afford (S)-N,3-dimethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (232.7 mg, 0.536 mmol, 39.1 % yield) as a light tan solid. ^{1}H NMR (DMSO-d_6) δ: 10.40 (s, 1H), 8.19 (q, J = 4.0 Hz, 1H), 7.57 - 7.66 (m, 3H), 6.95 - 7.04 (m, 2H), 3.93 - 4.02 (m, 1H), 3.54 - 3.64 (m, 1H), 3.38 (s, 3H), 2.87 (br. s., 4H), 2.74 (d, J = 4.5 Hz, 3H), 2.49 - 2.55 (m, 4H), 2.25 (s, 3H), 2.11 - 2.22 (m, 1H), 1.80 - 2.02 (m, 3H). [M+H] calc'd for $C_{24}H_{30}N_6O_2$, 435; found, 435.

Compound 142: (S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



[0624] To a suspension of (S)-3-(hydroxymethyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (0.1 g, 0.456 mmol), N-cyclopropyl-3-methyl-4-(piperazin-1-yl)benzamide dihydrochloride (0.179 g, 0.538 mmol), and (cyanomethyl)trimethylphosphonium iodide (0.188 g, 0.775 mmol) in Propiononitrile (Volume: 2.0 mL) was added N-ethyl-N-isopropylpropan-2-amine (0.556 mL, 3.19 mmol) at 23 °C. The reaction was stirred at 90 °C for 8 hr. The reaction mixture was cooled to room temperature, filtered, and rinsed with propiononitrile (3 x 1 mL). The resulting solid was reconstituted in DMSO (Volume: 3.0 mL) and purified via preparative mass trigger LCMS using a gradient eluant of 25-65% ACN:10 mM NH_4HCO_3 (aq). The collected fractions were combined and the ACN was removed via rotary evaporation to furnish a suspension. The suspension was filtered, rinsed with H2O (3 x 10 mL), and the resulting solid was dried *in vacuo* to provide (S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (0.0624 g, 0.135 mmol, 29.7 % yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.50 - 0.59 (m, 2 H) 0.60 - 0.70 (m, 2 H) 1.86 - 2.00 (m, 3 H) 2.14 - 2.20 (m, 1 H) 2.25 (s, 3 H) 2.47 - 2.50 (m, 4 H) 2.76 - 2.93 (m, 5 H) 3.34 - 3.44 (m, 3 H) 3.55 - 3.63 (m, 1 H) 3.93 - 4.02 (m, 1 H) 6.96 - 7.04 (m, 2 H) 7.56 - 7.67 (m, 3 H) 8.22 (d, *J*=4.29 Hz, 1 H) 10.45 (s, 1 H). ESI-MS : m/z 461.4 $(M+H)^+$. mp = 226.7-233.5 °C.

Compound 143: N-ethyl-4-(4-((6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide



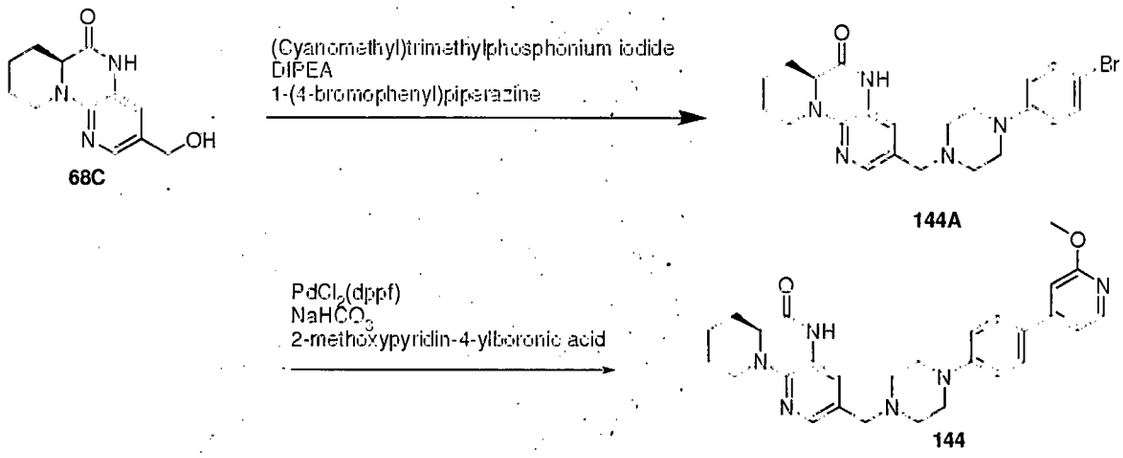
[0625] Compound 143A: Methyl 6-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)-5-nitronicotinate: Methyl 1H-pyrrole-2-carboxylate (5.78 g, 46.2 mmol) was dissolved in DMSO and cooled to 10 °C. NaH was added in two portions over 5 min. The reaction mixture was stirred at 10 °C for 10 min and methyl 6-chloro-5-nitronicotinate (5 g, 23.09 mmol) in DMSO (10 mL) was added slowly over 3 min. The red reaction mixture was allowed to warm to room temperature and stirred overnight. It was cooled to 0 °C and quenched with water (12 mL) and diluted with brine (50 mL). The mixture was washed with EtOAc (2 X 25 mL) and the aqueous layer was acidified to pH = 2 with 4.5 N HCl. It was extracted with EtOAc (1 X 100 mL) and the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to afford a yellow solid, which was dissolved in MeOH (100 mL) and cooled to 0 °C. Thionyl chloride (45 mL, 617 mmol) was added slowly over 5 min. The reaction mixture was stirred at 0 °C for 1h and then at room temperature overnight. It was concentrated in vacuo and the resulting solid was triturated with ethyl acetate (300 mL). The solid was filtered off and the filtrate was concentrated in vacuo. then washed with ethyl ether to afford methyl 6-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)-5-nitronicotinate (5.04 g, 16.51 mmol, 92 % yield) as a yellow solid, [M+H] calc'd for $C_{13}H_{11}N_3O_6$, 306; found, 306.

[0626] Compound 143B: Methyl 6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate: Methyl 6-(2-(methoxycarbonyl)-1H-pyrrol-1-yl)-5-nitronicotinate (5.00 g, 16.38 mmol) was dissolved in dichloromethane (Volume: 32 ml) and to this solution was added triphenyl phosphite (0.051 g, 0.164 mmol), ammonium metavanadate (0.115 g, 0.983 mmol) and Pt/C (5% wt.) (0.639 g, 0.164 mmol). The reaction mixture was hydrogenated at 100 psi at 25 °C for 36h. The reaction mixture was filtered through a short plug of celite and the plug and precipitate were washed well with methanol (100 mL) and then MeOH:DCM (100 mL, 1:1). The solids (celite and Pt/C) were continuously extracted with MeOH/DCM mixture (1:1) in a Soxlet extractor for 2d. The extracts were combined with the earlier filtrates, concentrated in vacuo, crystallized with MeOH (100 mL) and the resulting solid was filtered off and suspended in ethyl ether (200 mL). The solid were filtered off and dried in vacuum to afford methyl 6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate (2.15 g, 8.84 mmol, 54.0 % yield) as a grey solid. ^{1}H NMR (DMSO-d_6) δ 11.49 (s, 1H), 8.69 (s, 1H), 8.15 (br. s., 1H), 8.11 (s, 1H), 7.16 (d, J = 2.5 Hz, 1H), 6.78 (t, J = 3.0 Hz, 1H), 3.91 (s, 3H). [M+H] calc'd for $C_{12}H_9N_3O_3$, 244; found, 244.

[0627] Compound 143C: 3-(hydroxymethyl)pyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one: Methyl 6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate (2.0 g, 8.22 mmol) was suspended in THF (Volume: 27.4 ml) under nitrogen atmosphere and cooled to 0 °C. Sodium hydride (0.658 g, 16.45 mmol) was added in several portions over 7 min. The reaction mixture was stirred at 0 °C for 10 min, at room temperature for 20 min and cooled to below -50 °C. Lithium aluminum hydride (7.40 ml, 14.80 mmol) was added over the period of 5 min and the reaction was kept at a temperature between -30 and -20 °C for 1 h. The mixture was cooled to below -40 °C and MeOH (6 mL) was added. Water (5 mL) was added and then more MeOH (50 mL). The reaction mixture was stirred at rt for 10 min. The resulting precipitate was filtered, suspended in MeOH (100 mL) and filtered again. The solid was suspended with heating overnight in MeOH:DCM (1:1, 200 mL) and filtered hot. This solid was dissolved in MeOH/DCM (100 mL, 3:1) and loaded onto silica gel (12 g) then purified by flash column chromatography on silica gel (220 g SiO_2, gradient DCM:MeOH 100:1 - 85:15) to give 3-(hydroxymethyl)pyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (354 mg, 3.97 mmol, 48.3 % yield) as a white solid. ^{1}H NMR (DMSO-d6) δ 11.36 (br. s., 1H), 8.14 (d, J = 1.8 Hz, 1H), 8.10 (dd, J = 2.8, 1.5 Hz, 1H), 7.61 - 7.66 (m, 1H), 7.09 (dd, J = 3.8, 1.5 Hz, 1H), 6.71 (dd, J = 3.7, 2.9 Hz, 1H), 5.42 (br. s., 1H), 4.53 - 4.64 (m, 2H). [M+H] calc'd for $C_{11}H_9N_3O_2$, 216; found, 216.

[0628] Compound 143: N-ethyl-4-(4-((6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide: 3-(hydroxymethyl)pyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one (100 mg, 0.465 mmol), N-ethyl-4-(piperazin-1-yl)benzamide (119 mg, 0.511 mmol), (cyanomethyl)trimethylphosphonium iodide (158 mg, 0.651 mmol) and N,N-diisopropylethylamine (406 µl, 2.323 mmol) were suspended in propiononitrile (Volume: 1395 µl) and heated in a small closed vial for 7h at 90-120 °C (the temperature was increased by 10 °C after 4, 5 and 6 h. An additional portion of (cyanomethyl)trimethylphosphonium iodide (43.3 mg) was added after 4h. The reaction mixture was cooled to rt, filtered and the precipitate was washed with MeCN (5 mL) to give an off-white solid (168.4 mg) . The solid was heated to reflux in EtOH (15 mL) for 5 min and allowed to cool to ambient temperature. It was filtered and dried in vacuum to afford N-ethyl-4-(4-((6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide (112.5 mg, 0.261 mmol, 56.2 % yield) as a white solid. ^{1}H NMR (DMSO-d_6) δ: 11.31 (s, 1H), 8.08 - 8.17 (m, 3H), 7.71 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 1.8 Hz, 1H), 7.09 (dd, J = 3.7, 1.6 Hz, 1H), 6.93 (d, J = 8.8 Hz, 2H), 6.72 (dd, J = 3.7, 2.9 Hz, 1H), 3.62 (s, 2H), 3.20 - 3.28 (m, 6H), 2.52 - 2.59 (m, 4H), 1.09 (t, J = 7.2 Hz, 3H). [M+H] calc'd for $C_{24}H_{26}N_6O_2$, 431; found, 431.

Compound 144: (S)-3-((4-(4-(2-methoxypyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one

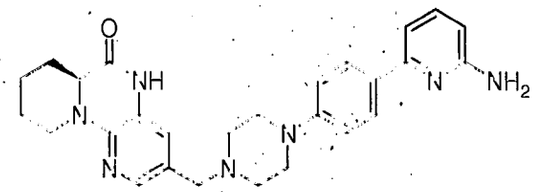


[0629] Compound 144A: (S)-3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one: Compound 144 was prepared using a procedure analogous to that described in connection with compound 68, except that 1-

(4-bromophenyl)piperazine was used instead of 4-(4-chlorophenyl)-1,2,3,6-tetrahydropyridine hydrochloride to give a white solid: [M+H] calc'd for $C_{22}H_{26}BrN_5O$, 456; found, 456.

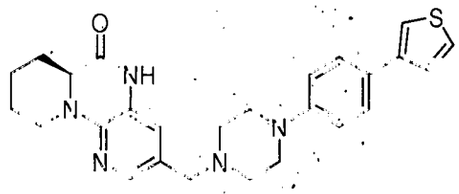
[0630] Compound 144: (S)-3-((4-(4-(2-methoxypyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one: (S)-3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one (.04 mmol), 2-methoxypyridin-4-ylboronic acid (0.060 mmol), FdCl2(dppf)-CH_2Cl_2 Adduct (3.27 mg, 4.00 μmol), sodium bicarbonate (0.500 ml, 0.500 mmol), dioxane (Volume: 1 ml) and a stir bar were sealed in a 5 mL microwave vial. The vial was heated to 135 °C for 30 minutes. The aqueous layer was removed from the vial and reaction mixture the filtered into a 1.8 mL HPLC submission vial. The reaction mixture was purified by LCMS to give a yellow solid: [M+H] calc'd for $C_{28}H_{32}N_6O_2$, 435; found, 435.

Compound 145: (S)-3-((4-(4-(6-aminopyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



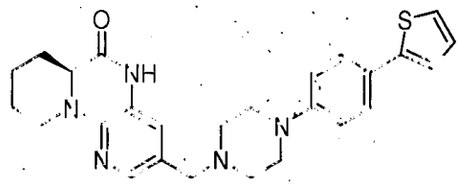
[0631] Compound 145 was prepared using a procedure analogous to that described in connection with compound 144, except that 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_7O$, 470; found, 470.

Compound 146: (S)-3-((4-(4-(thiophen-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



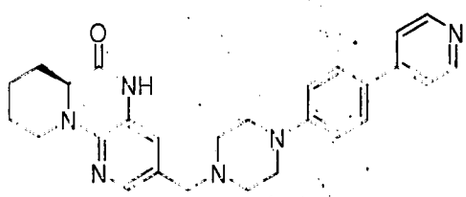
[0632] Compound 146 was prepared using a procedure analogous to that described in connection with compound 144, except that thiophen-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{26}H_{29}N_5OS$, 460; found, 460.

Compound 147: (S)-3-((4-(4-(thiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



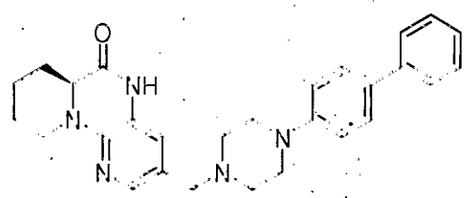
[0633] Compound 147 was prepared using a procedure analogous to that described in connection with compound 144, except that thiophen-2-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{26}H_{29}N_5OS$, 460; found, 460.

Compound 148: (S)-3-((4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



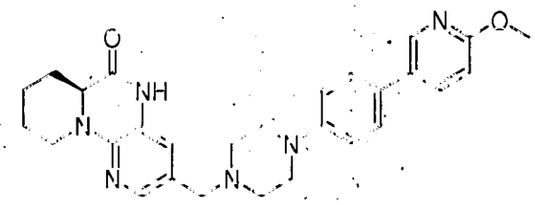
[0634] Compound 148 was prepared using a procedure analogous to that described in connection with compound 144, except that pyridin-4-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{30}N_6O$, 455; found, 455.

Comound 149: (S)-3-((4-(biphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



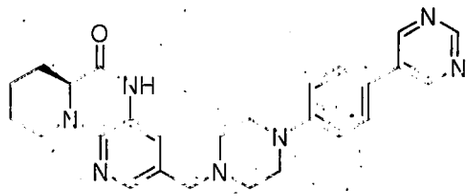
[0635] Compound 149 was prepared using a procedure analogous to that described in connection with compound 144, except that phenylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{31}N_5O$, 454; found, 454.

Compound 150: (S)-3-((4-(4-(6-methoxypyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



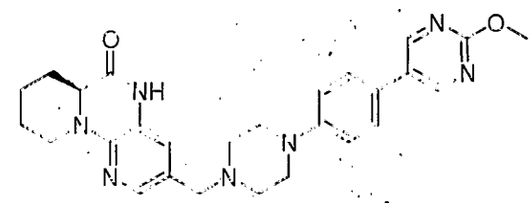
[0636] Compound 150 was prepared using a procedure analogous to that described in connection with compound 144, except that 6-methoxypyridin-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O_2$, 485; found, 485.

Compound 151: (S)-3-((4-(4-(pyrimidin-5-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one



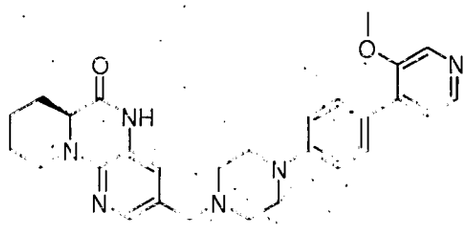
[0637] Compound 151 was prepared using a procedure analogous to that described in connection with compound 144, except that pyrimidin-5-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{26}H_{29}N_7O$, 456; found, 456.

Compound 152: (*S*)-3-((4-(4-(2-methoxypyrimidin-5-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



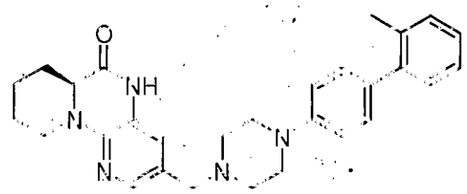
[0638] Compound 152 was prepared using a procedure analogous to that described in connection with compound 144, except that 2-methoxypyrimidin-5-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a green solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_7O_2$, 486; found, 486.

Compound 153: (*S*)-3-((4-(4-(3-methoxypyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



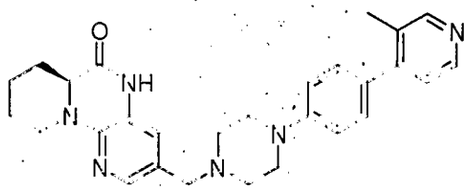
[0639] Compound 153 was prepared using a procedure analogous to that described in connection with compound 144, except that 3-methoxypyridin-4-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O_2$, 485; found, 485.

Compound 154: (*S*)-3-((4-(2'-methylbiphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



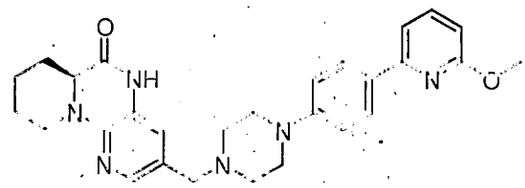
[0640] Compound 154 was prepared using a procedure analogous to that described in connection with compound 144, except that o-tolylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a gray solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{29}H_{33}N_5O$, 468; found, 468.

Compound 155: (*S*)-3-((4-(4-(3-methylpyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



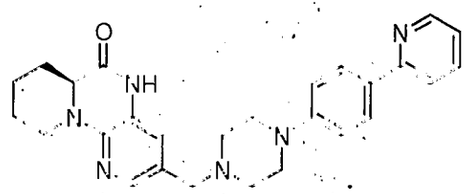
[0641] Compound 155 was prepared using a procedure analogous to that described in connection with compound 144, except that 3-methylpyridin-4-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O$, 469; found, 469.

Compound 156: (*S*)-3-((4-(4-(6-methoxypyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



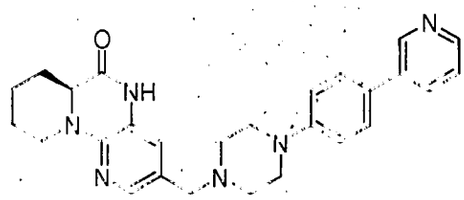
[0642] Compound 156 was prepared using a procedure analogous to that described in connection with compound 144, except that 2-methoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O_2$, 485; found, 485.

Compound 157: (*S*)-3-((4-(4-(pyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



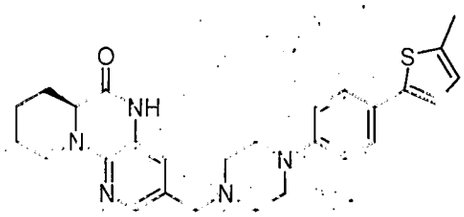
[0643] Compound 157 was prepared using a procedure analogous to that described in connection with compound 144, except that 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used instead of 2-methoxypyridin-4-ylboronic acid to give a yellow solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{30}N_6O$, 455; found, 455.

Compound 158: (*S*)-3-((4-(4-(pyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



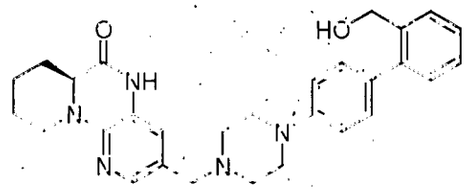
[0644] Compound 158 was prepared using a procedure analogous to that described in connection with compound 144, except that pyridin-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{30}N_6O$, 455; found, 455.

Compound 159: (*S*)-3-((4-(4-(5-methylthiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



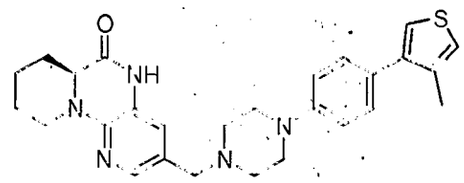
[0645] Compound 159 was prepared using a procedure analogous to that described in connection with compound 144, except that 5-methylthiophen-2-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_5OS$, 474; found, 474.

Compound 160: (*S*)-3-((4-(2'-(hydroxymethyl)biphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



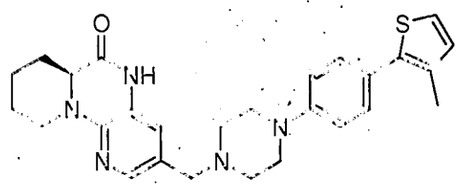
[0646] Compound 160 was prepared using a procedure analogous to that described in connection with compound 144, except that benzo[c][1,2]oxaborol-1(3H)-ol was used instead of 2-methoxypyridin-4-ylboronic acid to give a gray solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{29}H_{33}N_5O_2$, 484; found, 484.

Compound 161: (*S*)-3-((4-(4-(4-methylthiophen-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



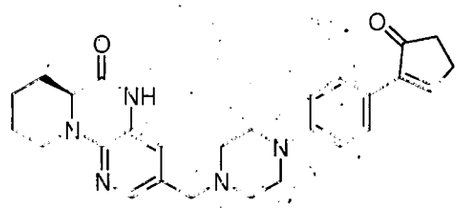
[0647] Compound 161 was prepared using a procedure analogous to that described in connection with compound 144, except that 4-methylthiophen-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_5OS$, 474; found, 474.

Compound 162: (*S*)-3-((4-(4-(3-methylthiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



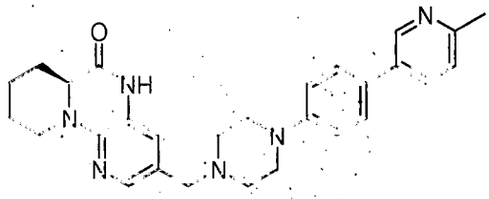
[0648] Compound 162 was prepared using a procedure analogous to that described in connection with compound 144, except that 3-methylthiophen-2-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a yellow solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_5OS$, 474; found, 474.

Compound 163: (*S*)-3-((4-(4-(5-oxocyclopent-1-enyl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



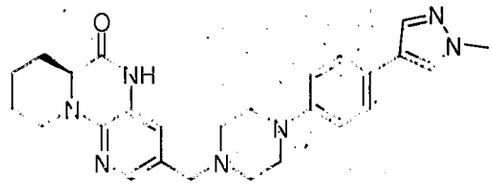
[0649] Compound 163 was prepared using a procedure analogous to that described in connection with compound 144, except that 5-oxocyclopent-1-enylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{27}H_{31}N_5O_2$, 458; found, 458.

Compound 164: (*S*)-3-((4-(4-(6-methylpyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



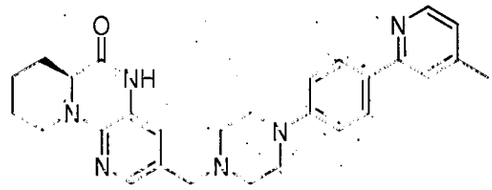
[0650] Compound 164 was prepared using a procedure analogous to that described in connection with compound 144, except that 6-methylpyridin-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a black solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O$, 469; found, 469.

Compound 165: (*S*)-3-((4-(4-(1-methyl-1*H*-pyrazol-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



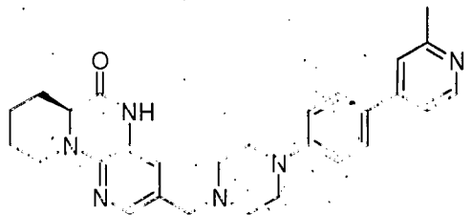
[0651] Compound 165 was prepared using a procedure analogous to that described in connection with compound 144, except that 1-methyl-1H-pyrazol-4-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a white solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{26}H_{31}N_7O$, 458; found, 458.

Compound 166: (*S*)-3-((4-(4-(4-methylpyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



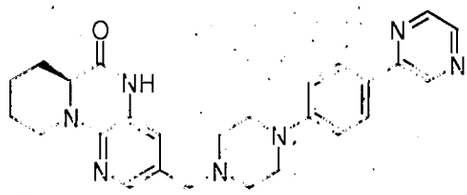
[0652] Compound 166 was prepared using a procedure analogous to that described in connection with compound 144, except that 4-methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine was used instead of 2-methoxypyridin-4-ylboronic acid to give a brown solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O$, 469; found, 469.

Compound 167: (*S*)-3-((4-(4-(2-methylpyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



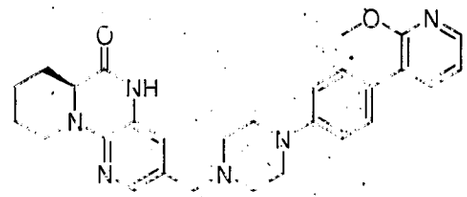
[0653] Compound 167 was prepared using a procedure analogous to that described in connection with compound 144, except that 2-methylpyridin-4-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a yellow solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O$, 469; found, 469.

Compound 168: (*S*)-3-((4-(4-(pyrazin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



[0654] Compound 168 was prepared using a procedure analogous to that described in connection with compound 144, except that pyrazin-2-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a tan solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{26}H_{29}N_7O$, 456; found, 456.

Compound 169: (*S*)-3-((4-(4-(2-methoxypyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5*H*-dipyrido[1,2-*a*:3',2'-*e*]pyrazin-6(6a*H*)-one



[0655] Compound 169 was prepared using a procedure analogous to that described in connection with compound 144, except that 2-methoxypyridin-3-ylboronic acid was used instead of 2-methoxypyridin-4-ylboronic acid to give a green solid as the TFA salt after purification by HPLC-MS: [M+H] calc'd for $C_{28}H_{32}N_6O_2$, 485; found, 485.

Biological Testing

[0656] The activity of compounds as PARP inhibitors may be assayed *in vitro*, *in vivo* or in a cell line. Provided below are descriptions of an *in vitro* enzymatic PARP activity assay for activity against PARP and a PARP cellular chemopotentiation assay.

Enzymatic PARP Assay

Dissociation Constant (K_D) From Surface Plasmon Resonance

Enzyme preparation

[0657] The catalytic domain of Human PARP was cloned and prepared as described in Kinoshita, T.; Nakanishi, I.; Warizaya, M.; Iwashita, A.; Kido, Y.; Hattori, K. and Fujii, T. 2006 FEBS Letters 556, 43-46. Purified enzyme was stored at -30 °C in 25 mM

Tris(hydroxymethyl)aminomethane (Tris) pH 7.4, 150 mM NaCl, 2 mM dithiothreitol (DTT) at a concentration of 6 mg/ml.

Biacore assays

[0658] Biacore affinity assays for test compounds were conducted on a Biacore T100 (GE Healthcare) as follows. A Series S Sensor Chip CM5 (part number BR-1006-68, GE Healthcare) was activated for amide coupling with an Amine Coupling Kit (part number BR-1000-50, GE Healthcare) as described by the manufacturer. The mobile phase buffer consisted of Biacore buffer HBS-P (part number BR-1003-68, GE Healthcare) supplemented with 1% v/v dimethylsulfoxide (DMSO), 0.5 mM Tris(2-carboxyethyl)phosphine hydrochloride (TCEP), and 5 mM MgCl2. Enzyme samples (2 µl / 6 mg/ml) stored at -80 °C were diluted to 0.080 mg/ml with 10 mM 4-morpholineethanesulfonic acid (MES) pH 6.5 and then mounted on the activated Biacore CM5 chip at a flow rate of 10 µl /min for 240 seconds. When successfully mounted, a signal of approximately 8,000 reflective units was observed. Test compounds were diluted 9 times 2-fold serially in mobile phase buffer (listed above) at 1% v/v DMSO final to generate a concentration gradient bracketing their anticipated K_Ds. Biacore mounted PARP was given a 1 minute exposure (association phase) to various concentrations of test compounds to observe a steady state equilibrium or an on rate. The exposure was followed with a dissociation phase of 5 minutes. The association and dissociation phases were at a flow rate of 50 µl /min and a temperature of 25 °C.

Biacore binding analysis

[0659] Rapid equilibrium model: If the test compound binding displayed rapid equilibrium, a plot of steady state response versus concentration was generated and the equation Rmax*[compound]/([compound]+K_D) was fit to the profile. Parameters Rmax (response at saturation) and K_D (binding constant) were calculated through a nonlinear least squares fitting of the equation to the data by use of the Biacore T100 analysis software.
Slow binding model: If the binding of the test compound did not achieve equilibrium within the 1 minute exposure, the association rate constant and the dissociation rate constant for the test compound were calculated through the simultaneous analysis of the family of progress curves obtained from the concentration gradient experiment. Parameter optimization was through a nonlinear least squares analysis of the association phase Response = Rmax*(1-exp(-(k_{on}[cmpd]+k_{off})*t)) and dissociation phase Response = Rmax*exp(-(k_{on}[cmpd]+k_{off})*t) by use

of the Biacore T100 analysis software. The binding constant K_D was calculated from the definition $K_D = k_{off}/k_{on}$

Inhibition Constant (IC_{50}) From PARP ELISA

[0660] Inhibition of PARP catalytic activity was determined by use of an ELISA-based colorimetric PARP/Apoptosis Assay kit (part number 4684-096-K HT, Trevigen). To each histone coated well in the 96-well plate supplied by the manufacturer (part number 4677-096-P) is added 39 µl of PARP buffer (part number 4671-096-02) and 1 µl of test compound dissolved in DMSO (diluted serially 3-fold 11 times). After mixing, 5 µl of 0.1 nM PARP (part number 4684-096-01) is added and the solution allowed to stand at ambient temperature for 10 minutes. PARP catalysis is initiated with the addition of 5 µl of 100 uM β-nicotinamide adenine dinucleotide (NAD+) (part number 4684-096-02) with activated DNA (part number 4671-096-06). After 10 minutes of catalysis the reaction is quenched by solvent aspiration followed by irrigation of the assay wells 4 times with phosphate buffered saline (PBS) containing 0.1% t-Octylphenoxypolyethoxyethanol (Triton® X-100). Mouse Anti- poly ADP ribose (PAR) monoclonal antibody, goat antimouse immunoglobulin G (IgG)- horse radish peroxidase (HRP) conjugate and HRP substrate are added according to the manufacture's specifications to generate a colorimetric signal proportional to PARP catalytic activity. An IC_{50} for the test compound is calculated from the equation Absorbance = (Amax-background)/(1+([cmpd]/IC_{50})^n)+background fit to the 12 point test compound concentration gradient via nonlinear least squares.

Potentiation Factor (PF_{50}) Determination From PARP Cellular Chemopotentiation Assay

[0661] Jurkat cell line was maintained according to the supplier (American Type Culture Collection (Rockville, MD)). Cells were seeded in 96-well tissue culture microplates at 10,000 cells per well and cultured for 24 hours prior to addition of compounds, TMZ (Temozolomide) or DMSO (dimethylsulfoxide) vehicle. After 96 hours of treatment, the conversion of MTS ([3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt], Promega, Madison, WI) by metabolically active cells was determined through measuring the $OD_{490\,nm}$ with a Spectramax microplate reader (Molecular Devices, San Diego, CA). To generate concentration-response curves, cells were treated in duplicate with a range of serial compound dilutions (final DMSO concentration was 0.5%) in the absence or presence of 100 µM TMZ chemoreagent. The percentage of viable cells per well was calculated by correction for background and normalizing against DMSO-treated cells. EC_{50}

values for inhibition of cell viability were calculated using XLfit4 MicroSoft Excel curve-fitting software. Chemopotentiation factor PF_{50} was calculated as the ratio of EC_{50} values of cells co-treated without and with TMZ, respectively..

[0662] It should be noted that a variety of other expression systems and hosts are also suitable for the expression of PARP, as would be readily appreciated by one of skill in the art.

[0663] TABLE 1 lists pK_D, pIC_{50} and PF_{50} values for select compounds of the present invention. Here, $pIC_{50} = -\log(IC_{50})$ and $pK_D = -\log(K_D)$ where IC_{50} and K_D are expressed in molar concentration.

TABLE 1: pK_D, pIC_{50} and PF_{50} Values of Exemplified Compounds Against PARP

COMPOUND	pK_D	pIC_{50}	PF_{50}
1			> 500
2	> 7.5		> 2000
3	6.1 – 7.5		> 10
4		7.4 – 7.8	> 2000
5	> 7.5	7.4 – 7.8	> 5000
6A			≥ 0
6		≥ 7.9	> 10
7			> 10
8			> 10
9			≥ 0
10	> 7.5	≥ 7.9	> 5000
11		7.4 – 7.8	> 10
12		7.4 – 7.8	> 10
13		7.4 – 7.8	> 5000
14			> 500
15			> 500
16			> 500
17			> 2000
18			> 10
19			≥ 0
20			≥ 0
21			> 2000
22			> 10
23			≥ 0
24		7.4 – 7.8	> 5000
25			≥ 0
26			> 10
28			≥ 0
29		≤ 7.3	> 500
31			≥ 0
32			≥ 0
34			≥ 0
35			≥ 0

COMPOUND	pK_D	pIC_{50}	PF_{50}
36			≥ 0
37		≤ 7.3	> 2000
38			≥ 0
39			≥ 0
40			> 10
41			≥ 0
42		≤ 7.3	> 500
45		7.4 – 7.8	> 10
46			≥ 0
47		≤ 7.3	> 10
48			≥ 0
49			≥ 0
50			≥ 0
51			≥ 0
52	> 7.5		≥ 0
53	6.1 – 7.5	≤ 7.3	≥ 0
54	≤ 6		
56	> 7.5		≥ 0
57	> 7.5		≥ 0
58	≤ 6		
59	> 7.5		≥ 0
60	≤ 6		
61	≤ 6		
63	6.1 – 7.5		≥ 0
64	> 7.5		≥ 0
65	≤ 6	≥ 7.9	> 10
66	≤ 6	7.4 – 7.8	> 10
67	> 7.5	7.4 – 7.8	≥ 0
68		≥ 7.9	> 5000
69		≥ 7.9	> 10
70		≤ 7.3	≥ 0
71		≥ 7.9	> 500
72		≥ 7.9	> 500
73		≥ 7.9	> 2000
74		≥ 7.9	> 10
75		7.4 – 7.8	> 500
76			≥ 0
77		7.4 – 7.8	> 10
78			> 10
79			> 10
80	> 7.5	≤ 7.3	≥ 0
81	6.1 – 7.5	≤ 7.3	≥ 0
82	6.1 – 7.5	≤ 7.3	≥ 0
83	≤ 6	7.4 – 7.8	≥ 0
84	6.1 – 7.5	≥ 7.9	≥ 0
85	6.1 – 7.5	7.4 – 7.8	≥ 0
86	> 7.5	7.4 – 7.8	> 500
87		7.4 – 7.8	> 10
88	> 7.5	≥ 7.9	≥ 0

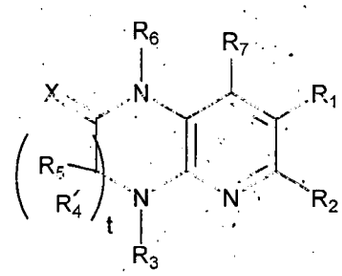
COMPOUND	pK_D	pIC_{50}	PF_{50}
89			> 10
90		≥ 7.9	> 10
91			> 2000
92			> 5000
93			≥ 0
94		≤ 7.3	≥ 0
95		≤ 7.3	≥ 0
96		≤ 7.3	
97			≥ 0
98			> 5000
99			> 5000
100			> 10
101		≤ 7.3	> 10
102		7.4 – 7.8	≥ 0
103		7.4 – 7.8	≥ 0
104		≤ 7.3	≥ 0
105		7.4 – 7.8	> 10
106		≥ 7.9	> 5000
107		7.4 – 7.8	> 2000
108		≥ 7.9	> 500
109		7.4 – 7.8	> 2000
110		7.4 – 7.8	> 5000
111		7.4 – 7.8	> 5000
112		≥ 7.9	> 10
113		≤ 7.3	> 2000
114		≤ 7.3	> 2000
115		7.4 – 7.8	> 2000
116		≥ 7.9	> 5000
117		7.4 – 7.8	> 5000
118		≥ 7.9	> 5000
120		≤ 7.3	≥ 0
121		7.4 – 7.8	≥ 0
122		≤ 7.3	≥ 0
123		7.4 – 7.8	> 10
124		≤ 7.3	≥ 0
125		≤ 7.3	≥ 0
126		7.4 – 7.8	> 5000
127		7.4 – 7.8	> 500
128		≤ 7.3	≥ 0
129		7.4 – 7.8	> 500
130		7.4 – 7.8	> 2000
131		≥ 7.9	> 500
132		≥ 7.9	> 2000
133		7.4 – 7.8	> 2000
134		7.4 – 7.8	> 5000
135		7.4 – 7.8	> 5000
136		≥ 7.9	> 5000
137		≥ 7.9	> 5000
138		≤ 7.3	≥ 0
139		≤ 7.3	≥ 0
140		≤ 7.3	≥ 0
141		≥ 7.9	> 500

COMPOUND	pK_D	pIC_{50}	PF_{50}
142		≥ 7.9	> 2000
144		≤ 7.3	
145		≤ 7.3	
146		7.4 – 7.8	
147		≤ 7.3	
148		7.4 – 7.8	
149		≤ 7.3	
150		≤ 7.3	
151		≤ 7.3	
152		7.4 – 7.8	
153		≤ 7.3	
154		≤ 7.3	
155		≤ 7.3	
156		≤ 7.3	
157		≤ 7.3	
158		≤ 7.3	
159		≤ 7.3	
160		≤ 7.3	
161		≤ 7.3	
162		≤ 7.3	
163		≤ 7.3	
164		7.4 – 7.8	
165		7.4 – 7.8	
166		7.4 – 7.8	
167		7.4 – 7.8	
168		7.4 – 7.8	
169		≤ 7.3	

[0664] It will be apparent to those skilled in the art that various modifications and variations can be made in the compounds, compositions, kits, and methods of the present invention without departing from the spirit or scope of the invention. Thus, it is intended that the present invention cover the modifications and variations of this invention provided they come within the scope of the appended claims and their equivalents.

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

t is selected from the group consisting of 1 and 2;

X is selected from the group consisting of O, S and NR_3;

R_1 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, amino(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl; hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_1 is $-L_1$-R_{13};

L_1 is absent or is a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{13} and the ring to which L_1 is attached, wherein the atoms of the linker providing the separation are each independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

R_2 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido; amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl,

hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_3 is selected from the group consisting of hydrogen, carbonyloxy, (C_{1-10})alkoxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_3 is $-L_2$-R_{18};

L_2 is absent or is a linker providing 1, 2, 3, 4, 5 or 6 atom separation between R_{18} and the ring to which L_2 is attached, wherein the atoms of the linker providing the separation are each independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur;

each R_4 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_5 is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino,

sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

or R_3 and one of R_4 and R_5, together with the atoms to which they are attached, form a substituted or unsubstituted ring selected from (C_{3-5})heterocycloalkyl and (C_{3-4})heteroaryl, the heterocycloalkyl moiety having 1 or 2 heteroatoms selected from N, O, and S, provided that at least one of the heteroatoms is a nitrogen atom, and the heteroaryl moiety having 1 or 2 nitrogen heteroatoms;

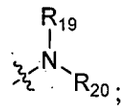
R_6 is selected from the group consisting of hydrogen, carbonyloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_7 is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_8 is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{13} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; or R_{13} has the formula:



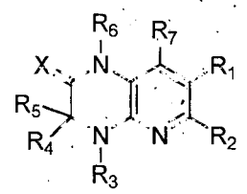
R_{16} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{19} and R_{20} are each independently selected from the group consisting of hydrogen, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted, or R_{19} and R_{20} are taken together to form a substituted or unsubstituted ring;

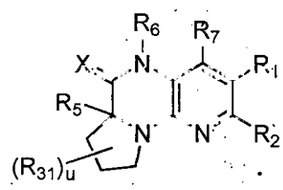
with the provisos that (a) if R_1 is hydrogen, chloro, methyl, 3,4-difluorophenyl, or 1-chloro-3-methyl-1-oxopentan-3-yl-aminocarbonyl, then R_6 is hydrogen, and (b) if the R_3 substituent and the R_4 and R_5 substituents are attached to adjacent nitrogen and carbon atoms, respectively, then at least one of R_5, R_4, and R_5 is not hydrogen.

2. The compound or pharmaceutically acceptable salt thereof according to claim 1 having the formula:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, and X are as defined in claim 1.

3. The compound or pharmaceutically acceptable salt thereof according to claim 2 having the formula:

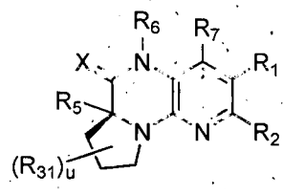


wherein R_1, R_2, R_5, R_6, R_7, and X are as defined in claim 1;

u is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

each R_{31} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

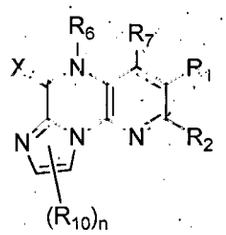
4. The compound or pharmaceutically acceptable salt thereof according to claim 3 having the formula:



or a stereoisomer thereof, wherein R_1, R_2, R_5, R_6, R_7, and X are as defined in claim 1, and u and R_{31} are as defined in claim 3.

5. The compound or pharmaceutically acceptable salt thereof according to claim 3 or claim 4, wherein each R_{31} is independently selected from the group consisting of hydrogen, halo, and a substituted or unsubstituted (C_{1-3})alkyl.

6. The compound or pharmaceutically acceptable salt thereof according to claim 1 having the formula:



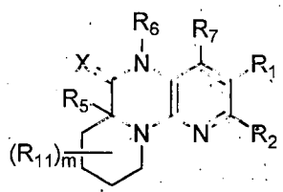
wherein R_1, R_2, R_6, R_7, and X are as defined in claim 1;

n is selected from the group consisting of 0, 1 and 2; and

each R_{10} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

7. The compound or pharmaceutically acceptable salt thereof according to claim 6, wherein each R_{10} is independently selected from the group consisting of hydrogen, halo, and a substituted or unsubstituted (C_{1-3})alkyl.

8. The compound or pharmaceutically acceptable salt thereof according to claim 1 having the formula:



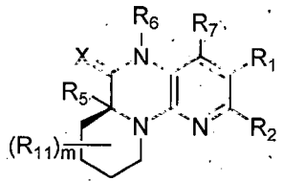
wherein R_1, R_2, R_5, R_6, R_7, and X are as defined in claim 1;

m is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8; and

each R_{11} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl,

(C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{3-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

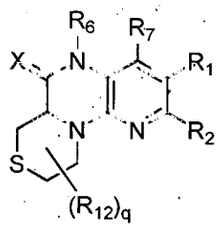
9. The compound or pharmaceutically acceptable salt thereof according to claim 3 having the formula:



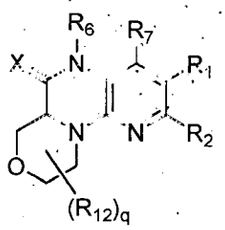
or a stereoisomer thereof, wherein R_1, R_2, R_5, R_6, R_7, and X are as defined in claim 1, and m and R_{11} are as defined in claim 8.

10. The compound or pharmaceutically acceptable salt thereof according to claim 3 or claim 9, wherein each R_{11} is independently selected from the group consisting of hydrogen, halo, and a substituted or unsubstituted (C_{1-3})alkyl.

11. The compound or pharmaceutically acceptable salt thereof according to claim 1 having the formula



or



wherein R_1, R_2, R_6, R_7, and X are as defined in claim 1;

q is selected from the group consisting of 0, 1, 2, 3, 4, 5 and 6; and

each R_{12} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy,

hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

12. The compound or pharmaceutically acceptable salt thereof according to claim 11, wherein each R_{12} is independently selected from the group consisting of hydrogen, halo, and a substituted or unsubstituted (C_{1-3})alkyl.

13. The compound or pharmaceutically acceptable salt thereof according to claim 1 or claim 2, wherein R_3 is selected from (C_{1-3})alkyl and aryl(C_{1-3})alkyl, each substituted or unsubstituted.

14. The compound or pharmaceutically acceptable salt thereof according to claim 1 or claim 2, wherein R_3 is $-L_2-R_{18}$, and

L_2 is absent or is a linker selected from the group consisting of $-(CR_{14}R_{15})_r-$, -CO-, -CS-, $-C(=NR_{16})-$, $-NR_{17}-$, -O-, -S-, -SO-, $-SO_2-$, and combinations thereof;

r is selected from the group consisting of 1, 2 and 3;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl,

oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{16} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{17} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

15. The compound or pharmaceutically acceptable salt thereof according to claim 14, wherein L_2 is $-CR_{14}R_{15}-$.

16. The compound or pharmaceutically acceptable salt thereof according to claim 14, wherein L_2 is $-CH_2-$.

17. The compound or pharmaceutically acceptable salt thereof according to any one of claims 14 to 16, wherein R_{18} is a substituted or unsubstituted phenyl.

18. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1, 2, and 14 to 17, wherein R_4 and R_5 are each independently selected from hydrogen, halo, and substituted or unsubstituted (C_{1-3})alkyl.

19. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein X is O.

20. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 18, wherein X is NR_8, and R_8 is selected from the group consisting of hydrogen and a substituted or unsubstituted (C_{1-3})alkyl.

21. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein R_1 is $-L_1-R_{13}$, and

L_1 is absent or is a linker selected from the group consisting of $-(CR_{14}R_{15})_r-$, -CO-, -CS-, $-C(=NR_{16})-$, $-NR_{17}-$, -O-, -S-, -SO-, $-SO_2-$, and combinations thereof;

R_{13} is as defined in claim 1;

r is selected from the group consisting of 1, 2 and 3;

R_{14} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

R_{15} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl,

sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

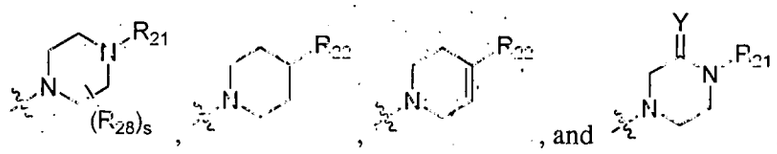
R_{16} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{17} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

22. The compound or pharmaceutically acceptable salt thereof according to claim 21, wherein R_{14}, R_{15}, R_{16}, and R_{17} are each independently selected from the group consisting of hydrogen, halo, and a substituted or unsubstituted (C_{1-3})alkyl.

23. The compound or pharmaceutically acceptable salt thereof according to claim 21, wherein L_1 is $-CH_2-$.

24. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein R_{13} is selected from:



wherein

s is selected from the group consisting of 0, 1, 2, 3, 4, 5, 6, 7 and 8;

Y is selected from the group consisting of O and S;

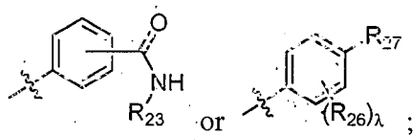
R_{21} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{22} and each R_{28} are independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

25. The compound or pharmaceutically acceptable salt thereof according to claim 24, wherein each R_{23} is selected from the group consisting of hydrogen, halo, and substituted or unsubstituted (C_{1-3}) alkyl.

26. The compound or pharmaceutically acceptable salt thereof according claim 24, wherein R_{21} or R_{22} is selected from phenyl and pyridinyl, each substituted or unsubstituted.

27. The compound or pharmaceutically acceptable salt thereof according to claim 24, wherein R_{21} or R_{22} has the formula:



;

wherein

λ is selected from the group consisting of 0, 1, 2, 3 and 4;

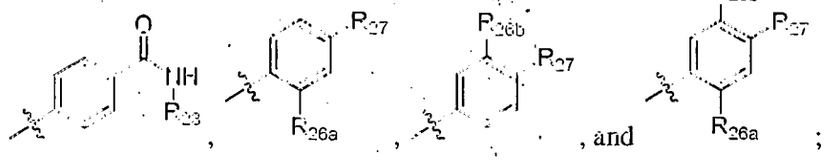
R_{23} is selected from the group consisting of hydrogen, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{1-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted;

each R_{26} is independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl,

(C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted; and

R_{27} is selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl, hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

28. The compound or pharmaceutically acceptable salt thereof according to claim 27, wherein R_{21} or R_{22} is selected from:



, , , and ;

wherein

R_{23} and R_{27} are as defined in claim 27;

R_{26a} and R_{26b} are each independently selected from the group consisting of hydrogen, halo, nitro, cyano, thio, oxy, hydroxy, carbonyloxy, (C_{1-10})alkoxy, (C_{4-12})aryloxy, hetero(C_{1-10})aryloxy, carbonyl, oxycarbonyl, amido, amino, (C_{1-10})alkylamino, sulfonamido, imino, sulfonyl, sulfinyl, (C_{1-10})alkyl, halo(C_{1-10})alkyl, hydroxy(C_{1-10})alkyl, carbonyl(C_{1-10})alkyl, thiocarbonyl(C_{1-10})alkyl, sulfonyl(C_{1-10})alkyl, sulfinyl(C_{1-10})alkyl, aza(C_{1-10})alkyl, (C_{1-10})oxaalkyl, (C_{1-10})oxoalkyl, imino(C_{1-10})alkyl, (C_{3-12})cycloalkyl(C_{1-5})alkyl, hetero(C_{3-12})cycloalkyl(C_{1-10})alkyl, aryl(C_{1-10})alkyl, hetero(C_{1-10})aryl(C_{1-5})alkyl, (C_{9-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{8-12})bicycloaryl(C_{1-5})alkyl, hetero(C_{1-10})alkyl, (C_{3-12})cycloalkyl, hetero(C_{3-12})cycloalkyl, (C_{9-12})bicycloalkyl,

hetero(C_{3-12})bicycloalkyl, (C_{4-12})aryl, hetero(C_{4-10})aryl, (C_{9-12})bicycloaryl and hetero(C_{4-12})bicycloaryl, each substituted or unsubstituted.

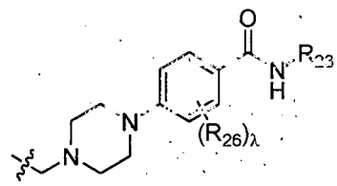
29. The compound or pharmaceutically acceptable salt thereof according to claim 27 or claim 28, wherein

R_{23} is selected from hydrogen, (C_{1-3})alkyl, and (C_{3-6})cycloalkyl;

R_{26}, R_{26a}, and R_{26b} are each independently selected from hydrogen and halo, and from (C_{1-3}) alkyl and (C_{1-3})alkoxy, each substituted or unsubstituted; and

R_{27} is selected from –CO-NH-R_{23}.

30. The compound or pharmaceutically acceptable salt thereof according to any one of claims 1 to 20, wherein R_1 has the formula:



wherein

λ is selected from the group consisting of 0, 1 and 2;

R_{23} is selected from the group consisting of (C_{1-3})alkyl and (C_{3-6})cycloalkyl; and

each R_{26} is independently selected from the group consisting of hydrogen, halo, (C_{1-3}) alkyl and (C_{1-3})alkoxy.

31. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein R_2 is selected from the group consisting of hydrogen, halo, and substituted or unsubstituted (C_{1-3})alkyl.

32. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein R_6 and R_7 are each independently selected from the group consisting of hydrogen and a substituted or unsubstituted (C_{1-3})alkyl.

33. The compound or pharmaceutically acceptable salt thereof according to any one of the preceding claims, wherein R_6 is hydrogen.

34. The compound according to claim 1, which is selected from the following compounds:

(S)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile;

(S)-N-methyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-ethyl 6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate;

(S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid;

(S)-N-ethyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-N-cyclopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-N-isopropyl-6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate;

(S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid;

(S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-3-((4-(2,4-difluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-chloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-2,3-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-2,6-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-3,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-3-fluoro-5-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)picolinonitrile;

(S)-3-((4-phenylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-acetylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((benzyl(methyl)amino)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-m-tolylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(3-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-methoxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-p-tolylpiperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(pyrimidin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(3-hydroxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-hydroxyphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(5-(trifluoromethyl)pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(3-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(1H-benzo[d]imidazol-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-iodophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(benzo[d]oxazol-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(5-chloropyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-(((4-methoxybenzyl)(methyl)amino)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(1,3,5-triazin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-methyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate;

(S)-3-((4-(3,5-difluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-chloro-3-fluorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-(trifluoromethyl)phenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(P)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(P)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(R)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-3,4-dimethyl-7-((4-phenylpiperidin-1-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-3,4-dimethyl-7-((3-oxo-4-phenylpiperazin-1-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-fluorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-3,4-dimethyl-7-((4-phenyl-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(3-chlorophenyl)piperazin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3,4-dimethyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-methyl 4-isopropyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[3,2-b]pyrazine-7-carboxylate;

(S)-7-(hydroxymethyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-isopropyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-ethyl-3-methyl-3,4-dihydropyrido[3,2-b]pyrazin-2(1H)-one;

(S)-methyl 4-ethyl-3-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate;

(S)-4-ethyl-7-(hydroxymethyl)-3-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,2-a]pyrido[3,2-e]pyrazin-6(5H)-one;

3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)imidazo[1,5-a]pyrido[3,2-e]pyrazin-6(5H)-one;

3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate;

3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-methyl 6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazine-3-carboxylate;

(S)-3-(hydroxymethyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile;

(S)-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-ethyl 4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate;

(S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid;

(S)-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-isopropyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-ethyl 6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate;

(S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinic acid;

(S)-N-methyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-N-ethyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

(S)-N-cyclopropyl-6-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinamide;

7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

methyl 4-methyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate;

7-(hydroxymethyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-methyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

4-benzyl-7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

methyl 4-benzyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate;

4-benzyl-7-(hydroxymethyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

4-benzyl-7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

4-benzyl-7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one;

methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate;

3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one;

3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one;

3-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one;

(R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile;

(R)-methyl 6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazine-3-carboxylate;

(R)-3-(hydroxymethyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one;

(R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(R)-3-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-6a,7,9,10-tetrahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-6(5H)-one ;

(R)-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(R)-ethyl 4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate;

(R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoic acid;

3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one;

methyl 6-oxo-5,6,6a,7,9,10-hexahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazine-3-carboxylate;

3-(hydroxymethyl)-6a,7,9,10-tetrahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-6(5H)-one;

7-((4-(4-chlorophenyl)-5,6-dihydropyridin-1(2H)-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

methyl 4-isopropyl-2-oxo-1,2,3,4-tetrahydropyrido[2,3-b]pyrazine-7-carboxylate;

7-(hydroxymethyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

7-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

7-((4-(4-chlorophenyl)piperidin-1-yl)methyl)-4-isopropyl-3,4-dihydropyrido[2,3-b]pyrazin-2(1H)-one;

7-[4-(4-chloro-phenyl)-piperazin-1-ylmethyl]-2-methyl-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one;

10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2,7-dicarboxylic acid 2-tert-butyl ester 7-methyl ester;

7-Hydroxymethyl-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester;

7-[4-(4-chloro-phenyl)-piperazin-1-ylmethyl]-10-oxo-1,3,4,9,10,10a-hexahydro-2,4a,5,9-tetraaza-phenanthrene-2-carboxylic acid tert-butyl ester;

7-[4-(4-chloro-phenyl)-piperazin-1-ylmethyl]-1,3,4,10a-tetrahydro-2H,9H-2,4a,5,9-tetraaza-phenanthren-10-one;

(R)-N-methyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(R)-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

6-(4-((6-oxo-5,6,6a,7,9,10-hexahydro-[1,4]oxazino[4,3-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinonitrile;

(S)-ethyl 4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzoate;

(S)-4-(4-((6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-methyl 6-oxo-6,6a,7,8-tetrahydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazine-3-carboxylate;

(S)-3-(hydroxymethyl)-7,8-dihydro-5H-azeto[1,2-a]pyrido[3,2-e]pyrazin-6(6aH)-one;

4-(4-((6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-3-yl)methyl)piperazin-1-yl)benzonitrile;

methyl 6-oxo-6,7,7a,8,9,10-hexahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepine-3-carboxylate;

3-(hydroxymethyl)-7a,8,9,10-tetrahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one;

3-((4-(4-chlorophenyl)piperazin-1-yl)methyl)-7a,8,9,10-tetrahydro-5H-pyrido[3,2-b]pyrrolo[1,2-d][1,4]diazepin-6(7H)-one;

4-((S)-3-methyl-4-(((P)-6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(R)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(R)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(R)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,9,10-hexahydropyrido[3,2-e][1,4]thiazino[4,3-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-fluoro-N-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N,3-dimethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-methoxy-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

N-ethyl-4-(4-((6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(6aS)-3-((2-methyl-4-(pyridin-2-yl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-ethyl 6-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)nicotinate;

(S)-3-((1-(4-chlorophenyl)piperidin-4-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-bromo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-5-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)picolinonitrile;

(S)-N-ethyl-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-ethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzenesulfonamide;

(S)-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzonitrile;

(S)-3-((4-(4-fluoro-2-methylphenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-fluoro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-fluoro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-cyclopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-isopropyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-chloro-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-3-((4-(4-(pyrrolidine-1-carbonyl)phenyl)piperazin-1-yl)methyl)-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-N,N-dimethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-ethyl-N-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N,3-dimethyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

(S)-N-cyclopropyl-3-methyl-4-(4-((6-oxo-5,6,6a,7,8,9-hexahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

N-ethyl-4-(4-((6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-3-yl)methyl)piperazin-1-yl)benzamide;

methyl 6-oxo-5,6-dihydropyrido[3,2-e]pyrrolo[1,2-a]pyrazine-3-carboxylate;

3-(hydroxymethyl)pyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one;

(S)-3-((4-(4-(2-methoxypyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-bromophenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(6-aminopyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(thiophen-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(thiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(pyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(biphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(6-methoxypyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(pyrimidin-5-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(2-methoxypyrimidin-5-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(3-methoxypyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(2'-methylbiphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(3-methylpyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(6-methoxypyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(pyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(pyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(5-methylthiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(2'-(hydroxymethyl)biphenyl-4-yl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(4-methylthiophen-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(3-methylthiophen-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(5-oxocyclopent-1-enyl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(6-methylpyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(4-methylpyridin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(2-methylpyridin-4-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(pyrazin-2-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

(S)-3-((4-(4-(2-methoxypyridin-3-yl)phenyl)piperazin-1-yl)methyl)-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:3',2'-e]pyrazin-6(6aH)-one;

a stereoisomer of any of the aforementioned compounds; and

a pharmaceutically acceptable salt of any of the aforementioned compounds.

35. A pharmaceutical composition comprising:

a compound or pharmaceutically acceptable salt thereof as defined in any one of the preceding claims; and

a pharmaceutically acceptable excipient.

36. A use as a medicament of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 34.

37. A use of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 34, for the manufacture of a medicament for the treatment of a disease or condition for which PARP activity contributes to the pathology and/or symptomology of the disease or condition.

38. A method of treating a disease or condition in a subject for which PARP activity contributes to the pathology and/or symptomology of the disease or condition, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 34.

39. A method of treating a disease or condition in a subject, the method comprising administering to the subject an effective amount of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 34, wherein the disease or condition is selected from cancers, cardiovascular diseases, metabolic diseases, inflammatory diseases, reperfusion injuries, ischemic conditions, and neurodegenerative diseases.

40. A combination of an effective amount of a compound or pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 34, and at least one additional pharmacologically active agent.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021669

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D471/14 C07D498/14 C07D513/14 A61K31/4985
A61K31/5365 A61K31/542 A61P25/00 A61P35/00 A61P9/00
A61P29/00

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)
C07D A61K A61P

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, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/009734 A1 (WYETH CORP [US]; GREEN DANIEL M [US]; GARRICK LLOYD M [US]; HAUZE DIAN) 26 January 2006 (2006-01-26)	1,2,13, 14,18, 19, 21-26, 31-33, 35-40
Y	claims 1,19,22,23,25,32 examples 201-204; table 14	1-40
Y	WO 2007/130468 A2 (CEPHALON INC [US]; DORSEY BRUCE D [US]; MILKIEWICZ KAREN L [US]; PIPPI) 15 November 2007 (2007-11-15) example 2-31,45,48-50,60,61,83, 85,91,92,116,133,135-137,139-146, 150-152,155-157,161,175,178; page 52, line 31 - page 53, line 9; claims 1,2,10,11	1-40

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[X] Further documents are listed in the continuation of Box C. [X] See patent family 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
2 July 2010	09/07/2010
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Rufet, Jacques

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/021669

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/11649 A2 (GUILFORD PHARM INC [US]) 11 March 1999 (1999-03-11) page 67, compounds 3 and 4; claims 1, 18	1-40
Y	WO 2005/058843 A1 (JANSSEN PHARMACEUTICA NV [BE]; MABIRE DOMINIQUE JEAN-PIERRE [FR]; VAN) 30 June 2005 (2005-06-30) claims 1,4-9; tables F-1	1-40
A	US 4 446 323 A (FREED MEIER E [US] ET AL) 1 May 1984 (1984-05-01) * abstract; claim 1; example 6	1,35,36
A	US 4 138 564 A (FREED MEIER E ET AL) 6 February 1979 (1979-02-06) the whole document	1,35,36
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Information on patent family members

International application No
PCT/US2010/021669

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		BR PI0512261 A	26-02-2008
		CA 2570968 A1	26-01-2006
		CN 101006078 A	25-07-2007
		EC SP067090 A	26-01-2007
		EP 1758895 A1	07-03-2007
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INHIBIDORES DE POLI (ADP-RIBOSA) POLIMERASA (PARP)

MEMORIA DESCRIPTIVA

La presente invención se refiere a compuestos que se pueden utilizar para inhibir la Poli (ADP-ribosa) Polimerasa (PARP), así como composiciones de materia, kits y artículos de manufactura que comprenden a estos compuestos. La invención también se refiere a métodos para inhibir la PARP y a los métodos de tratamiento que utilizan los compuestos de acuerdo a la presente invención. Además, la invención se refiere a métodos para preparar los compuestos de la presente invención, así como a los intermediarios útiles en dichos métodos.

ANTECEDENTES DE LA INVENCIÓN

La presente invención se refiere a inhibidores de la enzima poli(ADP-ribosa)polimerasa (PARP), previamente conocida como poli(ADP-ribosa)sintetasa y poli(ADP-ribosil)transferasa. Las PARP constituyen una super familia de proteínas que contienen los dominios catalíticos PARP. Estas proteínas incluyen PARP-1, PARP-2, PARP-3, vaultPARP y TiPARP. La PARP-I consiste de un dominio amino (N)-terminal de unión a ADN (DBD) que contiene dos dedos de zinc; un dominio de automodificación; y un dominio catalítico carboxi (C)-terminal.

PARP es una enzima nuclear y citoplasmática que degrada NAD+ en nicotinamida y ADP-ribosa para formar polímeros de ADP-ribosa largos y ramificados en las proteínas blanco, incluyendo topoisomerasas, histonas y PARP mismo. PARP ha estado implicado en diversos procesos biológicos, incluyendo la reparación de ADN, transcripción génica, progresión del ciclo celular (incluyendo la proliferación y diferenciación), muerte celular, funciones de la cromatina, estabilidad genómica (*por ejemplo*, cromosomal) y longitud del telómero.

La activación de PARP y la formación resultante de poli(ADP-ribosa) se puede inducir a través de quiebres de la hebra de ADN después de la exposición a quimioterapia, radiación ionizante,

radicales libres de oxígeno, o a óxido nítrico (NO). Debido a que este proceso de transferencia celular de ADP-ribosa está asociado con la reparación de la ruptura de la hebra de ADN en respuesta al daño del ADNA causado por radioterapia o por quimioterapia, puede contribuir a la resistencia que a menudo se desarrolla frente a varios tipos de terapias contra el cáncer. En consecuencia, se espera que la inhibición de PARP retarde la reparación de ADN intracelular y mejora los efectos antitumorales de las terapias contra el cáncer.

Además, las tankirasas (*por ejemplo*, tankirasa-1 y tankirasa-2) que se unen a la proteína telomerica TRF-1, un regulador negativo de la mantención de la longitud del telomero, poseen un dominio catalítico que es homólogo a PARP. Se ha propuesto que la función del telomero en células de humano es regulada mediante poli(ADP-ribosil)ación. Como una consecuencia de la regulación de la actividad de la telomerasa por la tankirasa, se espera que los inhibidores PARP sean útiles como agentes para ser utilizados en la terapia del cáncer (*por ejemplo*, para disminuir la longitud de vida de las células tumorales inmortales) o como terapia anti-envejecimiento, debido a que se cree que la longitud del telomero está asociada con la senescencia celular.

Por otra parte, la modulación PARP ha estado involucrada en las enfermedades vasculares y cardiovasculares, las enfermedades metabólicas, enfermedades inflamatorias, daños por reperfusión, condiciones isquémicas, enfermedades neurodegenerativas y otras.

Existe una necesidad continua por encontrar nuevos agentes terapéuticos para tratar enfermedades de humanos. PARP es un blanco especialmente atractivo para encontrar nuevos agentes terapéuticos debido a su rol importante en el cáncer, las enfermedades vasculares y cardiovasculares, enfermedades metabólicas, enfermedades inflamatorias, daños por reperfusión, condiciones isquémicas, enfermedades neurodegenerativas y otras enfermedades.

DESCRIPCION DE LA INVENCIÓN

La presente invención se relaciona con compuestos que tienen actividad para inhibir la poli(ADP-ribosa) polimerasa (PARP). La presente invención también provee composiciones, artículos de

manufactura y kits que comprenden estos compuestos. Además, la invención se relaciona con métodos para preparar los compuestos de la presente invención, así como intermediarios útiles en tales métodos. Los compuestos de la presente invención exhiben eficacia *in vivo* en modelos animales, potenciación celular aumentada, efectos farmacodinámicos fuertes y sostenidos en tumores y un tiempo de progresión tumoral (TTP) más prolongado.

En una modalidad, se provee una composición farmacéutica que comprende un inhibidor de PARP, de acuerdo con la presente invención, como un ingrediente activo. Las composiciones farmacéuticas de acuerdo con la invención pueden, opcionalmente, comprender entre 0,001 a 100% de uno o más inhibidores de esta invención.

Estas composiciones farmacéuticas pueden ser administradas o co-administradas por una gran variedad de vías, incluyendo, por ejemplo, las vías oral, parenteral, intraperitoneal, intravenosa, intra-arterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomática, por medio de inhalación, vaginalmente, intraocularmente, por entrega local (por ejemplo, a través de un catéter o un stent), subcutáneamente, intra-adiposamente, intra-articularmente o intratecalmente. Las composiciones también se pueden administrar o co-administrar en formas de dosificación de liberación lenta.

La invención también se refiere a los kits y otros artículos de manufactura para tratar enfermedades asociadas con poli(ADP-ribosa) polimerasa (PARP). En una modalidad, se provee un kit que comprende una composición que incluye al menos un inhibidor de poli(ADP-ribosa) polimerasa (PARP) de la presente invención, junto con instrucciones. Las instrucciones pueden indicar el estado de la enfermedad para la que se administrará la composición, información acerca del almacenamiento, de las dosis y/o instrucciones con respecto a la forma de administración de la composición.

Este kit también puede comprender materiales de envasado. El material de envasado puede comprender un contenedor para alojar la composición. El kit puede, opcionalmente, comprender componentes adicionales, tales como jeringas para la administración de la

composición. El kit puede comprender la composición en formas de dosis unitarias o múltiples.

En una modalidad adicional, se provee un artículo de manufactura que comprende una composición que incluye, al menos, un inhibidor de PARP de la presente invención, junto con materiales de envasado. El material de envasado puede comprender un contenedor para alojar la composición. El contenedor puede, opcionalmente, comprender una etiqueta que indica: el estado de la enfermedad para la cual se administra la composición, información acerca del almacenamiento, de las dosis y/o instrucciones con respecto a la forma de administración de la composición. El kit puede comprender la composición en formas de dosis unitarias o múltiples.

También se proveen métodos para la preparación de compuestos, composiciones y kits de acuerdo con la presente invención. Por ejemplo, en la presente descripción se proporcionan diversos esquemas sintéticos para sintetizar los compuestos de acuerdo con la presente invención.

También se proveen métodos para el uso de los compuestos, composiciones, kits y artículos de manufactura de acuerdo con la presente invención.

En una modalidad adicional, los compuestos, composiciones, kits y artículos de manufactura se utilizan para inhibir la poli(ADP-ribosa) polimerasa (PARP).

En otra modalidad, los compuestos, composiciones, kits y artículos de manufactura se utilizan para tratar un estado de una enfermedad, en la que la poli(ADP-ribosa) polimerasa (PARP) posee una actividad que contribuye a la patología y/o sintomatología de dicho estado de la enfermedad.

En otra modalidad, un compuesto de acuerdo con la presente invención se suministra a un individuo, en donde la actividad de PARP ha sido alterada dentro de dicho individuo, de preferencia, ha sido reducida.

En otra modalidad, una prodroga de un compuesto de acuerdo con la presente invención es administrada a un individuo, que se convierte en el compuesto *in vivo*, al inhibir la PARP.

En otra modalidad, se provee un método para inhibir la PARP, donde dicho método comprende la etapa de contactar la PARP con un compuesto de acuerdo con la presente invención.

En otra modalidad, se provee un método para inhibir la PARP, donde dicho método comprende la etapa de provocar que un compuesto de acuerdo con la presente invención se encuentre presente en un individuo, para así inhibir la PARP *in vivo*.

En otra modalidad, se provee un método para inhibir la PARP, donde dicho método comprende la etapa de administrar un primer compuesto a un individuo, que es convertido *in vivo* en un segundo compuesto, donde este segundo compuesto inhibe la PARO *in vivo*. Cabe señalar que los compuestos de la presente invención pueden ser el compuesto primero o segundo.

En otra modalidad, se provee un método terapéutico que comprende la administración de un compuesto de acuerdo con la presente invención.

En otra modalidad, se provee un método para tratar una condición en un paciente, donde se sabe que dicha condición es mediada por PARP o se puede tratar mediante inhibidores de PARP, donde el método comprende la administración al paciente de una cantidad terapéuticamente eficaz de un compuesto de acuerdo con la presente invención.

En otra modalidad, se provee un método para tratar un estado de una enfermedad, donde la PARP posee una actividad que contribuye con la patología y/o sintomatología de dicho estado de la enfermedad.

En otra modalidad, se provee un método para tratar un estado de una enfermedad, donde la PARP posee una actividad que contribuye con la patología y/o sintomatología de dicho estado de la enfermedad, donde dicho método comprende la etapa de: administrar un primer compuesto a un individuo, que se convierte *in vivo* en un segundo compuesto, de modo que el compuesto se encuentre presente en el individuo en una cantidad terapéuticamente eficaz para el estado de la enfermedad. Cabe señalar que los compuestos de la presente invención pueden ser el compuesto primero o segundo.

En otra modalidad, se provee un método para tratar un estado de una enfermedad, donde la PARP posee una actividad que contribuye con la patología y/o sintomatología de dicho estado de la enfermedad, donde dicho método comprende la etapa de: administrar un compuesto de acuerdo con la presente invención a un individuo, de modo que el compuesto se encuentre presente en el individuo en una cantidad terapéuticamente eficaz para el estado de la enfermedad. Cabe señalar que los compuestos de la presente invención pueden ser el compuesto primero o segundo.

En otra modalidad, se provee un método para utilizar un compuesto de acuerdo con la presente invención, para así poder preparar un medicamento para usar en el tratamiento de un estado de una enfermedad que se sabe es mediada por PARP o se trata mediante inhibidores de PARP.

En relación con todas las modalidades anteriormente mencionadas, cabe destacar que la presente invención intenta abarcar todas las formas ionizadas farmacéuticamente aceptables (por ejemplo: sales) y solvatos (por ejemplo: hidratos) de los compuestos, sin importar si tales formas ionizadas y solvatos son específicas, ya que el hecho de administrar agentes farmacéuticos en forma ionizada o de solvato se conoce ampliamente en el arte.

También se debe considerar que -independientemente de si se especifica una estereoquímica particular o no- al mencionar un compuesto se pretende abarcar todos los estereoisómeros posibles (por ejemplo: enantiómeros o diastereómeros, dependiendo del número de centros quirales), sin importar si el compuesto se encuentra presente como un isómero individual o como una mezcla de isómeros. Además, a menos que se indique lo contrato, el hecho de mencionar un compuesto pretende abarcar todas las formas de resonancia y tautómeros posibles. En relación con las reivindicaciones, el lenguaje "compuesto que comprende la fórmula", "compuesto que tiene la fórmula" y "compuesto de la fórmula" pretende abarcar el compuesto y todas las formas ionizadas y solvatos farmacéuticamente aceptables, todos los estereoisómeros posibles y todas las formas de resonancia y tautómeros posbles, a menos que se específicamente se indique lo contrario en una reivindicación en particular. Además, se debe

considerar que las prodrogas también se pueden administrar, las que son alteradas *in vivo* y se convierten en un compuesto de la presente invención. Se pretende que los diferentes métodos de uso de los compuestos de la presente invención -sin importar si se especifica la entrega de la prodroga- abarquen la administración de una prodroga que se convierte *in vivo* en un compuesto de la presente invención. También se debe considerar que ciertos compuestos de la presente invención se pueden alterar *in vivo*, antes de la inhibición de la PARP, y así ellos mismos pueden ser prodrogas para otro compuesto. Tales prodrogas de otro compuesto pueden o no, independientemente, tener actividad inhibidora de PARP.

DEFINICIONES

A menos que se defina de otra forma, los siguientes términos usados en la memoria descriptiva y las reivindicaciones deben tener los siguientes significados para los propósitos de la presente solicitud.

Se debe destacar, que como se utiliza en la memoria descriptiva y las reivindicaciones anexas, las formas singulares "un," "una" y "el" incluyen referentes plurales a menos que el contexto dicte de manera clara que es de otra forma. Además, las definiciones de los términos de química estándar se pueden encontrar en las obras de referencia, incluyendo Carey and Sundberg "ADVANCED ORGANIC CHEMISTRY 4TH ED." Vols. A (2000) and B (2001), Plenum Press, New York. También, a menos que se indique de otro modo, los métodos convencionales de espectroscopía de masa, NMR, HPLC, química de proteínas, bioquímica, las técnicas de ADN recombinante y la farmacología, se utilizan dentro de las contenidas en el conocimiento del arte.

El término "alicíclico" representa a un residuo que comprende una estructura de anillo no aromático. Los residuos alicíclicos pueden estar saturados o parcialmente insaturados con uno, dos o más enlaces dobles o triples. Los residuos alicíclicos también pueden comprender opcionalmente heteroátomos tal como nitrógeno, oxígeno y azufre. Los átomos de nitrógeno pueden estar opcionalmente cuaternizados o oxidados y los átomos de azufre pueden

estar opcionalmente oxidados. Ejemplos de residuos alicíclicos incluyen, pero no están limitados á residuos con anillos (C_{3-8}) tal como ciclopropilo, ciclohexano, ciclopentano, ciclopenteno, ciclopentadieno, ciclohexano, ciclohexeno, ciclohexadieno, cicloheptano, cicloheptено, cicloheptadieno, ciclooctano, cicloocteno, y ciclooctadieno.

El término "alifático" representa a un residuo caracterizado por una disposición lineal o ramificada de los átomos de carbono que lo constituyen y puede estar saturado o parcialmente insaturado con uno, dos o más enlaces dobles o triples.

El término "alquenilo" representa a una cadena carbonada lineal o ramificada, que contiene al menos un doble enlace carbono-carbono (-CR=CR'- o -CR=CR'R'', donde R, R' y R'' son cada uno independientemente hidrógeno o sustituyentes adicionales). Ejemplos de alquenilo incluyen vinilo, alilo, isopropenilo, pentenilo, hexenilo, heptenilo, 1-propenilo, 2-butenilo, 2-metil-2-butenilo, y similares. En modalidades particulares, "alquenilo," ya sea solo o representado junto a otro radical, puede ser un alquenilo(C_{2-20}), un alquenilo(C_{2-15}), un alquenilo(C_{2-10}), un alquenilo(C_{2-5}) o un alquenilo(C2-3). Alternativamente, "alquenilo," ya sea solo o representado junto a otro radical, puede ser un alquenilo(C_2), un alquenilo(C_3) o un alquenilo(C_4).

El término "alquenileno" representa a una cadena carbonada divalente lineal o ramificada, que contiene uno o más enlaces dobles carbono-carbono (-CR=CR'-, donde R y R' son cada uno independientemente hidrógeno o sustituyentes adicionales). Ejemplos de alquenileno incluyen eteno-1,2-diilo, propen-1,3-diilo, metilen-1,1-diilo, y similares. En modalidades particulares, "alquenileno," ya sea solo o representado junto a otro radical, puede ser un alquenileno(C_{2-20}), un alquenileno(C_{2-15}), un alquenileno(C_{2-10}), un alquenileno(C_{2-5}) o un alquenileno(C2-3). Alternativamente, "alquenileno," ya sea solo o representado junto a otro radical, puede ser un alquenileno(C_2), un alquenileno(C_3) o un alquenileno(C_4).

El término "alcoxi" representa a un residuo de oxígeno que posee un sustituyente alquilo adicional. Los grupos alcoxi de la presente invención pueden estar opcionalmente sustituidos.

El término "Alquilo" representado por si mismo significa o representa a un radical alifático que posee una cadena de átomos de carbono lineal o ramificado, saturado o insaturado, donde opcionalmente uno o más de los átomos de carbono se reemplazan con oxigeno (véase "oxaalquilo"), grupo carbonilo (véase "oxoalquilo"), azufre (véase "tioalquilo"), y/o nitrógeno (véase "azaalquilo"). alquilo(C_X) y alquilo(C_{X-Y}) son generalmente utilizados en donde X e Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquilo(C_{1-6}) incluye a los alquilos que poseen una cadena que tiene entre 1 y 6 carbonos (*por ejemplo*, metilo, etilo, propilo, isopropilo, butilo, *sec*-butilo, isobutilo, *ter*-butilo, vinilo, alilo, 1-propenilo, isopropenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-metilalilo, etinilo, 1-propinilo, 2-propinilo, y similares). Alquilo representado junto con otro radical (*por ejemplo*, como en arilalquilo, heteroarilalquilo y similares) representa a un radical alifático, divalente, lineal o ramificado, saturado o insaturado que posee el número de átomos indicados o cuando no se indican los átomos representa un enlace (*por ejemplo*, aril(C_{6-10})alquilo(C_{1-3}) incluye, a bencilo, fenetilo, 1-feniletilo, 3-fenilpropilo, 2-tienilmetilo, 2-piridinilmetilo y similares). En modalidades particulares, "alquilo", ya sea solo o representado junto con otro radical, puede ser un alquilo(C_{1-20}), un alquilo(C_{1-15}), un alquilo(C_{1-10}), un alquilo(C_{1-5}) o un alquilo(C_{1-3}). Alternativamente; "alquilo," ya sea solo o representado junto con otro radical, puede ser un alquilo(C_1), un alquilo(C_2) o un alquilo(C_3).

El término "alquileno", a menos que se indique de otra manera, representa a un radical alifático, divalente, lineal o ramificado, saturado o insaturado. alquileno(C_X) y alquileno(C_{X-Y}) son generalmente utilizados donde X e Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquileno(C_{1-6}) incluye metileno (-CH_2-), etileno (-CH_2CH_2-), trimetileno (-$CH_2CH_2CH_2$-), tetrametileno (-$CH_2CH_2CH_2CH_2$-) 2-butenileno (-CH_2CH=$CHCH_2$-), 2-metiltetrametileno (-$CH_2CH(CH_3)CH_2CH_2$-), pentametileno (-$CH_2CH_2CH_2CH_2CH_2$-) y similares. En modalidades particulares, "alquileno," ya sea solo o representado junto con otro radical, puede ser un alquileno(C_{1-20}), un alquileno(C_{1-15}), un alquileno(C_{1-10}), un alquileno(C_{1-5}) o un alquileno(C_{1-3}).

Alternativamente, "alquileno," ya sea solo o representado junto con otro radical, puede ser un alquileno(C_1), un alquileno(C_2) o un alquileno(C_3).

El término "alquilideno" representa a un radical alifático lineal o ramificado, saturado o insaturado conectado a la molécula parental a través de un doble enlace. Alquilideno(C_X) y alquilideno(C_{X-Y}) generalmente se utilizan donde X e Y indican el número de átomos de carbono en la cadena. Por ejemplo, alquilideno(C_{1-6}) incluye a metileno ($=CH_2$), etilideno ($=CHCH_3$), isopropilideno ($=C(CH_3)_2$), propilideno ($=CHCH_2CH_3$), alilideno ($=CH-CH=CH_2$), y similares. En modalidades particulares, "alquilideno," ya sea solo o representado junto con otro radical, puede ser un alquilideno(C_{1-20}), un alquilideno(C_{1-15}), un alquilideno(C_{1-10}), un alquilideno(C_{1-5}) o un alquilideno(C_{1-3}). Alternativamente, "alquilideno," ya sea solo o representado junto con otro radical, puede ser un alquilideno(C_1), un alquilideno(C_2) o un alquilideno(C_3).

El término "alquinilo" representa a una cadena carbonada lineal o ramificada que contiene al menos un enlace triple carbono-carbono (-C≡C- o -C≡CR, donde R es hidrógeno o un sustituyente adicional). Ejemplos de alquinilo incluyen etinilo, propargilo, 3-metil-1-pentinilo, 2-heptinilo y similares. En modalidades particulares, "alquinilo," ya sea solo o representado junto con otro radical, puede ser un alquinilo(C_{2-20}), un alquinilo(C_{2-15}), un alquinilo(C_{2-10}), un alquinilo(C_{2-5}) o un alquinilo(C2-3). Alternativamente, "alquinilo," ya sea solo o representado junto con otro radical, puede ser un alquinilo(C_2), un alquinilo(C_3) o un alquinilo(C_4).

El término "alquinileno" representa una cadena carbonada, divalente, lineal o ramificada que posee uno o más enlaces triples carbono-carbono (-CR≡CR'-, donde R y R' son cada uno independientemente hidrógeno o sustituyentes adicionales). Ejemplos de alquinilenos incluyen etino-1,2-diilo, propino-1,3-diilo, y similares. En modalidades particulares, "alquinileno," ya sea solo o representado junto con otro radical, puede ser un alquinileno(C_{2-20}), un alquinileno(C_{2-15}), un alquinileno(C_{2-10}), un alquinileno(C_{2-5}) o un alquinileno(C_{2-3}). Alternativamente, "alquinileno," ya sea solo o

representado junto con otro radical, puede ser un alquinileno(C_2), un alquinileno(C_3) o un alquinileno(C_4).

El término "Amido" representa al radical -C(=O)-NR-, -C(=O)-NRR', -NR-C(=O)- y/o -NR-C(=O)R', donde cada R y R' son independientemente hidrógeno o un sustituyente adicional.

El término "Amino" representa un residuo de nitrógeno que posee dos sustituyentes adicionales donde, por ejemplo, un átomo de hidrógeno o carbono está unido al nitrógeno. Por ejemplo, grupos aminos representativos incluyen $-NH_2$, $-NHCH_3$, $-N(CH_3)_2$, -NH(alquilo(C_{1-10})), -N(alquilo(C_{1-10}))$_2$, -NH(arilo), -NH(heteroarilo), -N(arilo)$_2$, -N(heteroarilo)$_2$, y similares. Opcionalmente, los dos sustituyentes junto con el nitrógeno también pueden formar un anillo. A menos que se indique de otra forma, los compuestos de la invención que contienen residuos amino pueden incluir derivados protegidos de los mismos. Los grupos protectores adecuados para los residuos amino incluyen acetilo, *ter*-butoxicarbonilo, benciloxicarbonilo, y similares.

El término "animal" incluye al humanos, y a mamíferos no humanos (*por ejemplo*, perros, gatos, conejos, ganado, caballo, ovejas, cabras, cerdos, ciervos, y similares) y no mamíferos (*por ejemplo*, aves, y similares).

El término "aromático" representa un residuo donde los átomos constituyentes forman un sistema de anillo insaturado, todos los átomos en el sistema de anillo están hibridizados sp^2 y el número total de electrones es igual a 4n+2. Un anillo aromático puede ser tal que los átomos en el anillo solamente son átomos de carbono o pueden incluir átomos de carbono y distintos de carbono (véase "heteroarilo").

El término "arilo" representa un ensamblaje de anillo mono cíclico o poli cíclico donde cada anillo es aromático o cuando está fusionado con uno o más anillos forma un ensamblaje de anillo aromático. Si uno o más átomos del anillo no es carbono (*por ejemplo*, N, S), el arilo es un heteroarilo. Generalmente se utilizan arilo(C_X) y arilo(C_{X-Y}) donde X e Y indican el número de átomos de carbono en el anillo. En modalidades particulares, "arilo," ya sea solo o representado junto con otro radical, puede ser un arilo(C_{3-14}), un

arilo(C_{3-10}), un arilo(C_{3-7}), un arilo(C_{8-10}) o un arilo(C_{5-7}). Alternativamente, "arilo," ya sea solo o representado junto con otro radical, puede ser un arilo(C_5), un arilo(C_6), un arilo(C_7), un arilo(C_8), un arilo(C_9) o un arilo(C_{10}).

El término "azaalquilo" representa un alquilo, como se define anteriormente con la excepción que uno o más de los átomos de carbono que forman la cadena de alquilo están reemplazados con átomos de nitrógeno sustituido o sin sustituir (-NR- o -NRR', donde R y R' son cada uno de manera independiente hidrógeno o sustituyentes adicionales). Por ejemplo, un azaalquilo(C_{1-10}) se refiere a una cadena que comprende entre 1 a 10 carbonos y uno o más átomos de nitrógeno.

El término "bicicloalquilo" representa a un ensamblaje de anillo bicíclico espiro o punteado, saturado o parcialmente saturado fusionado. En modalidades particulares, "bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloalquilo(C_{4-15}), un bicicloalquilo(C_{4-10}), un bicicloalquilo(C_{6-10}) o un bicicloalquilo(C_{8-10}). Alternativamente, "bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloalquilo(C_8), un bicicloalquilo(C_9) o un bicicloalquilo(C_{10}).

El término "bicicloarilo" representa, a un ensamblaje de anillo bicíclico espiro o punteado fusionado donde al menos uno de los anillos que comprende el ensamblaje es aromático. Generalmente se utilizan bicicloarilo(C_x) y bicicloarilo(C_{x-y}) donde x e y indican el número de átomos de carbono en el ensamblaje de anillo bicíclico y que están directamente unidos al anillo. En modalidades particulares, "bicicloarilo," ya sea solo o representado junto con otro radical, puede ser un (a bicicloarilo(C_{4-15}), un bicicloarilo(C_{4-10}), un bicicloarilo(C_{6-10}) o un bicicloarilo(C_{8-10}). Alternativamente, "bicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un bicicloarilo(C_8), un bicicloarilo(C_9) o un bicicloarilo(C_{10}).

El término "anillo punteado" y "anillo con puente" como se utiliza aquí se refiere a un anillo que está unido a otro anillo para formar un compuesto que posee una estructura bicíclica o policíclica donde dos átomos del anillo que son comunes a ambos anillos no están

unidos uno con el otro. Ejemplos no excluyentes de compuestos comunes que poseen un anillo punteado incluyen borneol, norbornano, 7-oxabiciclo[2.2.1]heptano, y similares. Uno o ambos anillos del sistema bicíclico también puede incluir heteroátomos.

El término "carbamoilo" representa al radical -OC(O)NRR', donde R y R' son cada uno de manera independientemente hidrógeno o sustituyentes adicionales.

El término "carbociclo" representa a un anillo que consiste de átomos de carbono.

El término "carbonilo" representa al radical -C(=O)- y/o -C(=O)R, donde R es hidrógeno o un sustituyente adicional. Se debe destacar que el radical carbonilo pueda además estar sustituido con una diversidad de sustituyentes para formar diferentes grupos carbonilo incluyendo ácidos, haluros de ácidos, aldehídos, amidas, esteres, y cetonas.

El término "carboxi" representa al radical -C(=O)-O- y/o -C(=O)-OR, donde R es hidrógeno o un sustituyente adicional. Se debe destacar que los compuestos de la invención que contienen residuos carboxi pueden incluir derivados protegidos de los mismos, es decir, donde está sustituido el oxigeno con un grupo protector. Grupos protectores adecuados para los residuos carboxi incluyen bencilo, *ter*-butilo, y similares.

El término "ciano" representa al radical -CN.

El término "Cicloalquilo" representa a un ensamblaje de anillo no aromático, saturado o parcialmente insaturado, monocíclico, bicíclico o policíclico. Cicloalquilo (C_X) y cicloalquilo(C_{X-Y}) Se utilizan de manera general donde X e Y indican el número de átomos de carbono en el ensamblaje de anillo. Por ejemplo, cicloalquilo(C_{3-10}) incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexenilo, 2,5-ciclohexadienilo, biciclo[2.2.2]octilo, adamantan-1-ilo, decahidronaftilo, oxociclohexilo, dioxociclohexilo, tiociclohexilo, 2-oxobiciclo[2.2.1]hept-1-ilo, y similares. En modalidades particulares, "cicloalquilo," ya sea solo o representado junto con otro radical, puede ser un cicloalquilo(C_{3-14}), un cicloalquilo(C_{3-10}), un cicloalquilo(C_{3-7}), un cicloalquilo(C_{8-10}) o un cicloalquilo(C_{5-7}). Alternativamente, "cicloalquilo," ya sea solo o

representado junto con otro radical, puede ser un cicloalquilo(C_5), un cicloalquilo(C_6), un cicloalquilo(C_7), un cicloalquilo(C_8), un cicloalquilo(C_9) o un cicloalquilo(C_{10}).

El término "Cicloalquileno" reresenta a yb ensamblaje de anillo divalente, saturado o parcialmente insaturado, monocíclico, bicíclico o policíclico. Donde cicloalquileno(C_X) y cicloalquileno(C_{X-Y}) se utilizan en general e los cuales X e Y indican el número de átomos de carbono en el ensamblaje de anillo. En modalidades particulares, "cicloalquileno," ya sea sólo o representado junto con otro radical, puede ser un cicloalquileno(C_{3-14}), un cicloalquileno(C_{3-10}), un cicloalquileno(C_{3-7}), un cicloalquileno(C_{8-10}) o un cicloalquileno(C_{5-7}). Alternativamente, "cicloalquileno," ya sea solo o representado junto con otro radical, puede ser un cicloalquileno(C_5), un cicloalquileno(C_6), un cicloalquileno(C_7), un cicloalquileno(C_8), un cicloalquileno(C_9) o un cicloalquileno(C_{10}).

El término "Enfermedad" incluye específicamente a cualquier condición insalubre de un animal o de parte del mismo e incluye una condición insalubre que puede ser causada por, o se un incidente por, una terapia médica o veterinaria aplicada a ese animal, es decir, los "efectos secundarios" de dicha terapia.

El término "anillo fusionado" como se utiliza aquí se refiere a un anillo que está unido a otro anillo para formar un compuesto que posee una estructura bicíclica donde los átomos del anillo que son comunes a ambos anillos se encuentran directamente unidos uno con otro. Ejemplos no exclusivos anillos fusionados comunes incluyen decalina, naftaleno, antraceno, fenantreno, indol, furano, benzofurano, quinolina, y similares. Los compuestos que poseen sistemas de anillos fusionados pueden estar saturados, parcialmente saturados, ser carbociclicos, heterociclicos, aromáticos, heteroaromáticos, y similares.

El término "halógeno" significa flúor, cloro, bromo o yodo.

El término "heteroalquilo" significa alquilo, tal como se define en esta solicitud, con la condición que uno o más de los átomos dentro de la cadena de alquilo es un heteroátomo. En modalidades particulares, "heteroalquilo," ya sea solo o representado

junto con otro radical, puede ser un heteroalquilo(C_{1-20}), un heteroalquilo(C_{1-15}), un heteroalquilo(C_{1-10}), un heteroalquilo(C_{1-5}), un heteroalquilo(C_{1-3}) o un heteroalquilo(C_{1-2}). Alternativamente, "heteroalquilo," ya sea solo o representado junto con otro radical, puede ser un heteroalquilo(C_1), un heteroalquilo(C_2) o un heteroalquilo(C_3).

El término "heteroarilo" representa un grupo monocíclico, bicíclico o policíclico aromático donde al menos un átomo del anillo es un heteroátomo y el resto de los átomos del anillo son carbono. Los grupos heteroarilo monocíclicos incluyen, pero no están limitados a, grupos aromáticos cíclicos que poseen cinco o seis átomos en el anillo, donde al menos un átomo del anillo es un heteroátomo y el resto de los átomos del anillo son carbono. Los átomos de nitrógeno pueden opcionalmente estar cuaternerizados y los átomos de azufre pueden opcionalmente estar oxidados. Los grupos heteroarilo de esta invención incluyen, pero no están limitados a, aquellos derivados de furano, imidazol, isotiazol, isoxazol, oxadiazol, oxazol, 1,2,3-oxadiazol, pirazina, pirazol, piridazina, piridina, pirimidina, pirrolina, tiazol, 1,3,4-tiadiazol, triazol y tetrazol. "Heteroarilo" también incluye, pero no está limitado a, anillos bicíclicos o tricíclicos, donde el anillo the heteroarilo está fusionado a uno o a dos anillos independientemente seleccionados del grupo que consiste de un anillo arilo, un anillo cicloalquilo, un anillo cicloalquenilo, y otro heteroarilo monocíclico o anillo heterocicloalquilo. Estos heteroarilos bicíclicos o tricíclicos incluyen, pero no están limitados a, aquellos derivados de benzo[b]furano, benzo[b]tiofeno, bencimidazol, imidazo[4,5-c]piridina, quinazolina, tieno[2,3-c]piridina, tieno[3,2-b]piridina, tieno[2,3-b]piridina, indolizina, imidazo[1,2a]piridina, quinolina, isoquinolina, ftalazina, quinoxalina, naftiridina, quinolizina, indol, isoindol, indazol, indolina, benzoxazol, benzopirazol, benzotiazol, imidazo[1,5-a]piridina, pirazolo[1,5-a]piridina, imidazo[1,2-a]pirimidina, imidazo[1,2-c]pirimidina, imidazo[1,5-a]pirimidina, imidazo[1,5-c]pirimidina, pirrolo[2,3-b]piridina, pirrolo[2,3-c]piridina, pirrolo[3,2-c]piridina, pirrolo[3,2-b]piridina, pirrolo[2,3-d]pirimidina, pirrolo[3,2-d]pirimidina, pirrolo[2,3-b]pirazina,

pirazolo[1,5-a]piridina, pirrolo[1,2-b]piridazina, pirrolo[1,2-c]pirimidina, pirrolo[1,2-a]pirimidina, pirrolo[1,2-a]pirazina, triazo[1,5-a]piridina, pteridina, purina, carbazol, acridina, fenazina, fenotiazeno, fenoxazina, 1,2-dihidropirrolo[3,2,1-*hi*]indol, indolizina, pirido[1,2-a]indol y 2(1H)-piridinona. Los anillos heteroarilos bicíclicos o tricíclicos pueden estar unidos a la molécula parental ya sea a través del grupo heteroarilo mismo o del grupo arilo, cicloalquilo, cicloalquenilo o heterocicloalquilo al cual está fusionado. Los grupos heteroarilo de esta invención pueden estar sustituidos o sin sustituir. En modalidades particulares, "heteroarilo," ya sea solo o representado junto con otro radical, puede ser un heteroarilo(C_{1-13}), un heteroarilo(C_{2-13}), un heteroarilo(C_{2-6}), un heteroarilo(C_{3-9}) o un heteroarilo(C_{5-9}). Alternativamente, "heteroarilo," ya sea solo o representado junto con otro radical, puede ser un heteroarilo(C_3), un heteroarilo(C_4), un heteroarilo(C_5), un heteroarilo(C_6), un heteroarilo(C_7), un heteroarilo(C_8) o un heteroarilo(C_9).

El término "Heteroátomo" se refiere a un átomo que no es un átomo de carbono. Ejemplos particulares de heteroátomos incluyen, pero no están limitados a, nitrógeno, oxígeno, y azufre.

El término "residuo de heteroátomo" incluye un residuo donde el átomo a través del cual el residuo está unido no es un carbono. Ejemplos de residuos de heteroátomo incluyen -NR-, $-N^{+}(O^{-})=$, -O-, -S- o $-S(O)_2-$, donde R es hidrógeno o un sustituyente adicional.

El término "heterobicicloalquilo" significa bicicloalquilo, tal como se define en esta solicitud, con la condición que uno o más de los átomos dentro del anillo es un heteroátomo. Por ejemplo heterobicicloalquilo(C_{9-12}) como se utiliza en esta solicitud incluye, pero no está limitado a, 3-aza-biciclo[4.1.0]hept-3-ilo, 2-aza-biciclo[3.1.0]hex-2-ilo, 3-aza-biciclo[3.1.0]hex-3-ilo, y similares. En modalidades particulares, "heterobicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloalquilo(C_{1-14}), un heterobicicloalquilo(C_{4-14}), un heterobicicloalquilo(C_{4-9}) o un heterobicicloalquilo(C_{5-9}). Alternativamente, "heterobicicloalquilo," ya sea solo o representado junto con otro radical, puede ser un

heterobicicloalquilo(C_5), heterobicicloalquilo(C_6), heterobicicloalquilo(C_7), heterobicicloalquilo(C_8) o un heterobicicloalquilo(C_9).

El término "heterobicicloariló" representa a bicicloarilo, como se define en esta solicitud, con la condición que uno o más de los átomos dentro del anillo es un heteroátomo. Por ejemplo, heterobicicloarilo(C_{4-12}) como se utiliza en esta solicitud incluye, pero no está limitado a, 2-amino-4-óxo-3,4-dihidropteridin-6-ilo, tetrahidroiso-quinolinilo, y similares. En modalidades particulares, "heterobicicloarilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloarilo(C_{1-14}), un heterobicicloarilo(C_{4-14}), un heterobicicloarilo(C_{4-9}) o un heterobicicloarilo(C_{5-9}). Alternativamente, "heterobicicloarilo," ya sea solo o representado junto con otro radical, puede ser un heterobicicloarilo(C_5), heterobicicloarilo(C_6), heterobicicloarilo(C_7), heterobicicloarilo(C_8) o un heterobicicloarilo(C_9).

El término "heterocicloalquilo" representa a cicloalquilo, como se define en esta solicitud, con la condición que uno o más de los átomos que forman el anillo es un heteroátomo seleccionado, independientemente de N, O, o S. Ejemplos no exclusivos de heterocicloalquilo incluyen piperidilo, 4-morfolilo, 4-piperazinilo, pirrolidinilo, perhidropirrolizinilo, 1,4-diazaperhidroepinilo, 1,3-dioxanilo, 1,4- dioxanilo y similares. En modalidades particulares, "heterocicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquilo(C_{1-13}), un heterocicloalquilo(C_{1-9}), un heterocicloalquilo(C_{1-6}), un heterocicloalquilo(C_{5-9}) o un heterocicloalquilo(C_{2-6}). Alternativamente, "heterocicloalquilo," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquilo(C_2), un heterocicloalquilo(C_3), un heterocicloalquilo(C_4), un heterocicloalquilo(C_5), un heterocicloalquilo(C_6), heterocicloalquilo(C_7), heterocicloalquilo(C_8) o un heterocicloalquilo(C_9).

El término "heterocicloalquileno" representa a un cicloalquileno, como se define en esta solicitud, con la condición

que uno o más de los átomos de carbono miembros del anillo está reemplazado por un heteroátomo. En modalidades particulares, "heterocicloalquileno," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquileno(C_{1-13}), un heterocicloalquileno(C_{1-9}), un heterocicloalquileno(C_{1-6}), un heterocicloalquileno(C_{5-9}) o un heterocicloalquileno(C_{2-6}). Alternativamente, "heterocicloalquileno," ya sea solo o representado junto con otro radical, puede ser un heterocicloalquileno(C_2), un heterocicloalquileno(C_3), un heterocicloalquileno(C_4), un heterocicloalquileno(C_5), un heterocicloalquileno(C_6), heterocicloalquileno(C_7), heterocicloalquileno(C_8) o un heterocicloalquileno(C_9).

El término "hidroxi" representa al radical -OH.

El término "IC_{50}" representa a la concentración molar de un inhibidor que produce un 50% de inhibición de la enzima objetivo.

El término "imino" representa al radical -CR(=NR') y/o -C(=NR')-, donde R y R' son cada uno independientemente hidrógeno o un sustituyente adicional.

El término "Isómeros" representa a los compuestos que poseen una formula molecular idéntica pero que se diferencian en la naturaleza o secuencia del enlace de sus átomos o en la disposición de sus átomos en el espacio. Los isómeros que difieren en la disposición de sus átomos en el espacio se denominan "estereoisómeros." Los estereoisómeros que no son imágenes especulares uno del otro se denominan "diastereómeros" y los estereoisómeros que no son imágenes especulares y sobre-imponibles se denominan "enantiómeros" o algunas veces "isómeros ópticos." Un átomo de carbono unido a cuatro sustituyentes no idénticos es denominado un "centro quiral." Un compuesto con un centro quiral posee dos formar enantioméricas de quiralidad opuesta. Una mezcla de dos formas enantioméricas se denomina una "mezcla racémica." Un compuesto que posee más de un centro quiral posee 2^{n-1} de pares enantioméricos, donde *n es* el número de centros quirales. Los compuestos con más de un centro quiral pueden existir como diastereómero individual o como una mezcla de diastereómeros, denominada una "mezcla diastereomérica." Cuando un centro quiral

está presente un estereoisómero se puede caracterizar a través de la configuración absoluta de ese centro quiral. La configuración absoluta se refiere a la disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales y se describen por las reglas de Cahn, Ingold y Prelog de secuenciación *R*- y *S*-. Las convenciones para la nomenclatura estereoquímica, los métodos para la determinación de la estereoquiometria y la separación de los estereoisómeros son bien conocidos en el arte (*por ejemplo*, véase "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992).

El término "grupo saliente" representa al grupo con el significado asociado de manera convencional con este en la química de síntesis orgánica, es decir, un átomo o grupo desplazable bajo condiciones de reacción (*por ejemplo*, alquilación). Ejemplos de grupos salientes incluyen, pero no están limitados a, halógenos (*por ejemplo*, F, Cl, Br e I), alquilo (*por ejemplo*, metilo y etilo) y sulfoniloxi (*por ejemplo*, mesiloxi, etanosulfoniloxi, bencenosulfoniloxi y tosiloxi); tiometilo, tieniloxi, dihalofosfinoiloxi, tetrahalofosfoxi, benciloxi, isopropiloxi, aciloxi, y similares.

El término "residuo que proporciona una separación de X átomo" y "conector que proporciona una separación de X átomo" entre dos residuos diferentes significa que la cadena de átomos que une directamente los dos residuos diferentes tiene X átomos en longitud. Cuando X está determinado como un rango (*por ejemplo*, X_1-X_2), entonces la cadena de átomos es al menos X_1 y no más de X_2 átomos de longitud. Se entiende que la cadena de átomos puede estar formada por una combinación de átomos incluyendo, por ejemplo, átomos de carbono, nitrógeno, azufre y oxígeno. Además, cada átomo puede opcionalmente a uno o más sustituyentes, tanto como las valencias lo permitan. Además, la cadena de átomos puede formar parte de un anillo. En consecuencia, en una modalidad, un residuo que proporciona X átomos de separación entre dos residuos diferentes (R y R') puede estar representado por R-$(L)_X$-R' donde cada L se selecciona de manera independiente del grupo que consiste de CR''R''', NR'''', O, S, CO,

CS, C=NR'''', SO, SO_2, y similares, donde cualquiera dos o más de R'', R''', R'''' y R''''' pueden ser tomados en conjunto para formar un anillo sustituido o sin sustituir.

El término "nitro" representa al radical $-NO_2$.

El término "oxaalquilo" representa un alquilo, tal como se ha definido antes, con la excepción que uno o más de los átomos de carbono que forman la cadena de alquilo están reemplazados con átomos de oxígeno (-O- o -OR, donde R es hidrógeno o un sustituyente adicional). Por ejemplo, un oxaalquilo(C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de oxígeno.

El término "oxoalquilo" representa a un alquilo, como se define antes, con la excepción de que uno o más de los átomos de carbono que forman la cadena de alquilo están reemplazados con grupos carbonilo (-C(=O)- o -C(=O)-R, donde R es hidrógeno o un sustituyente adicional). El grupo carbonilo puede ser un aldehído, cetona, éster, amida, ácido, o haluro de ácido. Por ejemplo, un oxoalquilo(C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 átomos de carbono y uno o más grupos carbonilo.

El término "oxi" representa al radical -O- o -OR, donde R es hidrógeno o un sustituyente adicional. En consecuencia, es destacable que el radical oxi puede además estar sustituido con una diversidad de sustituyentes para formar diferentes grupos oxi incluyendo hidroxi, alcoxi, ariloxi, heteroariloxi o carboniloxi.

El término "Farmacéuticamente aceptable" representa a aquel que es útil para preparar una composición farmacéutica que generalmente es segura, no tóxica y tampoco tóxica desde el punto de vista biológico ni de otro modo indeseable y que incluye a aquello que es aceptable para el uso veterinario así como también para el uso farmacéutico en humanos.

El término "sales farmacéuticamente aceptables" representa a las sales de compuestos de la presente invención las cuales son farmacéuticamente aceptables, como se he definido antes, y las cuales poseen la actividad farmacológica deseada. Dichas sales incluyen a las sales de adición ácida formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; o con ácidos orgánicos tal como ácido

acético, ácido propiónico, ácido hexanoico, ácido heptanóico, ácido ciclopentanopropionico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malonico, ácido succínico, ácido málico, ácido maleico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido *o*-(4-hidroxibenzoil)benzoico, ácido cinamico, ácido mandelico, ácido metanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido *p*-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido *p*-toluenosulfónico, ácido canforsulfónico, ácido 4-metilbiciclo[2.2.2]oct-2-eno-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metilenbis(3-hidroxi-2-eno-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido terciario butilacético, ácido lauril sulfúrico, ácido glucónico, ácido glutámico, ácido hidroxinaftoico, ácido salicílico, ácido esteárico, ácido mucónico y similares.

Las sales farmacéuticamente aceptables también incluyen las sales de adición de base que pueden formarse con los protones ácidos presentas que son capaces de reaccionar con las bases inorgánicas u orgánicas. Las bases inórgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio y hidróxido de calcio. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, *N*-metilglucamina y similares.

El término "anillo policíclico" incluye anillos bicíclicos y multi-cíclicos. Los anillos individuales que comprenden al anillo policíclico pueden estar fusionados, como anillos espiro anillos puenteados.

El término "Prodroga" representa a un compuesto que es convertible *in vivo* por vía metabólica en un inhibidor de acuerdo a la presente invención. La prodroga misma también puede o puede no tener actividad con respecto de una proteína blanco determinada. Por ejemplo, un compuesto que compone de un grupo hidroxi puede ser administrado como un éster que es convertido por hidrólisis *in vivo* en el compuesto hidroxi. Los ésteres adecuados que pueden ser convertidos *in vivo* en compuestos hidroxi incluyen acetatos, citratos, lactatos, fosfatos, tartratos, malonatos, oxalatos,

salicilatos, propionatos, succinatos, fumaratos, maleatos, metilen-bis-b-hidroxinaftoatos, gentisatos, isetionatos, di-*p*-toluoiltartratos, metanosulfonatos, etanosulfonatos, bencenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos, quinatos, ésteres de aminoácidos, y similares. De manera similar, un compuesto que comprende un grupo amina puede ser administrado como una amida que es convertida por hidrólisis *in vivo* en el compuesto amina.

El término "derivados protegidos" representa a los derivados de los inhibidores en donde se bloquea un sitio reactivo o sitios reactivos con grupos protectores. Los derivados protegidos son útiles en la preparación de inhibidores o ellos mismos pueden ser activos como inhibidores. Una lista comprensiva de grupos protectores adecuados se puede encontrar en T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

El término "Anillo" y "ensamblaje de anillo" representa a un sistema carbocíclico o un sistema heterocíclico e incluye sistemas aromáticos y no aromáticos. El sistema puede ser monocíclico, bicíclico o policíclico. Además, para los sistemas bicíclicos y policíclicos, los anillos individuales comprenden al anillo policíclico pueden estar fusionados, como anillos espiro o anillos punteados.

El término "individuo" y "paciente" incluye a humanos y a mamíferos no humanos (*por ejemplo*, perros, gatos, conejos, ganado, caballos, ovejas, cabras, cerdos, ciervos, y similares) y no mamíferos (*por ejemplo*, aves, y similares).

El término "sustituyente convertible en hidrógeno *in vivo*" representa a cualquier grupo que es convertible en un átomo de hidrógeno mediante medios enzimológicos o químicos incluyendo, pero no limitados a, hidrólisis e hidrogenolisis. Los ejemplos incluyen a los grupos hidrolizables, tales como grupos acilos, grupos que poseen un grupo oxicarbonilo, residuos de aminoácido, residuos peptídicos, o-nitrofenilsulfenilo, trimetilsililo, tetrahidro-piranilo, difenilfosfinilo, y similares. Ejemplos de grupos acilos incluyen formilo, acetilo, trifluoroacetilo, y similares. Ejemplos de grupos que poseen un grupo oxicarbonilo incluyen etoxicarbonilo, t-

butoxicarbonilo [$(CH_3)_3C$-OCO-], benciloxi-carbonilo, p-metoxibenciloxicarbonilo, viniloxicarbonilo, β-(p-toluenosulfonil)etoxicarbonilo, y similares. Ejemplos de residuos de aminoácido incluyen residuos de aminoácidos *per se* y residuos de aminoácidos que se encuentran protegidos con un grupo protector. Los residuos de aminoácidos adecuados incluyen, pero no están limitados a, residuos de Gly (glicina), Ala (alanina; $CH_3CH(NH_2)CO$-), Arg (arginina), Asn (asparagina), Asp (ácido aspártico), Cys (cisteína), Glu (ácido glutámico), His (histidina), Ile (isoleucina), Leu (leucina; $(CH_3)_2CHCH_2CH(NH_2)CO$-), Lys (lisina), Met (metionina), Phe (fenilalanina), Pro (prolina), Ser (serina), Thr (treonina), Trp (triptofano), Tyr (tirosina), Val (valina), Nva (norvalina), Hse (homoserina), 4-Hyp (4-hidroxiprolina), 5-Hyl (5-hidroxilisina), Orn (ornitina) y β-Ala. Ejemplos de grupos protectores adecuados incluyen a aquellos que se utilizan generalmente en síntesis de péptidos, incluyendo los grupos acilos (tal como formilo y acetilo), grupos arilmetiloxi-carbonilo (tales como benciloxicarbonilo y p-nitrobenciloxi-carbonilo), grupos t-butoxicarbonilo [$(CH_3)_3C$-OCO-], y similares. Residuos de péptidos adecuados incluyen residuos de péptidos que comprenden 2 o 5 y opcionalmente 2 o 3, tal como se dijo anteriormente de los residuos de aminoácidos. Ejemplos de tales residuos de péptidos incluyen, pero no están limitados a, residuos de tales péptidos como Ala-Ala [$CH_3CH(NH_2)CO$-$NHCH(CH_3)CO$-], Gly-Phe, Nva-Nva, Ala-Phe, Gly-Gly, Gly-Gly-Gly, Ala-Met, Met-Met, Leu-Met y Ala-Leu. Los residuos de estos aminoácidos o péptidos pueden estar presentes en configuraciones estereoquímicas de la forma D, la forma L o mezclas de los mismos. Además, el residuo de aminoácido o péptido puede tener un átomo de carbono asimétrico. Ejemplos de residuos de aminoácido adecuado que poseen un átomo de carbono asimétrico incluyen residuos de Ala, Leu, Phe, Trp, Nva, Val, Met, Ser, Lys, Thr y Tyr. Residuos de péptidos que poseen un átomo de carbono asimétrico incluyen residuos de péptidos que poseen uno o más constituyentes de residuos de aminoácido que poseen un átomo de carbono asimétrico. Ejemplos de grupos protectores de aminoácidos adecuados incluyen a aquellos que se utilizan generalmente en la síntesis de péptidos, incluyendo grupos acilo (tales como formilo y acetilo), grupos

arilmetiloxicarbonilo (tales como benciloxicarbonilo y p-nitrobenciloxicarbonilo), grupos t-butoxicarbonilo [$(CH_3)_3C$-OCO-], y similares. Otros ejemplos de sustituyentes "convertibles a hidrógeno *in vivo*" incluyen grupos hidrogenolizables posibles de eliminar por vía reductiva. Ejemplos de grupos hidrogenolizables posibles de eliminar por vía reductiva incluyen, pero no están limitados a, grupos arilsulfonilo (tal como o-toluenosulfonilo); grupos metilo sustituidos con fenilo o benciloxi (tales como bencilo, tritilo y benciloximetilo); grupos arilmetoxicarbonilo (tales como benciloxicarbonilo y o-metoxi-benciloxicarbonilo); y grupos halogenoetoxicarbonilo (tal como β,β,β-tricloroetoxicarbonilo y β-yodoetoxicarbonilo).

El término "Sustituido sin sustituir" significa que un residuo determinado puede consistir solamente de sustituyentes hidrógeno a través de las valencias disponibles (no sustituido) o puede además comprender uno o más sustituyentes diferentes de hidrogeno a través de las valencias disponibles (sustituido) que no se especifican de otro modo por el nombre del residuo determinado. Por ejemplo, isopropilo como un ejemplo de un residuo de etileno que está sustituido por $-CH_3$. En general, un sustituyente distinto de hidrogeno puede ser cualquier sustituyente que puede estar unido a un átomo del residuo determinado que se especifica como sustituido. Ejemplos de sustituyentes incluyen, pero no están limitados a residuos aldehído, alicíclico, alifático, alquilo(C_{1-10}), alquileno, alquilideno, amida, amino, aminoalquilo, aromático, arilo, bicicloalquilo, bicicloarilo, carbamoilo, carbociclilo, carboxilo, grupo carbonilo, ciclo-alquilo, cicloalquileno, éster, halógeno, heterobicicloalquilo, heterocicloalquileno, heteroarilo, heterobicicloarilo, hetero-cicloalquilo, oxo, hidroxi, iminocetona, cetona, nitro, oxaalquilo, y oxoalquilo, cada uno de los cuales también puede estar opcionalmente sustituido o sin sustituir. En una modalidad particular, ejemplos de sustituyentes incluyen, pero no están limitados a, hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}),

haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), hetero-bicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}). Además, el sustituyente está en si mismo opcionalmente sustituido por un sustituyente adicional. En una modalidad particular, ejemplos de sustituyentes adicionales incluyen, pero no están limitados a, hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}).

El término "sulfinilo" representa al radical -SO- y/o -SO-R, donde R es hidrógeno o un sustituyente adicional. Es notable que el radical sulfinilo además puede estar sustituido con una variedad de sustituyentes para formar diferentes grupos sulfinilo incluyendo ácidos sulfínicos, sulfinamidas, ésteres de sulfinilo, y sulfóxidos.

El término "sulfonilo" representa al radical $-SO_2-$ y/o $-SO_2-R$, donde R es hidrógeno o un sustituyente adicional. Se nota que el radical sulfonilo puede además estar sustituido con una variedad de sustituyentes para formar grupos sulfonilo diferentes incluyendo ácidos sulfónicos, sulfonamidas, ésteres de sulfonato, y sulfonas.

El término "cantidad terapéuticamente efectiva" representa a una cantidad que, cuando se administra a un animal para tratar una

enfermedad, es suficiente para efectuar dicho tratamiento para la enfermedad.

El término "tio" representa al reemplazo de un oxígeno por un azufre e incluye, pero no está limitado a, grupos que contienen -SR, -S- y =S.

El término "tioalquilo" representa a un alquilo, como se define anteriormente, con la excepción que uno o más de los átomos de carbono que forman la cadena de alquilo están reemplazados con átomos de azufre. (-S- o -S-R, donde R es hidrógeno o un sustituyente adicional). Por ejemplo, un tioalquilo(C_{1-10}) se refiere a una cadena que comprende entre 1 y 10 carbonos y uno o más átomos de azufre.

El término "tiocarbonilo" representa al radical -C(=S)- y/o -C(=S)-R, donde R es hidrógeno o un sustituyente adicional. Se nota que el radical tiocarbonilo puede además estar sustituido con una variedad de sustituyentes para formar diferentes grupos tiocarbonilo incluyendo tioácidos, tioamidas, tioésteres, y tiocetonas.

El término "tratamiento" o "tratando" significan cualquier administración de un compuesto de la presente invención e incluye:

(1) prevenir la enfermedad de ocurrir en un animal que puede estar predispuesto a la enfermedad pero que aun no la experimenta o presenta la patología o sintomatología de la enfermedad,

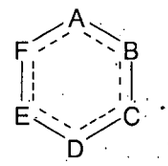
(2) inhibir la enfermedad en un animal que está experimentando o que presenta la patología o sintomatología de la enfermedad (*es decir,* que se détiene el desarrollo posterior de la patología y/o sintomatología), o

(3) mejorar la enfermedad en un animal que está experimentando o presentando la patología o sintomatología de la enfermedad (*es decir,* revirtiendo la patología y/o sintomatología).

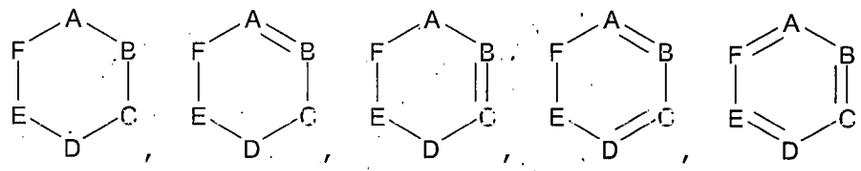
Es notable que con respecto a todas las definiciones aquí provistas, estas definiciones se deben interpretar como de sentido amplio o abierto en el sentido que sustituyentes adicionales más allá de aquellos que se han especificado pueden ser incluidos. Por lo cual, un C_1 alquilo indica que hay un átomo de carbono pero no indica cuales son los sustituyentes en el átomo de carbono. Por lo cual, un (C_1)alquilo comprende metilo (*es decir,* $-CH_3$) así como -CRR'R'' donde

R, R', y R'' pueden ser cada uno independientemente hidrógeno o un sustituyente adicional donde el átomo unido al carbono es un heteroátomo o ciano. Por lo cual, CF_3, CH_2OH y CH_2CN, por ejemplo, son todos (C_1)alquilos. De manera similar, los términos tal como alquilamino y similares comprenden dialquilamino y similares.

Un compuesto que posee la fórmula que es representada con un enlace de línea punteada, se pretende que incluya a las fórmulas que opcionalmente poseen cero, uno o más enlaces dobles, como se ejemplifica y se muestra más adelante:



representa



, etc.

Además, se pretende que los átomos que forman los compuestos de la presente invención incluyan a todas las formas isotópicas de tales átomos. Los isótopos, como se utiliza aquí, incluyen a aquellos átomos que poseen el mismo número atómico pero diferentes números másicos. A modo de ejemplo general y sin limitación, los isótopos de hidrógeno incluyen tritio y deuterio, y los isótopos de carbono incluyen ^{13}C y ^{14}C.

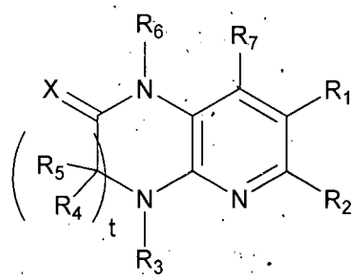
DESCRIPCION DETALLADA DE LA INVENCIÓN

La presente invención se refiere a compuestos que se pueden utilizar para inhibir PARP. La presente invención también se refiere a composiciones farmacéuticas, kits y artículos de manufactura que comprenden tales compuestos. Además, la presente invención se refiere a métodos e intermediarios útiles para preparar los compuestos. Además, la presente invención se refiere a métodos para utilizar a dichos compuestos. Es notable que los compuestos de la presente invención también puedan poseer actividad para otros miembros de la misma familia de proteína y por lo cual pueden ser utilizados para

tratar los estados de enfermedad asociados con estos otros miembros de familia.

Inhibidores PARP

En uno de sus aspectos, la presente invención se refiere a compuestos que son útiles como inhibidores PARP. En una modalidad, los inhibidores PARP de la presente invención comprenden:



o un polimorfo, solvato, éster, tautómero, enantiómero, sal farmacéuticamente aceptable o prodroga de lo mismo, donde

t se selecciona del grupo que consiste de 1 o 2;

X se selecciona del grupo que consiste de O, S y NR_8;

R_1 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), aminoalquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), imino-alquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterociclo-alquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobi-cicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_1 es $-L_1-R_{13}$;

L_1 está ausente o es un conector que proporciona una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{13} y el anillo al cual L_1 está

unido, donde los átomos del conector que proporcionan la separación son seleccionados del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

R_2 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobi-cicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_3 se selecciona del grupo que consiste de hidrógeno, carboniloxi, alcoxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_3 posee la fórmula $-L_2-R_{18}$;

L_2 está ausente o es un conector que proporciona una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{18} y el anillo al cual L_2 está unido, donde los átomos del conector que proporcionan la

separación son seleccionados del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

R_4 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobi-cicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_5 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobi-cicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

o cualquiera de los dos de R_3, R_4 y R_5 se toman juntos para formar un anillo sustituido o sin sustituir;

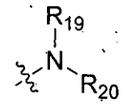
R_6 se selecciona del grupo que consiste de hidrógeno, carboniloxi, carbonilo, oxicarbonilo, amino, alquil-amino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_7 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_8 se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}),

azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{13} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_{13} posee la fórmula:



;

R_{18} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}),

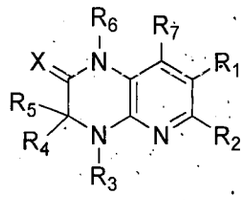
cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{19} y R_{20} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tio-carbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinil-alquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir, ó R_{19} y R_{20} se toman juntos para formar un anillo sustituido o sin sustituir.

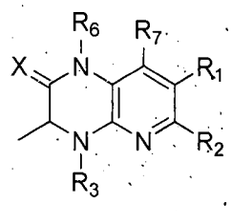
En una variación de la modalidad anterior, el compuesto no es: (i) 3-metilpirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona; (ii) 3-metoxipirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona; (iii) 2-(3-cloro-6-oxo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-5(6H)-il)-N-o-tolilacetamida; (iv) 2-(3-cloro-6-oxo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-5(6H)-il)-N-(3-(trifluorometil)fenil)acetamida; (v) ácido 5-Oxo-3-(2-trifluorometil-bencil)-2,3,4,4a,5,6-hexahidro-1H-pirazino[1,2-a]quinoxalina-8-carboxílico isopropilamida; (vi) ácido 3-(5-Fluoro-2-trifluorometil-benzoil)-5-oxo-2,3,4,4a,5,6-hexahidro-1H-pirazino[1,2-a]quinoxalin-8-carboxílico fenilamida; (vii) ácido 5-Oxo-3-(2-trifluorometil-benzoil)-2,3,4,4a,5,6-hexahidro-1H-pirazino[1,2-a]quinoxalin-8-carboxílico pentilamida; o (viii) ácido 3-(5-Fluoro-2-trifluorometil-

benzoil)-5-oxo-2,3,4,4a,5,6-hexahidro-1H-piracino[1,2-a]quinoxalin-8-carboxílico butilamida.

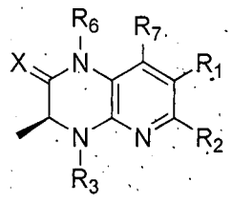
En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



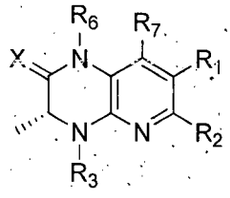
En otra modalidad, los inhibidores PARP de la presente invención comprenden:



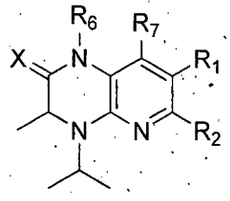
Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



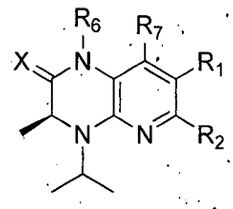
Aún en otra modalidad, los inhibidores PARP de la presente invención comprenden:



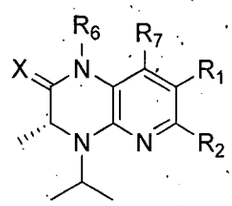
En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



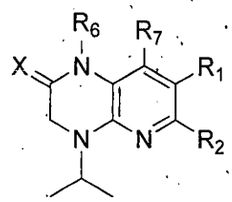
Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



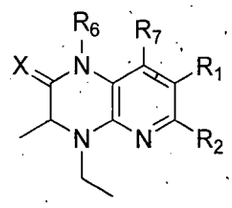
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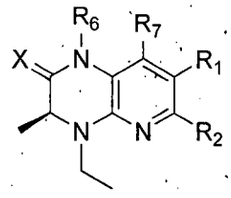
En otra modalidad, los inhibidores PARP de la presente invención comprenden:



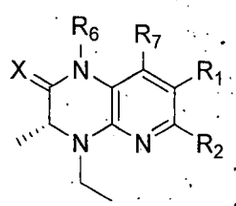
Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



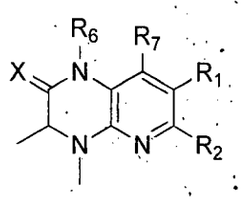
Aún en otra modalidad, los inhibidores PARP de la presente invención comprenden:



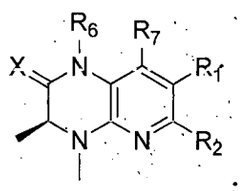
En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



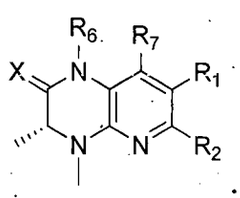
Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



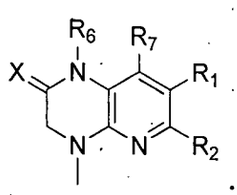
Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



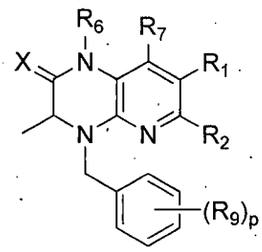
En otra modalidad, los inhibidores PARP de la presente invención comprenden:



Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



Aún en otra modalidad, los inhibidores PAPP de la presente invención comprenden:

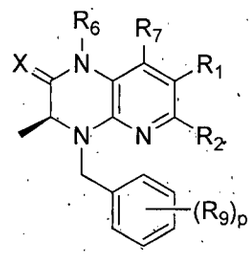


donde

p se selecciona del grupo que consiste de 0, 1, 2, 3, 4 y 5; y

R_9 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



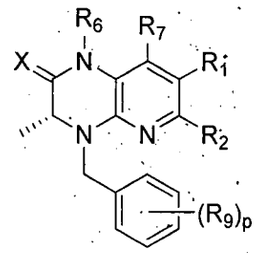
donde

p se selecciona del grupo que consiste de 0, 1, 2, 3, 4 y 5; y

R_9 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo,

amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



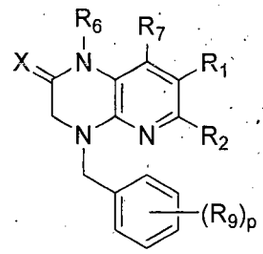
donde

p se selecciona del grupo que consiste de 0, 1, 2, 3, 4 y 5; y

R_9 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}),

heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

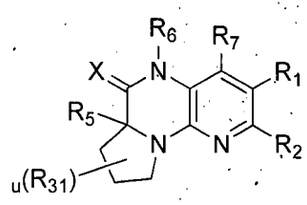


donde

p se selecciona del grupo que consiste de 0, 1, 2, 3, 4 y 5; y

R_9 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

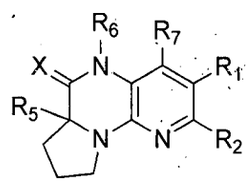


donde

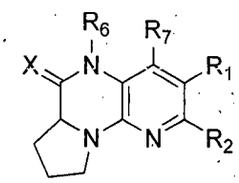
u se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{31} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

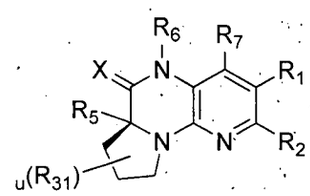
En otra modalidad, los inhibidores PARP de la presente invención comprenden:



En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

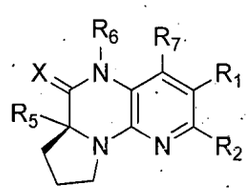


donde

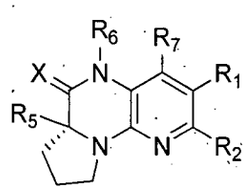
u se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{31} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

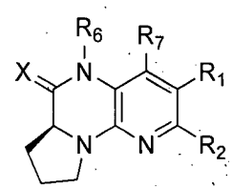
Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



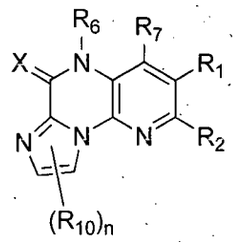
Aun en otra modalidad, los inhibidores PARP de la presente invención comprenden:



En otra modalidad, los inhibidores PARP de la presente invención comprenden:



En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

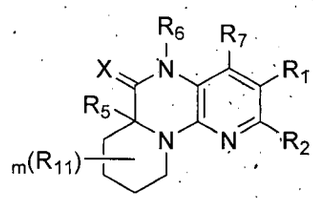


donde

n se selecciona del grupo que consiste de 0, 1 y 2; y

R_{10} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

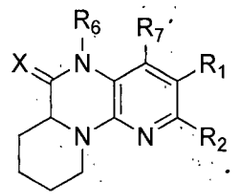


donde

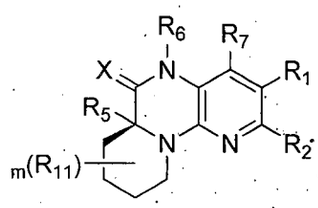
m se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8; y

R_{11} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra modalidad, los inhibidores PARP de la presente invención comprenden:



Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



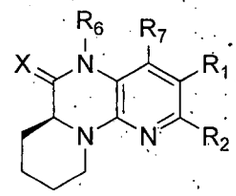
donde

m se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8; y.

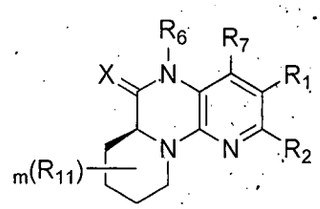
R_{11} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo,

amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

Aún en otra modalidad, los inhibidores PARP de la presente invención comprenden:



Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



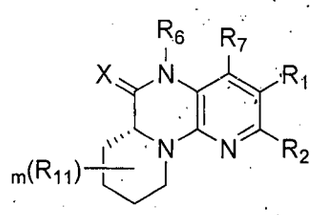
donde

m se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8; y

R_{11} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-

alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra modalidad, los inhibidores PARP de la presente invención comprenden:

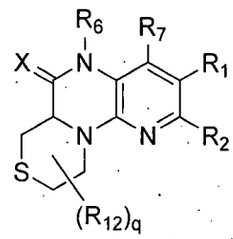


donde

m se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8; y

R_{11} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:

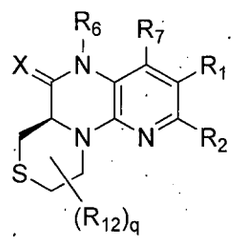


donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:



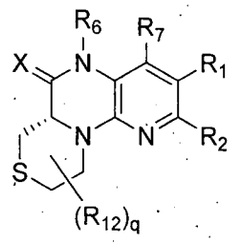
donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}),

ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



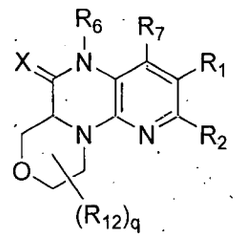
donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}),

heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

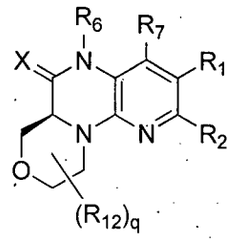


donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una modalidad adicional, los inhibidores PARP de la presente invención comprenden:

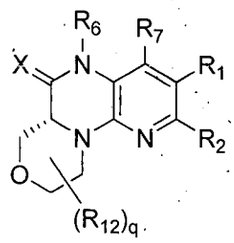


donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra modalidad, los inhibidores PARP de la presente invención comprenden:



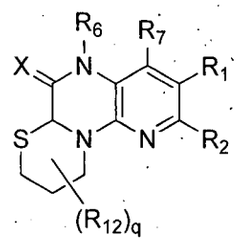
donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}),

cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra modalidad, los inhibidores PARP de la presente invención comprenden:

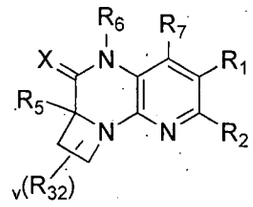


donde

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

R_{12} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una modalidad adicional, los inhibidores PARP de la presente invención comprenden:



donde

v se selecciona del grupo que consiste de 0, 1, 2, 3 y 4; y

R_{32} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación de cada una de las modalidades anteriores y sus variaciones, X es O.

En otra variación de cada una de las modalidades anteriores y sus variaciones,

R_1 es $-L_1-R_{13}$;

L_1 está ausente o es un conector que proporciona una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{13} y el anillo al cual L_1 está unido, donde los átomos del conector que proporcionan la separación son seleccionados del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre; y

R_{13} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo,

sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones,

L_1 está ausente o es un conector seleccionado del grupo que consiste de $-(CR_{14}R_{15})_r-$, -CO-, -CS-, $-C(=NR_{16})-$, $-NR_{17}-$, -O-, -S-, -SO-, $-SO_2-$ y las combinaciones de lo mismo;

r se selecciona del grupo que consiste de 1, 2 y 3;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}); carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}),

ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{16} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{17} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}),

arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones,

L_1 es $-CR_{14}R_{15}-$;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobi-cicloaril(C_{8-}

$_{12}$)alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional variación de cada una de las modalidades anteriores y sus variaciones, L_1 es $-CH_2-$. EN otra variación de cada una de las modalidades anteriores y sus variaciones, L_1 es $-CF_2-$. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, L_1 es $-NR_{17}-$. Aun en una variación de cada una de las modalidades anteriores y sus variaciones, L_1 es $-O-$.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_2 es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_2 es halógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_2 es un (C_{1-3}) alquilo sustituido o sin sustituir.

En una variación más de cada una de las modalidades anteriores y sus variaciones, R_3 es un alquilo(C_{1-3}) sustituido o sin sustituir. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_3 es metilo. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_3 es etilo. Aun en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_3 es propilo. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_3 es isopropilo. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_3 es un aril(C_{1-6})alquilo sustituido o sin sustituir. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_3 es un bencilo sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_3 posee la fórmula $-L_2-R_{18}$, donde L_2 está ausente o es un conector que proporciona una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{18} y el anillo al cual L_2 está unido, donde los átomos del conector que proporcionan la separación son

seleccionados del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre; y R_{13} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxa-alquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones,

L_2 está ausente o es un conector seleccionado del grupo que consiste de $-(CR_{14}R_{15})_r-$, $-CO-$, $-CS-$, $-C(=NR_{16})-$, $-NR_{17}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ y las combinaciones de lo mismo;

r se selecciona del grupo que consiste de 1, 2 y 3;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}),

bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{16} se selecciona del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{17} se selecciona del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}),

tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una variación más de cada una de las modalidades anteriores y sus variaciones,

L_2 es $-CR_{14}R_{15}-$;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}),

oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, L_2 es $-CH_2-$.

En otra variación más de cada una de las modalidades anteriores y sus variaciones, R_4 es a sustituido o sin sustituir alquilo(C_{1-3}). Aun en otra variación más de cada una de las modalidades anteriores y sus variaciones, R_4 es metilo. En una variación más de cada una de las modalidades anteriores y sus variaciones, R_4 es hidrógeno.

Incluso en una variación más de cada una de las modalidades anteriores y sus variaciones, R_3 y R_4, junto a los átomos a los cuales se encuentran unidos, se toman para formar un anillo de 3, 4, 5, 6, 7 o 8 miembros sustituido o sin sustituir. En una variación más de cada una de las modalidades anteriores y sus variaciones, R_3 y R_4, junto a los átomos a los cuales se encuentran unidos, se toman para formar un anillo heterocicloalquilo de 3, 4, 5, 6, 7 o 8 miembros sustituido o sin sustituir. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_3 y R_4, junto a los átomos a los cuales se encuentran unidos, se toman para formar un anillo heterocicloarilo 3, 4, 5, 6, 7 o 8 miembros sustituido o sin sustituir.

Aun en otra variación de cada una de las modalidades anteriores y sus variaciones, R_5 es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_5 es halógeno. Incluso en una variación más de cada una de las modalidades anteriores y sus variaciones, R_5 es un (C_{1-3}) alquilo sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_6 es hidrógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_6 es un (C_{1-3}) alquilo sustituido o sin sustituir.

Aun en otra variación de cada una de las modalidades anteriores y sus variaciones, R_7 es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_7 es halógeno. Incluso en una variación más de cada una de las modalidades anteriores y sus variaciones, R_7 es un (C_{1-3}) alquilo sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_8 es hidrógeno. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_8 es un alquilo(C_{1-3}) sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_9 es hidrógeno. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_9 es halógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_9 es un alquilo(C_{1-3}) sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{10} es hidrógeno. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{10} es halógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{10} es un alquilo(C_{1-3}) sustituido o sin sustituir.

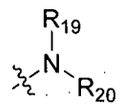
Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{11} es hidrógeno. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{11} es halógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{11} es un alquilo(C_{1-3}) sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{12} es hidrógeno. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{12} es halógeno. Incluso en otra variación de cada una de las modalidades

anteriores y sus variaciones, R_{12} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{13} se selecciona del grupo que consiste de cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} se selecciona del grupo que consiste de heterocicloalquilo(C_{3-12}), heterobicicloalquilo(C_{3-12}), hetero-arilo(C_{1-10}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:

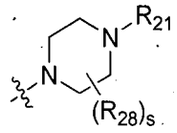


donde

R_{19} y R_{20} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})-alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), hetero-bicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir, o R_{19} y R_{20} se toman juntos para formar un anillo sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{13} es un piperazinilo sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula



donde

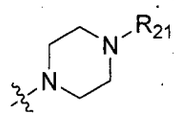
s se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8;

R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{28} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}),

bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

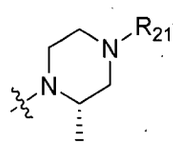
En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:



donde

R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), hetero-bicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:

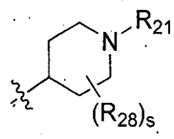


donde

R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})

alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:



donde

s se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8;

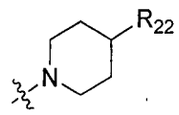
R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{28} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}),

oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} es un piperidinilo sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:

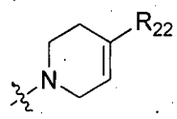


donde

R_{22} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{13} es un 1,2,3,6-tetrahidropiridinilo sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:

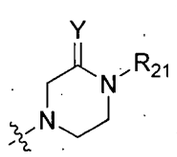


donde

R_{22} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{13} es un 3-oxo-piperazinilo sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{13} posee la fórmula:



donde

Y se selecciona del grupo que consiste de O y S; y

R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, Y es O.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{14} es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{14} es halógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{14} es a sustituido o sin sustituir (C_{1-3}) alquilo.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{15} es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{15} es halógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{15} es un (C_{1-3}) alquilo sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{16} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{16} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{17} se selecciona del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo,

alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterociclo-alquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobiciclo-aril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{17} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{17} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{18} es un fenilo sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{19} es hidrógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{19} es un alquilo(C_{1-3}) sustituido o sin sustituir.

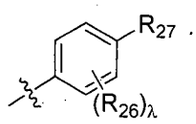
En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{20} es hidrógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{20} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{19} y R_{20} se toman juntos para formar un anillo sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{19} y R_{20} se toman juntos para formar un heterocicloalquilo(C_{3-12}) sustituido o sin sustituir. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{19} y R_{20} se toman juntos para formar un heterobiciclоalquilo(C_{3-12}) sustituido o sin sustituir. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{19} y R_{20} se toman juntos para formar un heteroarilo(C_{1-10}) sustituido o sin sustituir. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{19} y R_{20} se toman

juntos para formar un heterobicicloarilo(C_{4-12}) sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} se selecciona del grupo que consiste de cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} es un fenilo sustituido o sin sustituir. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{21} es un 4-clorofenilo sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{21} es un piridinilo sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



donde

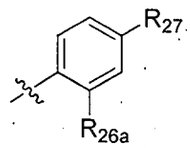
λ se selecciona del grupo que consiste de 0, 1, 2, 3 y 4;

cada R_{26} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}),

bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



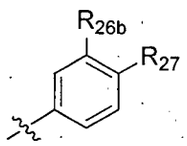
donde

R_{26a} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}),

heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



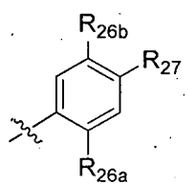
donde

R_{26b} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}),

bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}); carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



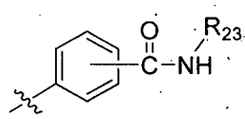
donde

R_{26a} y R_{26b} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}),

sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:

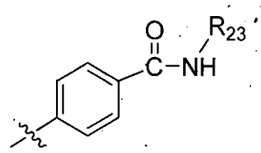


donde

R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-

alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10}) alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



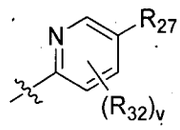
donde

R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10}) alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} está sustituido con un sustituyente seleccionado del grupo que consiste de halógeno, ciano y un carbonilo sustituido o sin sustituir. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} está sustituido con un sustituyente que tiene la fórmula $-C(=O)-R_{24}$, donde R_{24} se selecciona del grupo que consiste de hidrógeno, tio, oxi, hidroxi,

carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxa-alquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



donde

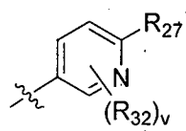
v se selecciona del grupo que consiste de 0, 1, 2 y 3;

cada R_{32} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}),

bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{21} posee la fórmula:



donde

v se selecciona del grupo que consiste de 0, 1, 2 y 3;

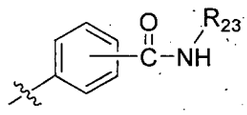
cada R_{32} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}),

bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} se selecciona del grupo que consiste de cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} es un fenilo sustituido o sin sustituir. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{22} es un 4-clorofenilo sustituido o sin sustituir. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} es un piridinilo sustituido o sin sustituir.

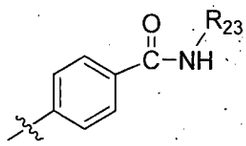
Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



donde

R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10}) alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), hetero-bicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



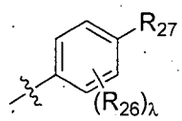
donde

R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}),

arilo(C_{4-12}), heteroarilo(C_{1-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} está sustituido con un sustituyente seleccionado del grupo que consiste de halógeno, ciano y un carbonilo sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} está sustituido con un sustituyente que tiene la fórmula $-C(=O)-R_{24}$, donde R_{24} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12}) alquilo(C_{1-5}), heterobicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



donde

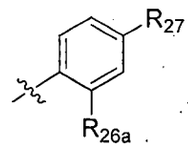
λ se selecciona del grupo que consiste de 0, 1, 2, 3 y 4;

cada R_{26} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}),

sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



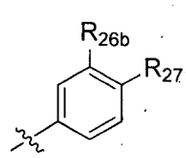
donde

R_{26a} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo,

amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:

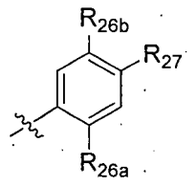


donde

R_{26b} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



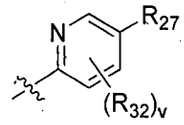
donde

R_{26a} y R_{26b} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxi-carbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tio-carbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinil-alquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxo-alquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), aril-alquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}),

bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



donde

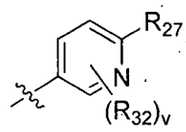
v se selecciona del grupo que consiste de 0, 1, 2 y 3;

cada R_{32} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), hetero-aril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12}) alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}),

arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12}) alquilo(C_{1-5}), heterobi-cicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{22} posee la fórmula:



donde

v se selecciona del grupo que consiste de 0, 1, 2 y 3;

cada R_{32} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12}) alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}),

hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), ciclo-alquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero-arilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{23} es un alquilo(C_{1-3}) sustituido o sin sustituir. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{23} es un cicloalquilo(C_{3-6}) sustituido o sin sustituir. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{23} es metilo, etilo, propilo, isopropilo o ciclopropilo.

Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{24} es hidroxilo. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{24} es un alcoxi(C_{1-3}) sustituido o sin sustituir. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{24} es un alquilamino(C_{1-3}) sustituido o sin sustituir. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{24} es hidrógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{24} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26} es halógeno. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26} es un alquilo(C_{1-3}) sustituido o sin sustituir. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26} es un alcoxi(C_{1-3})

sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26} es flúor, cloro, metilo o metoxi.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26a} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26a} es halógeno. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26a} es un alquilo(C_{1-3}) sustituido o sin sustituir. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26a} es un alcoxi(C_{1-3}) sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26a} es flúor, cloro, metilo o metoxi.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26b} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26b} es halógeno. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{26b} es un alquilo(C_{1-3}) sustituido o sin sustituir. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26b} es un alcoxi(C_{1-3}) sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{26b} es flúor, cloro, metilo o metoxi.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es -CO-NH-R_{23}; y R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), aril-alquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}),

heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es $-CO-O-R_{23}$; y R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), aril-alquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es $-SO_2-O-R_{23}$; y R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), aril-alquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{27} es $-CO-NR_{29}R_{30}$; y R_{29} y R_{30} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})-alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), aril-alquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), hetero-alquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{1-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir, o R_{29} y R_{30} se toman juntos para formar un anillo sustituido o sin sustituir.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{27} es ciano. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es halógeno. Además, en una variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es cloro. En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{27} es flúor.

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{28} es hidrógeno. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{28} es halógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{28} es un alquilo(C_{1-3}) sustituido o sin sustituir. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{28} es un alcoxi(C_{1-3}) sustituido o sin sustituir. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{28} es un amino sustituido o sin sustituir. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{28} es tio.

Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{29} es hidrógeno. Además en una variación de cada una de las modalidades anteriores y sus variaciones, R_{29} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones, R_{30} es hidrógeno. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{30} es un alquilo(C_{1-3}) sustituido o sin sustituir.

Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{31} es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{31} es halógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{31} es un alquilo(C_{1-3}) sustituido o sin sustituir.

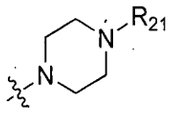
Además en otra variación de cada una de las modalidades anteriores y sus variaciones, R_{32} es hidrógeno. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{32} es halógeno. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, R_{32} es un alquilo(C_{1-3}) sustituido o sin sustituir.

En otra variación de cada una de las modalidades anteriores y sus variaciones,

R_1 es $-L_1-R_{13}$;

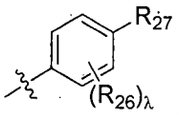
L_1 es $-CH_2-$;

R_{13} posee la fórmula:



;

R_{21} posee la fórmula:



;

λ se selecciona del grupo que consiste de 0, 1 y 2;

cada R_{26} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, alquilo(C_{1-3}) y alcoxi(C_{1-3});

R_{27} es $-CO-NH-R_{23}$; y

R_{23} se selecciona del grupo que consiste de alquilo(C_{1-3}) y cicloalquilo(C_{3-6}).

Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, n es 0. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, n es 1. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, l es 0. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, l es 1. Además en una variación de cada una de las modalidades anteriores y sus variaciones, l es 2. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, m es 0. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, m es 1. Además en una variación de cada una de las modalidades anteriores y sus variaciones, p es 0. En otra variación de cada una de las modalidades anteriores y sus variaciones, p es 1. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, q es 0. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, q es 1. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, r es 1. Además en una variación de cada una de las modalidades anteriores y sus variaciones, r es 2. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, s es 0. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, s es 1. Además en una variación de cada una de las modalidades anteriores y sus variaciones, s es 2. En otra variación de cada una de las modalidades anteriores y sus variaciones, t es 1. Incluso en otra variación de cada una de las modalidades anteriores y sus variaciones, u es 0. Además en otra variación de cada una de las modalidades anteriores y sus variaciones, u es 1. En una variación adicional de cada una de las modalidades anteriores y sus variaciones, v es 0. Incluso en una variación adicional de cada una de las modalidades anteriores y sus variaciones, v es 1.

En otro de sus aspectos, la presente invención se refiere a métodos para preparar compuestos que son útiles como inhibidores PARP.

Incluso en otro de sus aspectos, la presente invención se refiere a intermediarios que son útiles para preparar inhibidores PARP.

Se debe considerar que los compuestos de la presente invención pueden estar en la forma de una sal farmacéuticamente aceptable, un éster biohidrolizable, una amida biohidrolizable, un carbamato biohidrolizable, un solvato, un hidrato o prodroga de lo mismo. Por ejemplo, el compuesto opcionalmente comprende un sustituyente que es convertible *in vivo* en un sustituyente diferente tal como hidrógeno.

Se debe considerar además que el compuesto puede estar presente como una mezcla de estereoisómeros, o el compuesto puede estar presente como un estereoisómero único.

En otro de sus aspectos, se provee una composición farmacéutica que comprende un compuesto de acuerdo a cualquiera de las modalidades y variaciones anteriores; y uno o más excipientes farmacéuticamente aceptables. En una variación particular, la composición es a formulación sólida adaptada para la administración oral. En otra variación particular, la composición es una formulación líquida adaptada para la administración oral. Incluso en otra variación particular, la composición es una tableta. Incluso en otra variación particular, la composición es una formulación líquida adaptada para la administración parenteral.

La presente invención también provee una composición farmacéutica que comprende un compuesto de acuerdo a cualquiera de las modalidades y variaciones anteriores, donde la composición está adaptada para la administración a través de una ruta seleccionada del grupo que consiste de la vía oral, parenteral, intraperitoneal, intravenosa, intraarterial, transdérmica, sublingual, intramuscular, rectal, transbucal, intranasal, liposomal, a través de inhalación, vaginal, intraocular, suministrada por vía local (por ejemplo mediante un catéter o stent), subcutánea, intraadiposal, intraarticular, e intratecal.

Incluso en otro de sus aspectos, se provee un kit que comprende un compuesto de cualquiera de las modalidades y variaciones anteriores; y las instrucciones que comprenden una o más formas de

información seleccionada del grupo que consiste de indicar un estado de enfermedad para el cual la composición va a ser administrada, información acerca del almacenamiento para la composición, información acerca de la dosis e instrucciones acerca de cómo administrar la composición. EN una variación particular, el kit comprende el compuesto en una forma de dosis múltiples.

Aun en otro de sus aspectos, se provee un artículo de manufactura que comprende un compuesto de cualquiera de las modalidades y variaciones anteriores; y materiales de envasado. En una variación, el material de envasado comprende un contenedor para albergar al compuesto. En una variación particular, el contenedor comprende una etiqueta que indica uno o más miembros del grupo que consiste de un estado de enfermedad para el cual el compuesto se debe administrar, información acerca del almacenamiento, información acerca de la dosis y/o instrucciones información acerca de cómo administrar el compuesto. En otra variación, el artículo de manufactura comprende el compuesto en una forma de dosis múltiples.

En uno adicional de sus aspectos, se provee un método terapéutico que comprende administrar un compuesto de cualquiera de las modalidades y variaciones anteriores a un individuo.

En otro de sus aspectos, se provee un método para inhibir PARP que comprende poner en contacto PARP con un compuesto de cualquiera de las modalidades y variaciones anteriores.

Incluso en otro de sus aspectos, se provee un método para inhibir PARP que comprende causar que un compuesto de cualquiera de las modalidades y variaciones anteriores esté presente en un individuo para poder inhibir PARP *in vivo*.

En uno de sus aspectos adicionales, se provee un método para inhibir PARP que comprende administrar un primer compuesto a un individuo que es convertido *in vivo* en un segundo compuesto donde el segundo compuesto inhibe PARP *in vivo*, siendo el segundo compuesto un compuesto de acuerdo a una cualquiera de las modalidades y variaciones anteriores.

En otro de sus aspectos, se provee un método para tratar un estado de enfermedad el cual PARP posee actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el

método comprende causar que un compuesto de cualquiera de las modalidades y variaciones anteriores esté presente en un individuo es una cantidad terapéuticamente efectiva para el estado de enfermedad.

Incluso en otro de sus aspectos, se provee un método para tratar un estado de enfermedad para el cual PARP posee una actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el método comprende administrar un compuesto de cualquiera de las modalidades y variaciones anteriores a un individuo, donde el compuesto está presente en el individuo en una cantidad terapéuticamente efectiva para el estado de enfermedad.

En uno de sus aspectos adicionales, se provee un método para tratar un estado de enfermedad para el cual PARP posee una actividad que contribuye a la patología y/o sintomatología del estado de enfermedad, donde el método comprende administrar un primer compuesto a un individuo que es convertido *in vivo* en un segundo compuesto donde el segundo compuesto inhibe PARP *in vivo*, siendo el segundo compuesto un compuesto de acuerdo a cualquiera de las modalidades y variaciones anteriores.

En una variación de cada uno de los métodos anteriores para el estado de enfermedad se seleccipna del grupo que consiste de los tipos de cáncer (incluyendo aquellos cáncer donde el daño del ADN es por (por ejemplo, alquilación) agentes, drogas citotóxicas, terapia por radiación y/o inhibidores de la topoisomerasa que son de cuidado estándar (*por ejemplo*, en combinación con quimio- y/o radiosensibilizantes para el tratamiento de cáncer); tipos de cáncer que son deficientes en Recombinación homóloga (HR) reparación de ADN dependiente de DSB; tumores deficientes de BRCA-I y BRCA-2; cáncer de vejiga; cáncer de origen sanguíneo (*por ejemplo*, leucemia linfoblástica aguda ("ALL"), leucemia linfoblástica aguda de células B, leucemia linfoblástica aguda de células T, leucemia mieloblástica aguda ("AML"), leucemia promielocítica aguda ("APL"), leucemia monoblástica aguda, leucemia eritroleucémica aguda, leucemia megacarioblástica aguda, leucemia mielomonocítica aguda, leucemia no linfocítica aguda, leucemia indiferenciada aguda, leucemia mielocítica crónica ("CML"), leucemia linfocítica crónica ("CLL"), leucemia de células velludas y mieloma múltiple); cáncer óseo; cáncer

mamario; carcinomas (*por ejemplo*, carcinoma de células escamosas, carcinoma de células basales, adenocarcinoma, carcinoma de glándulas sudoríparas, carcinoma de glándulas sebáceas, carcinoma papilar, adenocarcinomas papilares, cistadenocarcinoma, carcinoma medular, carcinoma broncogénico, carcinoma de células renales, carcinoma de ducto biliar, coriocarcinoma, seminoma, carcinoma embrional, carcinoma pulmonar de células pequeñas, carcinoma de vejiga y carcinoma epitelial); CNS y cáncer de cerebro (*por ejemplo*, glioma (*por ejemplo*, astrocitoma pilocítico, astrocitoma, astrocitoma, astrocitoma anaplásico, o glioblastoma multiformes), astrocitoma pilocítico, astrocitoma, astrocitoma anaplásico, glioblastoma multiforme, meduloblastoma, craniofaringioma, ependimoma, pinealoma, hemangioblastoma, neuroma acústico, oligodendroglioma, meningioma, schwanoma vestibular, adenoma, cáncer metastático cerebral, meningioma, tumor vertebral y meduloblastoma); cáncer cervical; cáncer de colon; cáncer colorectal; cáncer esófago; hepatomas; cáncer de cabeza y cuello; cáncer renal; leucemias agudas y crónicas (*por ejemplo*, leucemias linfoblásticas, mielogenicas, linfocíticas y mielocíticas); cáncer hepático; cáncer pulmonar; linfomas (*por ejemplo*, tal como enfermedad de Hodgkin, linfoma de no Hodgkin, mieloma múltiple, macroglobulinemia de Waldenstrom, enfermedad de cadena pesada y policitemia vera); melanomas; cáncer nasal; neuroblastomas; cáncer oral; cáncer ovárico; cáncer pancreático; cáncer de próstata; retinoblastomas; cáncer de piel; tumores sólidos (*por ejemplo*, tal como fibrosarcoma, mixosarcoma, liposarcoma, condriosarcoma, sarcoma osteogénico, cordoma, angiosarcoma, endoteliosarcoma, linfangiosarcoma, linfangioendoteliosarcoma, sinovioma, mesotelioma, tumor de Ewing, leiomiosarcoma y Rabdomiosarcoma); cáncer de estómago; cáncer testicular; cáncer de garganta; cáncer uterino y tumor de Wilms); enfermedades cardiovasculares (incluyendo falla cardíaca crónica; ateroesclerosis; falla cardíaca congestiva; choque circulatorio; cardiomiopatía; transplante cardíaco; infarto al miocardio y arritmia cardíaca (*por ejemplo*, fibrilación atrial, taquicardia supraventricular, vibración atrial y taquicardia paroxímal)); enfermedades vasculares diferentes de enfermedades cardiovasculares (incluyendo oclusión arterial

periférica; tromboangitis obliterans; enfermedad y fenómeno de Reynaud; acrocianosis; eritromelalgia; trombosis venosa; venas varicosas; fístula arteriovenosa; linfedema y lipedema); enfermedades metabólicas enfermedades metabólicas (incluyendo diabetes (*por ejemplo*, diabetes melitus (*por ejemplo*; diabetes Tipo I (Diabetes Melitus Insulino Dependiente), diabetes Tipo II (Diabetes Melitus No Insulino Dependiente), diabetes gestacional, diabetes autoinmune, insulinopatías, diabetes debida a enfermedad pancreática, diabetes asociada con otras enfermedades endócrinas (tal como Síndrome de Cushing, acromegalia, feocromocitoma, glucagonoma, aldosteronismo primario o somatostatinoma), síndrome de resistencia a la insulina Tipo A, síndrome de resistencia a la insulina Tipo B, diabetes lipatrófica, y diabetes inducida por toxinas de células β); y complicaciones diabéticas (*por ejemplo*, catarata diabética, glaucoma, retinopatía, nefropatía (*por ejemplo*, microalbuminuria y nefropatía diabética), mononeuropatía, neuropatía autonómica, polineuropatía, gangrena del pie, enfermedad arterial coronaria ateroesclerotica, enfermedad arterial periférica, coma hiperglicémico-hiperosmolar no cetotico, mononeuropatías, neuropatía autonómica, úlceras del pie, problemas articulares, complicaciones de la piel o de la membrana mucosa (*por ejemplo*, infección, "shin spot" o pápulas, infección por cándida o necrobiosis lipoidica obesidad diabética), hiperlipidemia, hipertensión, síndrome de resistencia a la insulina, enfermedad arterial coronaria, úlceras del pie, problemas de las articulaciones, infecciones fúngicas, infecciones bacterianas, cardiomiopatía, vasculitis por complejo inmune y lupus eritematoso sistémico (SLE))); enfermedades inflamatorias (incluyendo condiciones que resultan del rechazo de transplante de órganos; enfermedades inflamatorias crónicas de las articulaciones (*por ejemplo*, artritis, artritis reumatoidea, osteoartritis y enfermedades oseas asociadas con una resorción osea aumentada); enfermedades inflamatorias del intestino (*por ejemplo*, ileitis, colitis ulcerosa, síndrome de Barrett y enfermedad de Crohn); enfermedades pulmonares inflamatorias (*por ejemplo*, asma, síndrome de distrés respiratorio del adulto y enfermedad crónica obstructiva de la vía aérea); enfermedades inflamatorias oculares (*por ejemplo*, distrofia de la córnea, tracoma,

oncocerciasis, uveitis, simpateticoftalmitis y endoftalmitis); enfermedades inflamatorias crónicas de las encías (*por ejemplo*, gingivitis y periodontitis); tuberculosis; lepra; enfermedades inflamatorias del riñón (*por ejemplo*, complicaciones uremicas, glomerulonefritis y nefrosis); enfermedades inflamatorias de la piel (*por ejemplo*, esclerodermatitis, soriasis y eczema); enfermedades inflamatorias del sistema nervioso central (*por ejemplo*, enfermedades crónicas de desmielinización del sistema nervioso, esclerosis múltiple, neurodegeneración relacionada con SIDA, enfermedad de Alzheimer, meningitis infecciosa, encefalomielitis, enfermedad de Parkinson, enfermedad de Huntington, esclerosis lateral amiotrófica y encefalitis viral o autoinmune); enfermedades inflamatorias cardíacas (*por ejemplo*, cardiomiopatía, enfermedad cardíaca isquémica, hipercolesterolemia y ateroesclerosis); enfermedades que pueden tener componentes inflamatorios importantes (*por ejemplo*, preeclampsia, falla hepática crónica, trauma de la médula espinal y cerebral y síndrome de disfunción múltiple de órganos (MODS) (falla orgánica múltiple (MOF))); inflamación sistémica del organismo, ejemplificado por shock por gram-positivos o gram negativos, shock hemorrágico o anafiláctico, o shock inducido por quimioterapia de cáncer en respuesta a citoquinas pro-inflamatorias, (*por ejemplo*, shock asociado con citoquinas pro-inflamatorias; y shock inducido, por ejemplo, por un agente quimioterapéutico que es administrado como un tratamiento para el cáncer); daños por reperfusión, daños por reperfusión, incluyendo aquellos que resultan de episodios que ocurren de manera natural y durante un procedimiento quirúrgico (*por ejemplo*, daño por reperfusión intestinal; daño por reperfusión miocárdica; daño por reperfusión que resulta de una cirugía de bypass cardiopulmonar, cirugía de reparación de aneurisma aórtico, cirugía de endarterectomía de carótida, o shock hemorrágico; y daño por reoxigenación que resulta del transplante de órganos tal como corazón, pulmón, hígado, riñón, páncreas, intestino ó cornea); condiciones isquémicas, incluyendo aquellas que resultan del transplante de órganos (*por ejemplo*, angina estable, angina inestable, isquemia miocárdica, isquemia hepática, isquemia arterial mesentérica, isquemia intestinal, isquemia crítica de extremidades,

isquemia crónica crítica de extremidades, isquemia cerebral, isquemia cardíaca aguda, enfermedad isquémica renal, enfermedad isquémica hepática, desorden isquémico retinal, choque séptico; y una enfermedad isquémica del sistema nervioso central (*por ejemplo*, accidente vascular o isquemia cerebral)); enfermedades neurodegenerativas (*por ejemplo*, ; desórdenes del sistema hematolinfoide; desórdenes del sistema endocrino y neuro endocrino; desórdenes del tracto urinario; desórdenes del sistema respiratorio; desórdenes del sistema reproductivo femenino; desórdenes del sistema reproductivo masculino; infecciones retrovirales; daño retinal; senescencia de la piel; daño de la piel inducido por UV; enfermedad o falla renal aguda o crónica; disfunción celular relacionada con la edad; y enfermedades relacionadas con la síntesis de ácidos grasos (*por ejemplo*, obesidad, diabetes y enfermedad cardiovascular).

En otra variación de cada uno de los métodos anteriores, el PARP es un PARP-1, PARP-2, PARP-3, vaultPARP o TiPARP. Es notable que los compuestos de la presente invención también pueden poseer actividad inhibidora para otros miembros de la familia PARP y por lo cual se pueden utilizar para atender los estados de enfermedad asociados con estos otros miembros de la familia. Además, los compuestos de la presente invención también pueden poseer actividad inhibidora para las tankirasas (*por ejemplo*, tankirasa-1 y tankirasa-2) y por lo cual se pueden utilizar para tratar los estados de enfermedad asociados con estas proteínas blanco.

Sales, Hidratos y Prodrogas de los Inhibidores de la PARP.

Se debe reconocer que los compuestos de la presente invención se pueden encontrar presentes y, opcionalmente, se pueden administrar en forma de sales, hidratos y prodrogas que se convierten *in vivo* en los compuestos de la presente invención. Por ejemplo, dentro del alcance de la presente invención se puede convertir los compuestos de la presente invención y utilizarlos en la forma de sus sales farmacéuticamente aceptables, que derivan de varios ácidos y bases orgánicos e inorgánicos, según los procedimientos ampliamente conocidos en el arte.

Cuando los compuestos de la presente invención poseen la forma de una base libre, éstos se pueden preparar como una sal de adición ácida farmacéuticamente aceptable, mediante la reacción de la forma de base libre del compuesto con un ácido orgánico o inorgánico farmacéuticamente aceptable, por ejemplo, hidrohaluros, tales como clorhidratos, bromhidratos, yohidratos; otros ácidos minerales y sus sales correspondientes, tales como sulfato, nitrato, fosfato, etc.; y alquilo y monoarilsulfonatos, tales como etansulfonato, toluensulfonato y bencensulfonato; y otros ácidos orgánicos y sus sales correspondientes, tales como acetato, tartrato, maleato, succinato, citrato, benzoato, salicilato y ascorbato.

Otras sales de adición ácida de la presente invención incluyen, pero no se limitan a; adipato, alinato, arginato, aspartato, bisulfato, bisulfito, bromuro, butirato, camforato, camforsulfonato, caprilato, cloruro, clorobenzoato, ciclopentanpropionato, digluconato, dihidrogenofosfato, dinitrobenzoato, dodecilsulfato, fumarato, galacterato (de ácido múcico), galacturonato, glucoheptonato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hipurato, clorhidrato, bromhidrato, yodhidrato, 2-hidroxietansulfonato, yoduro, isetionato, iso-butirato, lactato, lactobionato, malato, malonato, mandelato, metafosfato, metansulfonato, metilbenzoato, monohidrogenofosfato, 2-naftalenesulfonato, nicotinato, nitrato, oxalato, oleato, pamoato, pectinato, persulfato, fenilacetato, 3-fenilpropionato, fosfato, fosfonato y ftalato. Se debe reconocer que las formas de base libre típicamente diferirán de sus respectivas formas de sales, en algún grado, con respecto a sus propiedades físicas, tales como la solubilidad en solventes polares; aparte de eso, las sales son equivalentes a sus respectivas formas de base libre para los propósitos de la presente invención.

Cuando los compuestos de la presente invención poseen forma de un ácido libre, se puede preparar una sal de adición ácida farmacéuticamente aceptable, al hacer reaccionar la forma de ácido libre del compuesto con una base orgánica o inorgánica, farmacéuticamente aceptable. Ejemplos de tales bases son los

hidróxidos de metales alcalinos, incluyendo hidróxidos de potasio, sodio y litio; hidróxidos de metales alcalinotérreos, tales como hidróxidos de bario y calcio; alcóxidos de metales alcalinos, por ejemplo, etanolato de potasio y propanolato de sodio; y varias bases orgánicas, tales como hidróxido de amonio, piperidina, dietanolamina y N-metilglutamina. También se incluyen las sales de aluminio de los compuestos de la presente invención. Otras sales de base de la presente invención incluyen, pero no se limitan a: sales de cobre, férrica, ferrosa, de litio, de magnesio, mangánica, manganosa, de potasio, de sodio y de zinc, Las sales de base orgánica incluye, pero no se limitan a, sales de aminas primarias, secundarias y terciarias, aminas sustituidas, incluyendo aminas sustituidas de origen natural, aminas cíclicas y resinas básicas de intercambio iónico, por ejemplo, arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, iso-propilamina, lidocaína, lisina, meglumina, N-metil-D-glucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purinas, teobromina, trietanolamina, trietilamina, trimetilamine, tripropilamina y tris-(hidroximetil)-metilamina (trometamina). Se debe reconocer que las formas de ácido libre típicamente diferirán de sus respectivas formas de sales, en algún grado, con respecto a sus propiedades físicas, tales como la solubilidad en solventes polares; aparte de eso, las sales son equivalentes a sus respectivas formas de ácido libre para los propósitos de la presente invención.

Los N-óxidos de los compuestos de acuerdo con la presente invención se pueden preparar mediante métodos conocidos para aquellas personas de conocimiento general del arte. Por ejemplo, los N-óxidos se pueden preparar mediante el tratamiento de una forma sin oxidar del compuesto con un agente oxidante (por ejemlo: ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-cloroperoxibenzoico o similares) en un solvente orgánico inerte adecuado (por ejemplo: un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0°C. De otra

forma, los N-óxidos de los compuestos se pueden preparar a partir del N-óxido de un material de partida apropiado.

Los derivados de prodroga de los compuestos de acuerdo con la presente invención se pueden preparar mediante la modificación de sustituyentes de los compuestos de la presente invención, los que se convierten luego *in vivo* en sustituyentes diferentes. Cabe destacar que en muchas instancias, las mismas prodrogas también caen dentro del alcance del rango de los compuestos de acuerdo con la presente invención. Por ejemplo, las prodrogas se pueden preparar mediante la reacción de un compuesto con un agente de carbamilación (por ejemplo: 1,1-aciloxiaquilcarbonocloridato, para-nitrofenil carbonato o similares) o un agente acilante. Otros ejemplos de métodos de preparación de prodrogas se describen en Saulnier et al.(1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985.

También se pueden preparar derivados protegidos de los compuestos de la presente invención. Ejemplos de las técnicas aplicables para la creación de grupos protectores y su remoción se pueden encontrar en T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

Convenientemente, los compuestos de la presente invención también se pueden preparar o formar durante el proceso de la invención, como solvatos (por ejemplo: hidratos). Los hidratos de los compuestos de la presente invención se pueden preparar convenientemente mediante re-cristalización, a partir de una mezcla de solvente orgánico/acuoso, por medio del uso de solventes orgánicos, tales como dioxina, tetrahidrofurano o metanol.

Tal como se emplea en la presente descripción, una "sal farmacéuticamente aceptable" pretende abarcar cualquier compuesto de acuerdo con la presente invención que se utilice en la forma de una sal del mismo, especialmente en aquellos casos donde la sal otorga al compuesto propiedades farmacocinéticas mejoradas, en comparación con la forma libre del compuesto o una forma de sal diferente del compuesto. Inicialmente, la forma de sal farmacéuticamente aceptable puede también otorgar propiedades farmacocinéticas deseables al compuesto, de las que previamente éste carecía, e incluso pueden afectar positivamente la farmacodinámica del compuesto, con respecto

a su actividad terapéutica en el cuerpo. Un ejemplo de una propiedad farmacocinética que puede afectar favorablemente es la forma en la que el compuesto es transportado a través de las membranas celulares, la que a su vez puede afectar directa y positivamente la absorción, distribución, biotransformación y excreción del compuesto. Mientras la vía de administración de la composición es importante, y varios factores anatómicos, fisiológicos y patológicos pueden afectar críticamente la biodisponibilidad, la solubilidad del compuesto depende usualmente del carácter de su forma de sal particular utilizada. Un técnico en el arte sabrá apreciar que una solución acuosa del compuesto proporcionará la absorción más rápida del compuesto, por parte del cuerpo del individuo tratado, mientras que soluciones y suspensiones de lípidos, así como formas sólidas de dosificación, darán como resultado una absorción más lenta del compuesto.

Composiciones que comprenden Inhibidores de PARP

Una amplia variedad de composiciones y métodos de administración se pueden utilizar junto con los compuestos de la presente invención. Tales composiciones pueden incluir, además de los compuestos de la presente invención, excipientes farmacéuticos convencionales y otros agentes convencionales, farmacéuticamente inactivos. Adicionalmente, las composiciones pueden incluir agentes activos, junto con los compuestos de la presente invención. Estos agentes activos adicionales pueden incluir compuestos adicionales de acuerdo con la invención y/o uno o más agentes farmacéuticamente activos. Las composiciones pueden encontrarse en forma gaseosa, líquida, semi-líquida o sólida, formuladas de una forma adecuada para la vía de administración a emplear. Para la administración oral se utilizan típicamente cápsulas y tabletas. Para la administración parenteral, se utiliza típicamente la reconstitución de un polvo liofilizado, preparado de la forma que se indica en la presente descripción. Las composiciones que comprenden compuestos de la presente invención se pueden administrar o co-administrar por vía oral, parenteral, intraperitoneal, intravenosa, intra-arterial, transdérmica, sublingual, intramuscular, rectal, transbucal,

intranasal, liposomática, por medio de inhalación, vaginalmente, intraocularmente, por entrega local (por ejemplo, a través de un catéter o un stent), subcutáneamente, intra-adiposamente, intra-articularmente o intratecalmente. Los compuestos y/o las composiciones de acuerdo con la presente invención también se pueden administrar o co-administrar en formas de dosificación de liberación lenta.

Los inhibidores de PARP y las composiciones que los comprenden se pueden administrar o co-administrar en cualquier forma de dosificación convencional. La co-administración en el contexto de la presente invención pretende significar la administración de más de un agente terapéutico, uno de los cuales incluye un inhibidor de PARP, durante el transcurso de un tratamiento coordinado, para lograr un mejor resultado clínico. Esta co-administración también puede ser co-extensiva, es decir, que se desarrolle durante periodos de tiempo que coinciden entre sí.

Las soluciones o suspensiones que se utilizan para la aplicación parenteral, intradérmica, subcutánea o tópica pueden, opcionalmente, incluir uno o más de los siguientes componentes: un diluyente estéril, tal como agua para inyecciones, una solución salina, aceite no volátil, polietilenglicol, glicerina, propilenglicol u otro solvente sintético, agente antimicrobianos, tales como alcohol bencílico y metilparabenos; antioxidantes, tales como ácido ascórbico y bisulfito de sodio; agentes quelantes, como ácido etilendiaminotetraacético (EDTA); soluciones tampón, tales acetatos, citratos y fosfatos; agentes para ajustar la acidez o alcalinidad de la composición, tal como agentes alcalinos o acidificantes o soluciones tampón, como carbonatos, bicarbonatos, fosfatos, ácido clorhídrico y ácidos orgánicos, como ácido acético y ácido cítrico. Las preparaciones parenterales pueden, opcionalmente, estar comprendidas en ampollas, jeringas desechables o en pequeños frascos de dosis múltiples o unitarias, elaborados con vidrio, plástico u otro material adecuado.

Cuando los compuestos de acuerdo con la presente invención exhiben una solubilidad deficiente se pueden utilizar métodos para solubilizar los compuestos. Tales métodos son conocidos por aquellos

técnicos en el arte e incluyen, pero no se limitan a, el uso de co-solventes, tales como dimetilsulfóxido (DMSO), uso de surfactantes, tales como TWEEN o la disolución en bicarbonato de sodio acuoso. Los derivados de los compuestos, tales como las prodrogas de los compuestos, también se pueden utilizar en la formulación de composiciones farmacéuticas eficaces.

Después de mezclar o incorporar compuestos de acuerdo con la presente invención a una composición, se puede formar una solución, suspensión, emulsión o similar. La forma de la composición resultante dependerá de varios factores, incluyendo el modo de administración deseado y la solubilidad del compuesto en el portador o vehículo seleccionado. La concentración eficaz que se requiere para mejorar la enfermedad tratada se puede determinar empíricamente.

Las composiciones de acuerdo con la presente invención se pueden proveer, opcionalmente, para la administración a humanos y animales, en formas unitarias de dosificación, tales como tabletas, cápsulas, píldoras, polvos, polvos secos para inhaladores, gránulos, soluciones o suspensiones parenterales estériles y soluciones o suspensiones orales, y emulsiones de aceite/agua que contienen cantidades adecuadas de los compuestos, en particular, las sales farmacéuticamente aceptables, preferentemente, las sales sódicas de los mismos. Típicamente, los compuestos y sus derivados farmacéutica y terapéuticamente activos se formulan y administran en formas unitarias de dosificación o en formas de dosificación múltiples. Las formas unitarias de dosificación, tal como se indican en la presente descripción, se refieren a unidades físicamente discretas, adecuadas para individuos humanos y animales y que se envasan individualmente, tal como se conoce en el arte. Cada dosis unitaria contiene una cantidad predeterminada de un compuesto terapéuticamente activo, suficiente para producir el efecto terapéutico deseado, en asociación con el portador, vehículo o diluyente farmacéutico requerido. Ejemplos de formas unitarias de dosificación incluyen ampollas, jeringas y tabletas o cápsulas individualmente envasadas. Las formas unitarias de dosificación se pueden administrar en fracciones o en varias unidades. Una forma de dosificación múltiple corresponde a una pluralidad de formas unitarias de dosificación idénticas, envasadas

en un solo contenedor para ser administrada en una forma segregada de dosificación unitaria.

Ejemplos de formas de dosificación múltiples incluyen frascos pequeños, botellas de tabletas o cápsulas o botellas de ½ ó 3,7 L. Por este motivo, la forma de dosificación múltiple corresponde a una pluralidad de dosis unitarias que no se encuentran segregadas en el envase. Adicionalmente a uno o más compuestos de acuerdo con la presente invención, la composición puede comprender: un diluyente como lactosa, sucralosa, fosfato dicálcico o carboximetilcelulosa; un lubricante como estearato de magnesio, estearato de calcio y talco; y un agente aglutinante como almidón, gomas naturales, tal como goma de gelatina-acacia, glucosa, melaza, polivinilpirrolidona, celulosas y sus derivados, povidona, crospovidona y otros agentes aglutinantes conocidos por aquellos técnicos en el arte.

Las composiciones líquidas farmacéuticamente administrables pueden, por ejemplo, prepararse mediante disolución, dispersión o, de otra forma, por medio de la mezcla de un compuesto activo, tal como se definió anteriormente, y adyuvantes farmacéuticos opcionales en un vehículo, tal como por ejemplo, agua, una solución salina, dextrosa acuosa, glicerol, glicoles, etanol y similares, para así formar una solución o suspensión. Si se desea, la composición farmacéutica a administrar puede contener también cantidades menores de sustancias auxiliares, tales como agentes humectantes, agentes emulsificantes o agente de solubilización, agentes tampón de pH y similares, por ejemplo: acetato, citrato de sodio, derivados de ciclodextrina, monolaurato de sorbitán, acetato sódico de trietanolamina, oleato de trietanolamina y otros agentes similares. Los métodos existentes para preparar tales formas de dosificación se conocen en el arte o serán evidentes para aquellos expertos en este arte, por ejemplo: ver Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. En todo caso, la composición o formulación a administrar contendrá una cantidad suficiente de un inhibidor de la presente invención para reducir la actividad de PARP in vivo, tratando así el estado de la enfermedad del individuo. Opcionalmente, las formas de dosificación o composiciones pueden comprenden uno o más compuestos de acuerdo con

la presente invención, en el rango entre 0,005 a 100% (peso/peso) donde el equilibrio comprende sustancias adicionales, tales como las que se mencionan en la presente descripción. Para la administración oral, una composición farmacéuticamente aceptable puede, opcionalmente, comprender uno o más excipientes comúnmente utilizados, tales como por ejemplo, cantidades farmacéuticas de manitol, lactosa, almidón, estearato de magnesio, talco, derivados de celulosa, croscarmelosa sódica, glucosa, sucarosa, carbonato de magnesio, sacarina sódica, talco. Tales composiciones incluyen soluciones, suspensiones, tabletas, cápsulas, polvos, polvos secos para inhaladores y formulaciones de liberación sostenida, tales como - pero no limitándose a - implantes y sistemas de entrega microencapsulada, y polímeros biocompatibles y biodegradables, tales como colágeno, etilenvinil acetato, polianhídridos, ácido poliglicólico, poliortoésteres, ácido poliláctico y otros. Los métodos para preparar estas formulaciones son conocidos por aquellos técnicos en el arte. Las composiciones pueden, opcionalmente, contener entre 0,01 y 100% (peso/peso) de uno o más inhibidores de PARP, opcionalmente entre 00,1 y 95% y, opcionalmente, entre 1 y 95%.

Las sales, preferentemente las sales sódicas, de los inhibidores se pueden preparar con vehículos que protegen el compuesto contra su rápida eliminación del cuerpo, tales como formulaciones o recubrimientos de liberación temporal. Las formulaciones pueden, además, incluir otros compuestos activos para obtener las combinaciones de propiedades deseadas.

Formulaciones para administración oral

Las formas farmacéuticas de dosificación oral pueden ser líquidas, en gel o sólidas. Ejemplos de formas de dosificación sólida incluye - pero no se limitan a - tabletas, cápsulas, gránulos y polvos a granel. Ejemplos más específicos de tabletas orales incluyen pastillas comprimidas y masticables y tabletas que pueden estar recubiertas entéricamente, recubiertas con azúcar o con una película. Ejemplos de cápsulas incluyen cápsulas de gelatina blanda o dura. Los gránulos y polvos se pueden proveer en formas efervescentes y no

efervescentes. Cada uno se puede combinar con otros ingredientes conocidos por los técnicos en el arte.

En ciertas modalidades, los compuestos de acuerdo con la presente invención se proveen como formas sólidas de dosificación, preferentemente cápsulas o tabletas. Las tabletas, píldoras, cápsulas, trociscos y similares pueden, opcionalmente, contener uno o más de los siguientes ingredientes o compuestos de naturaleza similar: un aglutinante, un diluyente, un agente de desintegración, un lubricante, un agente deslizante, un endulzante y un saborizante.

Ejemplos de aglutinantes que se pueden utilizar incluye, pero no se limitan a, celulosa microcristalina, goma tragacanto, una solución de glucosa, mucílago de acacia, una solución de gelatina, sucralosa y pasta de almidón.

Ejemplos de lubricantes que se pueden utilizar incluyen, pero no se limitan a, talco, almidón, magnesio o estearato de magnesio, licopodio y ácido esteárico.

Ejemplos de diluyentes que se pueden utilizar incluyen, pero no se limitan a, lactosa, sucralosa, almidón, caolín, sal, manitol y fosfato dicálcico.

Ejemplos de agentes deslizantes que se pueden utilizar incluyen, pero no se limitan a, dióxido de silicona coloidal.

Ejemplos de agentes de desintegración que se pueden utilizar incluyen, pero no se limitan a, croscarmelosa sódica, glicolato de almidón sódico, ácido algínico, almidón de maíz, almidón de papa, bentonita, metilcelulosa, agar u carboximetilcelulosa.

Ejemplos de agentes colorantes que se pueden utilizar incluyen, pero no se limitan a, cualquiera de los colorantes solubles en agua, aprobados y certificados por FD y C, y sus mezclas; y colorantes insolubles en agua, aprobados y certificados por FD y C, suspendidos en hidrato de alúmina.

Ejemplos de agentes endulzantes que se pueden utilizar incluyen, pero no se limitan a, sucralosa, lactosa, manitol y agentes endulzantes artificiales, tales como ciclamato de sodio y sacarina y cualquier saborizante secado por aspersión.

Ejemplos de agentes saborizantes que se pueden utilizar incluyen, pero no se limitan a, sabores naturales extraídos de

plantas, tales como frutas y mezclas de sintéticas de compuestos que producen una sensación placentera, tales como, pero no restringidos a, menta y salicilato de metilo.

Ejemplos de agentes humectantes que se pueden utilizar incluyen, pero no se limitan a, monoestearato de propilenglicol, monooleato de sorbitán, monolurato de dietilenglicol y lauril éter de polioxietileno.

Ejemplos de recubrimientos anti-eméticos que se pueden utilizar incluyen, pero no se limitan a, ácidos grasos, grasas, ceras, goma laca, goma laca amoniacal y ftalato de acetato de celulosa.

Ejemplos de recubrimientos en películas que se pueden utilizar incluyen, pero no se limitan a, hidroetilcelulosa, carboximetilcelulosa sódica, polietilenglicol 4000 y ftalato de acetato de celulosa.

Si se desea administración oral, la sal del compuesto puede, opcionalmente, proveerse en una composición que la proteja del ambiente ácido del estómago. Por ejemplo, la composición se puede formular en un recubrimiento entérico que mantenga su integridad en el estómago y libere el compuesto activo en el intestino. La composición también se puede formular en combinación con un antiácido u otro ingrediente.

Cuando la forma unitaria de dosificación es una cápsula, opcionalmente puede comprender -adicionalmente- un vehículo líquido, tal como un aceite graso. Además, las formas unitarias de dosificación pueden comprender, en forma opcional y adicional, varios otros materiales que modifiquen la forma física de la unidad de dosificación, por ejemplo, recubrimientos de azúcar y otros agentes entéricos.

Los compuestos de acuerdo con la presente invención también se pueden administrar como un componente de un elíxir, suspensión, jarabe, oblea, producto en polvo, goma de mascar o productos similares. Un jarabe puede opcionalmente comprender, además de los compuestos activos, sucralosa como un agente endulzante, y ciertos preservantes, tinturas, colorantes y saborizantes.

Los compuestos de la presente invención también se pueden mezclar con otros materiales activos que no impidan la acción deseada, o con materiales que complementen dicha acción, tales como antiácidos, bloqueadores de H2 y diuréticos. Por ejemplo, si un compuesto se utiliza en el tratamiento del asma o hipertensión, se puede emplear con otros agentes broncodilatadores y antihipertensivos, respectivamente.

Ejemplos de vehículos farmacéuticamente aceptables que se pueden incluir en las tabletas que comprenden los compuestos de la presente invención incluyen, pero no se limitan a, aglutinantes, lubricantes, diluyentes, agentes de desintegración, agentes colorantes, agentes saborizantes y agentes humectantes. Las tabletas con recubrimiento entérico, precisamente por su recubrimiento entérico, resisten la acción del ácido del estómago y se disuelven o desintegran en el intestino neutral o alcalino. Las tabletas recubiertas con azúcar pueden corresponder a tabletas comprimidas, a las que se les aplica diferentes capas de sustancias farmacéuticamente aceptables. Las tabletas recubiertas por películas pueden corresponder a tabletas comprimidas que han sido recubiertas con polímeros u otro recubrimiento adecuado. Varias tabletas comprimidas pueden corresponder a tabletas comprimidas elaboradas mediante uno o más ciclos de compresión que utilizan las sustancias farmacéuticamente aceptables que se mencionaron previamente. Los agentes colorantes también se pueden utilizar en las tabletas. Los agentes saborizantes y endulzantes pueden utilizarse en las tabletas y son especialmente útiles en la formación de tabletas y grageas masticables.

Ejemplos de formas líquidas de dosificación oral que se pueden utilizar incluyen, pero no se limitan a, soluciones acuosas, emulsiones, suspensiones, soluciones y/o suspensiones reconstituidas a partir de gránulos no efervescentes y preparaciones efervescentes, reconstituidas a partir gránulos efervescentes.

Ejemplos de soluciones acuosas que se pueden utilizar incluyen, pero no se limitan a, elíxires y jarabes. Tal como se emplea en la presente descripción, los elíxires se refieren a preparaciones hidroalcohólicas, endulzadas y transparentes. Ejemplos

de vehículos farmacéuticamente aceptables que se pueden utilizar en los elíxires incluyen, pero no se limitan a, solventes. Ejemplos particulares de solventes que se pueden utilizar incluyen glicerina, sorbitol, alcohol etílico y jarabe. Tal como se emplea en la presente descripción, los jarabes se refieren a soluciones acuosas y concentradas de un azúcar, por ejemplo, sucralosa. Opcionalmente, los jarabes pueden comprender, además, un agente preservante.

Las emulsiones se refieren a sistemas de 2 fases, en las cuales un líquido se dispersa en la forma de pequeños glóbulos a través del otro líquido. Opcionalmente, las emulsiones pueden ser emulsiones de aceite en agua o de agua en aceite. Ejemplos de vehículos farmacéuticamente aceptables que se pueden utilizar en las emulsiones incluyen, pero no se limitan a, líquidos no acuosos, agentes emulsificantes y agentes preservantes.

Ejemplos de sustancias farmacéuticamente aceptables que se pueden utilizar en gránulos no efervescentes, para ser reconstituidos en una forma líquida de dosificación oral, incluyen agentes diluyentes, endulzantes y humectantes.

Ejemplos de sustancias farmacéuticamente aceptables que se pueden utilizar en gránulos efervescentes, para ser reconstituidos en una forma líquida de dosificación oral, incluyen ácidos orgánicos y una fuente de dióxido de carbono.

Opcionalmente, los agentes colorantes y saborizantes se pueden utilizar en todas las formas de dosificación anteriores.

Ejemplos particulares de agentes preservantes que se pueden utilizar incluyen glicerina, metilo y propilparabeno, ácido benzoico, benzoato de sodio y alcohol.

Ejemplos particulares de líquidos no acuosos que se pueden utilizar en las emulsiones incluyen aceite mineral y aceite de semillas de algodón.

Ejemplos particulares de agentes emulsificantes que se pueden utilizar incluyen gelatina, acacia, tragacanto, bentonita y surfactantes, tales como monooleato de polioxietilen sorbitán.

Ejemplos particulares de agentes de suspensión que se pueden utilizar incluyen carboximetilcelulosa sódica, pectina, tragacanto, goma veegum y acacia. Los diluyentes incluyen lactosa y

sucralosa. Los agentes endulzantes incluyen sucralosa, jarabes, glicerina y agentes endulzantes artificiales, tales como ciclamato de sodio y sacarina.

Ejemplos particulares de agentes humectantes que se pueden utilizar incluyen monoestearato de propilenglicol, monooleato de sorbitán, monolaurato de dietilenglicol y lauril éter de polioxietileno.

Ejemplos particulares de ácidos orgánicos que se pueden utilizar incluyen ácido cítrico y tartárico.

Las fuentes de dióxido de carbono que se pueden utilizar en las composiciones efervescentes incluyen bicarbonato de sodio y carbonato de sodio. Los agentes colorantes incluyen cualquiera de los colorantes solubles en agua, aprobados y certificados por FD y C, y sus mezclas.

Ejemplos particulares de agentes saborizantes que se pueden utilizar incluyen sabores naturales extraídos de plantas, tales como frutas y mezclas de sintéticas de compuestos que producen una sensación placentera.

Para una forma de dosificación sólida, la solución o suspensión, en, por ejemplo, propilencarbonato, aceites vegetales o triglicéridos, de preferencia se encapsula en una cápsula de gelatina. Tales soluciones y su preparación y encapsulación se divulgan en las patentes US Nos. 4.328.245, 4.409.239 y 4.410.545. Para una forma de dosificación líquida, la solución, por ejemplo, en un polietilenglicol, puede encontrarse diluida con una cantidad suficiente de un vehículo líquido farmacéuticamente aceptable, por ejemplo, agua, para así poder medirse fácilmente para su administración.

Alternativamente, se pueden preparar formulaciones orales líquidas o semi-sólidas disolviendo o dispersando el compuesto activo o la sal en aceites vegetales, glicoles, triglicéridos, ésteres de propilénglicol (por ejemplo, propilén carbonato) y otros vehículos como tales, y encapsulando estas soluciones o suspensiones en cuerpos de cápsulas de gelatina dura o blanda. Otras formulaciones útiles

incluyen a aquellas que se indican en las patentes US Nos. Re 28.819 y 4.358.603.

Inyectables, Soluciones, y Emulsiones

La presente invención también está dirigida a composiciones diseñadas para administrar los compuestos de la presente invención a través de administración parenteral, generalmente caracterizada por inyección subcutánea, intramuscular o intravenosa. Los inyectables se pueden preparar en cualquier forma convencional, por ejemplo como soluciones o suspensiones líquidas, formas sólidas adecuadas para la solución o suspensión en líquido antes de la inyección, co como emulsiones.

Ejemplos de excipientes que se pueden utilizar en conjunto con los inyectables de acuerdo a la presente invención incluyen, pero no están limitados a agua, suero fisiológico, dextrosa, glicerol o etanol. Las composiciones inyectables opcionalmente también pueden comprender cantidades menores de sustancias auxiliares no tóxicas tales como agentes de humectación o emulsionantes, agentes reguladores de pH, estabilizadores, mejoradores de la solubilidad, y otros agentes como tal, tal como por ejemplo, acetato de sodio, monolaurato de sorbitan, trietanolamina oleato y ciclodextrinas. También se contempla aquí, la implantación de un sistema de liberación lenta o de liberación sostenida, tal que se mantenga un nivel constante de dosis (véase, *por ejemplo*, la patente US No. 3.710.795). El porcentaje de compuesto activo contenido en tales composiciones parenterales es altamente dependiente de la naturaleza específica del mismo, así como la actividad del compuesto y las necesidades del individuo.

La administración parenteral de las formulaciones incluyen las administraciones intravenosas, subcutáneas e intramusculares. Las preparaciones para la administración parenteral incluyen soluciones estériles listas para inyección, los productos secos solubles y estériles, tal como los polvos liofilizados que se describen aquí, listos para ser combinados con un solvente justo antes del uso, incluyendo tabletas hipodérmicas, suspensiones estériles listas para inyección, productos estériles insoluble secos listos para ser

combinados con un vehículo justo antes del uso y emulsiones estériles. Las soluciones pueden ser acuosas o no acuosas.

Cuando se administra por vía intravenosa, los ejemplos de vehículos adecuados incluyen, pero no están limitados u suero salino fisiológico o un suero salino tamponado (PBS), y soluciones que contienen agentes espesantes y solubilizantes, tales como glucosa, polietilénglicol, y polipropilénglicol y mezclas de los mismos.

Ejemplos de vehículos farmacéuticamente aceptables que opcionalmente se pueden utilizar en preparaciones parenterales incluyen, pero no están limitados a vehículos acuosos, vehículos no acuosos, agentes antimicrobianos, agentes isotónicos, tampones, antioxidantes, anestésicos locales, agentes de suspensión y de dispersión, agentes emulsionantes, agentes secuestrantes o quelantes y otras sustancias farmacéuticamente aceptables.

Ejemplos de vehículos acuosos que opcionalmente se pueden utilizar incluyen Inyección de cloruro de sodio, Inyección Ringers, Inyección de dextrosa isotónica, Inyección de agua estéril, Inyección de Dextrosa y Ringers lactato.

Ejemplos de vehículos parenterales no acuosos que opcionalmente se pueden utilizar incluyen aceites fijos de origen vegetal, aceite de semilla de algodón, aceite de maíz, aceite de sésamo y aceite de cacahuate.

A las preparaciones parenteral se pueden agregar agentes antimicrobianos e concentraciones bacteriostáticas o fungistáticas, particularmente cuando las preparaciones son envasadas en envases de múltiples dosis y por lo cual son diseñados para ser almacenados y para retirar múltiples alícuotas. Ejemplos de agentes antimicrobianos que se pueden utilizar incluyen fenoles o cresoles, mercuriales, alcohol bencílico, clorobutanol, ésteres de ácido metil y propil p-hidroxibenzóico, timerosal, cloruro de benzalconio y cloruro de bencetonio.

Ejemplos de agentes isotónicos que se pueden utilizar incluyen cloruro de sodio y dextrosa. Ejemplos de agentes reguladores de pH o tampones que se pueden utilizar incluyen fosfato y citrato. Ejemplos de antioxidantes que se pueden utilizar incluyen bisulfato de sodio. Ejemplos de anestésicos locales que se pueden utilizar

incluyen clorhidrato de procaína. Ejemplos de agentes de suspensión y dispersión que se pueden utilizar incluyen carboximetilcelulosa de sodio, hidroxipropil metilcelulosa y polivinilpirrolidona. Ejemplos de agentes emulsionantes que se pueden utilizar incluyen Polisorbato 80 (TWEEN 80). Un agente secuestrante o quelante de iones metálicos incluye EDTA.

Los vehículos farmacéuticos que opcionalmente también se pueden elegir incluyen alcohol etílico, polietilénglicol y propilénglicol para vehículos miscibles en agua e hidróxido de sodio, ácido clorhídrico, ácido cítrico o ácido láctico para el ajuste del pH.

La concentración de un inhibidor en la formulación parenteral se puede ajustar de modo que se pueda administrar en una inyección una cantidad farmacéuticamente efectiva suficiente para producir el efecto farmacológico deseado. La concentración exacta de un inhibidor y/o dosis a ser utilizada dependerá finalmente de la edad, peso y condición del paciente o animal tal como se sabe en el estado del arte.

Las preparaciones parenterales de dosis unitaria se pueden envasar en una ampolla, un frasco o una jeringa con una aguja. Todas las preparaciones para la administración parenteral deben estar estériles, tal como es sabido y se practica en el estado del arte.

Los inyectables se pueden diseñar para la administración local y sistémica. En general, se formula una dosis terapéuticamente efectiva para contener una concentración de al menos alrededor de 0,1% p/p hasta alrededor de 90% p/p o más, preferentemente más de 1% p/p del inhibidor PARP al/los tejido(s) tratado (s). El inhibidor se puede administrar una vez, o se puede dividir en un número de dosis menores a ser administradas a intervalos de tiempo. Se entiende que la dosis precisa y la duración del tratamiento será una función de la ubicación en la cual se administrará la composición por vía parenteral, el vehículo y otras variables que se pueden determinar de manera empírica utilizando protocolos de ensayo conocidos o a través de extrapolación a partir de datos de ensayo *in vivo* o *in vitro*. Se debe hacer notar que las concentraciones y los valores de dosis también pueden variar con la edad del individuo tratado. Además se

debe entender que para cualquier individuo particular, pueden ser necesarios regímenes de dosis específica a ser ajustados a lo largo del tiempo de acuerdo a la necesidad individual y al razonamiento profesional de la persona que administra o que supervisa la administración de las formulaciones. Por lo cual, los rangos de concentración que aquí se establecen están dirigidos a ser ejemplares y no se pretende que limiten el espectro o la práctica de las formulaciones reivindicadas.

El inhibidor PARP opcionalmente puede ser suspendido en una forma micronizada u otra forma adecuada o puede ser derivatizado para producir un producto activo más soluble o para producir una prodroga. La forma de la mezcla resultante depende de un número de factores, qué incluyen el modo de administración que se pretende y la solubilidad del compuesto en el portador o vehículo seleccionado. La concentración efectiva es suficiente para mejorar los síntomas del estado de enfermedad y se puede determinar de manera empírica.

Polvos liofilizados

Los compuestos de la presente invención también se pueden preparar como polvos liofilizados, los cuales pueden ser reconstituidos para la administración como soluciones, emulsiones y otras mezclas. Los polvos liofilizados también se pueden formular como sólidos o geles.

El polvo liofilizado estéril se puede preparar disolviendo el compuesto en una solución tampón de fosfato de sodio que contiene dextrosa u otro excipiente adecuado. La posterior filtración estéril de la solución seguida por la liofilización bajo condiciones estándar conocidas para aquellos expertos en el arte, proporciona la formulación deseada. Brevemente, el polvo liofilizado opcionalmente puede ser preparada disolviendo dextrosa, sorbitol, fructosa, jarabe de maíz, xilitol, glicerina, glucosa, sacarosa u otro agente adecuado, alrededor de 1-20%, preferentemente alrededor de 5 a 15%, en u tampón adecuado, tal como citrato, fosfato de sodio o de potasio u otro tampón conocido como tal para aquellos expertos en el arte, por lo general, a alrededor de pH neutro. Entonces, un inhibidor PARP se agrega a la mezcla resultante, preferentemente por sobre la

temperatura ambiente, más preferentemente a alrededor de 30-35°C, y se agita hasta que se disuelve. La mezcla resultante se diluye agregando más tampón a una concentración deseada. La mezcla resultante se filtra estéril o se trata para remover particulados y para asegurar la esterilidad, y se colocó en porciones en frascos para liofilización. Cada frasco puede contener una dosis única o múltiples dosis del inhibidor.

Administración Tópica

Los compuestos de la presente invención también se pueden administrar como mezclas tópicas. Las mezclas tópicas se pueden utilizar para la administración local y sistémica. La mezcla resultante puede ser una solución, suspensión, emulsiones o similares y son formuladas como cremas, geles, ungüentos, emulsiones, soluciones, elíxires, lociones, suspensiones, tinturas, pastas, espumas, aerosoles, irrigaciones, sprays, supositorios, vendas, parches dérmicos o cualquier otro tipo de formulaciones adecuadas para la administración tópica.

Los inhibidores PARP se pueden formular como aerosoles para aplicación tópica, tal como por inhalación (véase, las patentes US 4.044.126, 4.414.209, y 4.364.923, que describen aerosoles para la entrega de un esteroide útil para el tratamiento de enfermedades inflamatorias, particularmente asma). Estas formulaciones para la administración al tracto respiratorio pueden estar en la forma de un aerosol o una solución para un nebulizador, o como un polvo microfino para insuflación, solo o en combinación con un vehículo inerte tal como lactosa. En u caso como tal, las partículas de la formulación por lo general tendrán diámetros de menos 50 micrones, preferentemente de menos de 10 micrones.

Los inhibidores también se pueden formular para la aplicación local o tópica, tal como para la aplicación tópica a la piel y a las membranas mucosas, tal como al ojo, en la forma de geles, cremas, y lociones y para la aplicación al ojo o para la aplicación intracisternal o intraespinal. La administración tópica es considerada para la entrega transdérmica y también para la administración a los ojos o a ala mucosa, o para terapias de

inhalación. También se pueden administrar soluciones nasales del inhibidor PARP solo o en combinación con otros excipientes farmacéuticamente aceptables.

Formulaciones para otras rutas de Administración

Dependiendo del estado de enfermedad que se esta tratando, es además posible utilizar otras rutas de administración, tales como la aplicación tópica, parches transdérmicos, y la administración rectal. Por ejemplo, las formas de dosis farmacéutica para la administración rectal son supositorios rectales, cápsulas y tabletas para efecto sistémico. Los supositorios rectales que se utilizan aquí representan cuerpos sólidos para la inserción en el recto que se funde o se ablanda a temperatura corporal liberando uno o más ingredientes farmacológicamente o terapéuticamente activos. Las sustancias farmacéuticamente aceptables utilizadas en los supositorios rectales son bases o vehículos y agentes para elevar el punto de fusión. Ejemplos de bases incluyen manteca de cacao (aceite de teobroma), glicerina-gelatina, carbowax, (polioxietilénglicol) y mezclas adecuadas de mono-, di- y triglicéridos o de ácidos grasos. Se pueden utilizar combinaciones de las diversas bases. Los agentes para elevar el punto de fusión de los supositorios incluyen spermaceti (esperma de ballena) y cera. Los supositorios rectales se pueden preparar ya sea a través del método de comprimido o por moldeo. El peso típico de un supositorio rectal es de alrededor de 2 a 3 g. Las tabletas y cápsulas para la administración rectal pueden ser elaboradas utilizando la misma sustancia farmacéuticamente aceptable y a través de los mismos métodos que para las formulaciones para la administración oral.

Ejemplos de Formulaciones

Los siguientes son ejemplos particulares de formulaciones de tableta oral, intravenosa y que opcionalmente se pueden utilizar con compuestos de la presente invención. Es importante considerar que estas formulaciones se pueden variar dependiendo del compuesto particular que se está utilizando y de la indicación para la cual la formulación se va a utilizar.

FORMULACIÓN ORAL

Compuesto de la presente invención	10-100 mg
Monohidrato de Acido Cítrico	105 mg
Hidróxido de Sodio	18 mg
Saborizante	
Agua	csp hasta 100 mL

FORMULACIÓN INTRAVENOSA

Compuesto de la presente invención	0,1-10 mg
Dextrosa Monohidrato	csp. Hasta ser Isotónica
Monohidrato de Acido Cítrico	1.05 mg
Hidróxido de Sodio	0.18 mg
Agua para Inyección	csp h1.0 mL

FORMULACIÓN DE TABLETA

Compuesto de la presente invención	1%
Celulosa Microcristalina	73%
Acido Esteárico	25%
Sílice Coloidal	1%.

Kits Que Comprenden Inhibidores PARP

La invención está además dirigida a kits y a otros artículos de manufactura para tratar enfermedades asociadas con PARP. Es importante destacar que se pretende que las enfermedades abarquen todas aquellas condiciones para las cuales PARP posee una actividad que contribuye a la patología y/o sintomatología de la condición.

En una modalidad, se provee un kit que comprende una composición que comprende al menos un inhibidor de la presente invención en combinación con instrucciones. Las instrucciones pueden indicar el estado de enfermedad para el cual la composición se administrará, la información acerca del almacenamiento, la información acerca de la dosificación y/o instrucciones respecto de cómo administrar la composición. El kit también puede comprender materiales de envasado. El material de envasado puede comprende un

envase para contener la composición. Opcionalmente el kit también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en forma de una dosis única o de múltiples dosis.

En otra modalidad, se provee un artículo de manufactura que comprende una composición que comprende al menos un inhibidor de la presente invención en combinación con materiales de envasado. El material de envasado puede comprender un envase para contener la composición. El envase opcionalmente puede comprender una etiqueta o rótulo que indica el estado de enfermedad para el cual la composición se administrará, información acerca del almacenamiento, información acerca de la dosificación y/o instrucciones respecto de cómo administrar la composición. Opcionalmente el kit también puede comprender componentes adicionales, tales como jeringas para la administración de la composición. El kit puede comprender la composición en forma de una dosis única o de múltiples dosis.

Se debe destacar que el material de envasado utilizado en los kits y artículos de manufactura de acuerdo a la presente invención puede formar una pluralidad de envases divididos tal como una botella con divisiones o dividida o un sobre de aluminio dividido. El envase puede tener cualquier figura o forma convencional como se sabe en el estado del arte el cual está hecho de un material farmacéuticamente aceptable, por ejemplo una caja de papel o de cartón, una botella o pote de vidrio o de plástico, una bolsa re-sellable (por ejemplo, para contener una "carga de relleno" de tabletas para ser colocadas en una envase diferente), o un envase en blister con dosis individuales para presionar hacia fuera del envase de acuerdo a un esquema terapéutico. El envase que se utiliza dependerá de la forma de dosis exacta involucrada, por ejemplo en general una caja de cartón convencional no se utilizará para contener una suspensión líquida. Es posible que se pueda utilizar más de un envase, juntos dentro de otro envase único pata comercializar una única forma de dosis. Por ejemplo, en una botella pueden estar contenidas tabletas, donde la botella puede estar contenida en una caja de cartón. En general el kit incluye guías para la administración de los componentes separados. La forma del kit es

particularmente ventajosa cuando los componentes separados son administrados preferentemente en formas de dosis diferentes (*por ejemplo*, oral, tópica, transdérmica y parenteral), se administran a intervalos de dosis diferentes, o cuando se desee la valoración o consideración de los componentes individuales de la combinación por el médico que la prescribe.

Un ejemplo particular de un kit de acuerdo a la presente invención es el conocido envase en blister. Los envases en blister son bien conocidos en la industria del envasado y están siendo ampliamente utilizados para el envasad de formas de dosis unitaria farmacéuticas (tabletas, cápsulas, y similares). En general los envases en blister consisten de una lámina de material relativamente rígido recubierto con una lámina que preferentemente es de un material plástico transparente. Durante el proceso de envasado se forman cavidades en la lámina de plástico. Las cavidades poseen el tamaño y forma de las tabletas o cápsulas individuales a ser envasada o pueden tener el tamaño la forma para acomodar múltiples tabletas y/o cápsulas a ser envasadas. En seguida, se colocan las tabletas o cápsulas en las cavidades respectivamente y la lámina de material relativamente rígido se sella contra la lámina de plástico y la cara de la lámina que está contraria a la dirección en la cual se formaron las cavidades. Como resultado, las tabletas o cápsulas se sellan de manera individual o se sellan de manera colectiva, como se desee, dentro de las cavidades entre le lámina de plástico y la lámina u hoja de material relativamente rígido. Preferentemente la resistencia de la hoja de material relativamente rígido es tal que las tabletas o cápsulas se pueden retirar de envase en blister aplicando presión manual sobre las cavidades con lo cual se forma una abertura en la hoja y el lugar de la cavidad. Entonces la tableta o cápsula puede ser retirada a través de dicha abertura.

Otra modalidad específica de un kit es un dosificador diseñado para dosificar las dosis diarias una a la vez en el orden del uso que se les pretende dar. Preferentemente, el dosificador está equipado con una ayuda para la memoria, de modo que además facilite el cumplimiento del régimen. Un ejemplo de una ayuda para la memoria como tal es un contador mecánico que indica el número de dosis

diarias que se han entregado. Otro ejemplo de una ayuda para la memoria como tal es un micro-chip de memoria operado con batería acoplado con una pantalla de lectura de cristal líquido, o una señal de recordatorio audible la cual, por ejemplo, lee la fecha en la cual se ha tomado la última dosis diaria y/o le recuerda a uno cuando se debe tomar la siguiente dosis.

Dosis, Huésped y Seguridad

Los compuestos de la presente invención son estables y se pueden utilizar de manera segura. En particular, los compuestos de la presente invención son útiles como inhibidores PARP para una variedad de individuos (*por ejemplo*, humanos, no mamíferos que no son humanos y no mamíferos). La dosis óptima puede variar dependiendo de tales condiciones como, por ejemplo, el tipo de individuo, el peso corporal del individuo, la ruta de administración, y las propiedades específicas del compuesto particular que se está usando. En general, La dosis diaria para la administración oral a un adulto (peso corporal de alrededor de 60 kg) es de alrededor de 1 a 1.000 mg, alrededor de 3 a 300 mg, o de alrededor de 10 a 200 mg. Se apreciará que la dosis diaria se puede entregar en una administración única o en porciones múltiples (*por ejemplo*, 2 o 3) por día.

Terapias de Combinación

Una amplia variedad de agentes terapéuticos pueden tener un efecto terapéutico aditivo o sinérgico con los inhibidores PARP de acuerdo a la presente invención. Se pueden utilizar terapias de combinación que comprenden uno o más compuestos de la presente invención con uno o más agentes terapéuticos diferentes, por ejemplo, para: 1) aumentar el/los efecto(s) terapéutico(s) del uno o más compuestos de la presente invención y/o del uno o más agentes terapéuticos diferentes; 2) reducir lo efectos secundarios que exhiben el uno o más compuestos de la presente invención y/o el uno o más agentes terapéuticos diferentes; y/o 3) reducir la dosis efectiva del uno o más compuestos de la presente invención y/o del uno o más agentes terapéuticos diferentes.

En una modalidad, se provee un método para tratar un estado de enfermedad proliferativo celular que comprende tratar las

células con un compuesto de acuerdo a la presente invención en combinación con un agente anti-proliferativo, donde las células con tratadas con el compuesto de acuerdo a la presente invención antes, en el mismo momento, y/o después que las células son tratadas con el agente anti-proliferativo, lo que es conocido aquí como una terapia de combinación. Es importante considerar que el tratamiento entregando un agente antes del otro es conocido aquí como una terapia secuencial, incluso si los agentes también se administran juntos. Se distingue que la terapia de combinación está dirigida a cubrir el caso cuando los agentes son administrados antes o después uno del otro (terapia secuencial) así como cuando los agentes son administrados al mismo momento.

Ejemplos de agentes terapéuticos que se pueden utilizar en combinación con inhibidores PARP incluyen, pero no están limitados a, agentes anticancerígenos, agentes alquilantes, agentes antibióticos, agentes antimetabólicos, agentes hormonales, agentes derivados de planta, y agentes biológicos.

Los agentes alquilantes son compuestos polifuncionales que tienen la capacidad de sustituir grupos alquilo por iones de hidrógeno. Ejemplos de agentes alquilantes incluyen, pero no están limitados a, biscloroetilaminas (mostazas nitrogenadas, por ejemplo clorambucilo, ciclofosfamida, ifosfamida, mecloretamina, melfalano, mostaza uracilo), aziridinas (por ejemplo tiotepa), alquil alcona sulfonatos (por ejemplo busulfano), nitrosoureas (por ejemplo carmustina, lomustina, estreptozocina), agentes alquilantes no clásicos (altretamina, dacarbazina, y procarbazina), compuestos de platino (carboplastino y cisplatino). Estos compuestos reaccionan con grupos fosfato, amino, hidroxilo, sulfihidrilo, carboxilo, e imidazol. Bajo condiciones fisiológicas, estas drogas ionizan y producen iones cargados positivamente que atacan a los ácidos nucleicos y proteínas susceptibles, conduciendo a la detención del ciclo celular y/o a la muerte celular. La terapia de combinación que incluye a un inhibidor PARP y un agente alquilante puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes antibióticos son un grupo de drogas que son producidas de una forma similar a los antibióticos como una modificación de productos naturales. Ejemplos de agentes antibióticos incluyen, pero no están limitados a, antraciclinas (por ejemplo doxorubicina, daunorubicina, epirubicina, idarubicina y antracenodiona), mitomicina C, bleomicina, dactinomicina, plicatomicina. Estos agentes antibióticos interfieren con el crecimiento celular dirigiéndose a componentes celulares diferentes. Por ejemplo, por lo general se piensa que las antraciclinas interfieren con la acción de la ADN topoisomerasa II en las regiones de ADN transcripcionalmente activo, lo cual lleva a tener cortes en la hebra de ADN. En general se cree que la bleomicina actúa quelando hierro y forma un complejo activado, el cual se une a las bases de ADN, causando cortes en la hebra y la muerte celular. La terapia de combinación que incluye a un inhibidor PARP y un agente antibiótico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes antimetabólicos son un grupo de drogas que interfieren con los procesos metabólicos vitales de la fisiología y proliferación de las células cancerosas. Las células cancerosas que proliferan activamente requieren de la síntesis continua de grandes cantidades de ácidos nucleicos, proteínas, lípidos, y de otros constituyentes celulares vitales. Muchos de los antimetabolitos inhiben la síntesis de los nucleósidos purina o pirimidina o inhiben las enzimas de la replicación del ADN. Algunos antimetabolitos también interfieren con la síntesis de ribonucleósidos y ARN y/o el metabolismo de aminoácidos y también con la síntesis de proteína. Interfiriendo la síntesis de los constituyentes celulares vitales, es que los antimetabolitos pueden retrasar p detener el crecimiento de las células cancerosas. Ejemplos de agentes antimetabólicos incluyen, pero no están limitados a, fluorouracilo (5-FU), floxuridina (5-FUdR), metotrexato, leucovorina, hidroxiurea, tioguanina (6-TG), mercaptopurina (6-MP), citarabina, pentostatina, fosfato de fludarabina, cladribina (2-CDA), asparaginasa, y gemcitabina. La terapia de combinación que incluye un inhibidor PARP y un agente

antimetabólico puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes hormonales son un grupo de drogas que regulan el crecimiento y desarrollo de sus órganos blanco. La mayoría de los agentes hormonales son esteroides sexuales y sus derivados y análogos de los mismos, tales como estrógenos, andrógenos, y progestinas. Estos agentes hormonales pueden ser útiles como antagonistas de los receptores para los esteroides sexuales para regular negativamente la expresión del receptor u la transcripción de los genes vitales. Ejemplos de tales agentes hormonales son los estrógenos sintéticos (por ejemplo dietilstibestrol), antiestrógenos (por ejemplo tamoxifeno, toremifeno, fluoximesterol y raloxifeno), antiandrógenos (bicalutamida, nilutamida, flutamida), inhibidores de aromatasa (por ejemplo, aminoglutetimida, anastrozol y tetrazol), ketoconazol, acetato de goserelina, leuprolido, acetato de megestrol y mifepristona. La terapia de combinación que incluye un inhibidor PARP y un agente hormonal puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes derivados de plantas son un grupo de drogas que son derivados de plantas o modificados en base a la estructura molecular de los agentes. Ejemplos de agentes derivados de plantas incluyen, pero no están limitados a, alcaloides vinca (por ejemplo, vincristina, vinblastina, vindesina, vinzolidina y vinorelbina), podofilotoxinas (por ejemplo, etoposido (VP-16) y teniposido (VM-26)), taxanos (por ejemplo, paclitaxel y docetaxel). Por lo general estos agentes derivados de plantas actúan como agentes antimitóticos que se unen a tubulina e inhiben la mitosis. Se piensa que las podofilotoxinas tales como etoposido interfieren con la síntesis de ADN interactuando con la topoisomerasa II, resultando en el corte de la hebra de ADN. La terapia de combinación que incluye un inhibidor PARP y un agente derivado de plantas puede tener efectos sinérgicos terapéuticos sobre el cáncer y reducir los efectos secundarios asociados con estos agentes quimioterapéuticos.

Los agentes biológicos son un grupo de biomoléculas que producen como respuesta la regresión del cáncer/tumor cuando se utilizan solas o en combinación con quimioterapia y/o radioterapia. Ejemplos de agentes biológicos incluyen, pero no están limitados a, proteínas inmuno-moduladoras tales como citoquinas, anticuerpos monoclonales contra antígenos tumorales, genes supresores de tumor, y vacunas contra el cáncer. La terapia de combinación que incluye un inhibidor PARP y un agente biológico puede tener efectos sinérgicos terapéuticos sobre el cáncer, aumentando la respuesta inmune del paciente a las señales tumorigénicas, y reducir los efectos secundarios potenciales asociados con este agente quimioterapéutico.

Las citoquinas poseen una actividad inmunomoduladora profunda. Algunas citoquinas tales como interleuquina-2 (IL-2, aldesleuquina) e interferón han demostrado actividad antitumoral y han sido aprobadas para el tratamiento de pacientes con carcinoma metastásico de células renales y con carcinoma metastásico maligno. La IL-2 es un factor de crecimiento de células T que es central para las respuestas inmunes mediadas por células T. Se piensa que los efectos antitumorales selectivos de IL-2 en algunos pacientes son el resultado de una respuesta inmune mediada por células que discrimina entre propio y no propio. Ejemplos de interlequinas que se pueden utilizar en conjunto con un inhibidor PARP incluyen, pero no están limitados a, interleuquina 2 (IL-2), e interleuquina 4 (IL-4), interleuquina 12 (IL-12).

El interferón incluye más de 23 subtipos relacionados con las actividades que se sobreponen, encontrándose todos los subtipos de IFN dentro del espectro de la presente invención. El IFN ha demostrado actividad contra muchas malignidades sólidas y hematológicas, pareciendo estas últimas ser particularmente sensibles.

Otras citoquinas que se pueden usar en conjunto con un inhibidor PARP incluyen aquellas citoquinas que ejercen efectos profundos sobre la hematopoyesis y las funciones inmunes. Ejemplos de tales citoquinas incluyen, pero no están limitados a eritropoyetina, CSF de granulocitos (filgrastina), y granulocitos, CSF de macrófagos (sargramostima). Estas citoquinas se pueden utilizar en conjunto con

un inhibidor PARP par5a reducir la toxicidad mielopoyética inducida por la quimioterapia.

También se pueden utilizar otros agentes inmuno-moduladores diferentes de las citoquinas en conjunto con un inhibidor PARP para inhibir el crecimiento celular anormal. Ejemplos de tales agentes inmuno-moduladores incluyen, pero no están limitados a bacilo Calmette-Guerin, levamisol, y octreotido, un octapéptido de larga acción que imita los efectos de la hormona somatostatina que existe de manera natural.

Los anticuerpos monoclonales contra los antígenos tumorales son anticuerpos que responden contra antígenos expresados por los tumores, preferentemente antígenos específicos a tumores. Por ejemplo, el anticuerpo monoclonal HERCEPTIN® (Trastruzumab) responde contra el receptor 2 del factor de crecimiento epidérmico humano (HER2) que es sobre-expresado en algunos tumores mamarios incluyendo el cáncer mamario metastásico. La sobre-expresión de la proteína HER2 se asocia con una enfermedad más agresiva y de mala prognosis en clínica. HERCEPTIN® se utiliza como un agente único para el tratamiento de pacientes con cáncer mamario metastático cuyos tumores sobre-empresan la proteína HER2. La terapia de combinación que incluye un inhibidor PARP y HERCEPTIN® puede tener efectos sinérgicos terapéuticos sobre tumores, especialmente sobre cánceres metastásicos.

Otro ejemplo de anticuerpos monoclonales contra antígenos tumorales es RITUXAN® (Rituximab) el cual responde contra CD20 sobre células de linfoma y reduce de manera selectiva las células $CD20^+$ pre-B y B maduras normales y malignas. RITUXAN® se utiliza como un agente único para el tratamiento de pacientes con linfoma no Hodgkin de células B CD20+, de grado menor ó folicular, con reincidencia o refractario. La terapia de combinación que incluye un inhibidor PARP y RITUXAN® puede tener efectos sinérgicos terapéuticos no solo en el linfoma, sino que también sobre otras formas o tipos de tumores malignos.

Los genes de supresión de tumor son genes que funcionan inhibiendo el crecimiento y los ciclos de división celular, previniendo de ese modo el desarrollo de la neoplasia. Las mutaciones

en los genes de supresión de tumor provocan que la célula ignore a uno o más de los componentes de la red de señales inhibidoras, superando el ciclo celular los puntos de verificación y resultando en una mayor velocidad de crecimiento controlado de células cancerosas. Ejemplos de los supresores de genes tumorales incluyen, pero no están limitados a, DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA1, y BRCA2.

DPC-4 está involucrado en cáncer pancreático y participa en una ruta citoplasmática que inhibe la división celular. NF-1 codifica una proteína que inhibe Ras, una proteína inhibidora citoplasmática. NF-1 está involucrado en neurofibroma y en feocromocitomas del sistema nervioso y en leucemia mieloide. NF-2 codifica una proteína nuclear que está involucrada en meningioma, schwanoma, y ependimoma del sistema nervioso. RB codifica la proteína pRB, una proteína nuclear que es el inhibidor principal del ciclo celular. RB está involucrada en retinoblastoma así como en cáncer óseo, de vejiga, cáncer pulmonar de células pequeñas y en cáncer mamario. P53 codifica la proteína p53 que regula la división celular y puede inducir apoptosis. La mutación y/o inactividad de p53 se encuentra en un amplio rango de tipos de cáncer. WT1 está involucrado en tumor de Wilms de riñón. BRCA1 está involucrado en cáncer mamario y ovárico, y ERCA2 está involucrado en cáncer mamario. El gen supresor de tumor se puede transferir a las células tumorales donde ejerce sus funciones supresoras de tumor. La terapia de combinación que incluye un inhibidor PARP y un supresor de tumor pueden tener efectos sinérgicos terapéuticos en los pacientes que sufren de diversas formas de cáncer.

Las vacunas anticáncer son un grupo de agentes que inducen la respuesta inmune corporal específica a los tumores. Muchas vacunas para el cáncer que se encuentran en investigación y desarrollo y en ensayos clínicos son antígenos asociados a tumores (TAA). Los TAA son estructuras (es decir proteínas, enzimas o carbohidratos) los cuales están presentes en las células tumorales y relativamente ausentes o disminuidas en células normales. En virtud de ser razonablemente único para la célula tumoral, los TAA proveen blancos al sistema inmune para reconocer y provocar su destrucción. Ejemplos de TAA incluyen, pero no están limitados a gangliosidos (GM2), antígeno

prostático específico (PSA), alfa-fetoproteína (AFP), antígeno carcinoembrionario (CEA) (producido por los cáncer de colon y otros adenocarcinomas, por ejemplo cáncer mamario, pulmonar, gástrico, y de páncreas), antígenos asociados a melanoma (MART-1, gp100, MAGE 1,3 tirosinasa), papilomavirus E6 y los fragmentos E7, células completas o porciones/lisados de células tumorales autólogas y células tumorales alogénicas.

Se puede utilizar un adyuvante para aumentar la respuesta inmune a los TAA. Ejemplos de adyuvantes incluyen, pero no están limitados a, bacilo Calmette-Guerin (BCG), lipopolisacáridos endotoxinas, hemocianina de keyhole limpet (GKLH), interleuquina-2 (IL-2), factor de estimulación de colonias de granulocitos-macrófagos (GM-CSF) y citoxano, un agente quimioterapéutico que se cree reduce la supresión inducida por tumor cuando se administra en dosis bajas.

Ejemplos adicionales de agentes terapéuticos que se pueden usar en combinación con los inhibidores PARP incluyen, pero no están limitados a, inhibidores de la señalización Pl3/Akt. Ejemplos de los inhibidores Pl3/Akt que se pueden utilizar en combinación con los inhibidores PARP incluyen, pero no están limitados a, los inhibidores del receptor de factor de crecimiento epidermal de humano (HER2). Ejemplos de inhibidores HER2 incluyen, pero no están limitados a, Herceptin® (Trastruzumab) y Tykerb® (Lapatinib). Tykerb®, es una molécula pequeña que se puede administrar por vía oral, que inhibe los componentes de la tirosina quinasa de los receptores ErbB1 y ErbB2. La estimulación de ErbB1 y ErbB2 está asociada con la proliferación celular y con múltiples procesos involucrados en la progresión del tumor, la invasión, y la metástasis. Se ha informado la sobre-expresión de estos receptores en una variedad de tumores en humanos y está asociada a una mala prognosis y una reducida sobrevida total.

Ejemplos adicionales de agentes terapéuticos que se pueden usar en combinación con inhibidores PARP incluyen, pero no están limitados a, inhibidores de la histona deacetilasa (HDAC). Ejemplos de inhibidores HDAC que se pueden usar en combinación con inhibidores PARP incluyen, pero no están limitados a, ácido suberoilanilida hidroxámico (SAHA).

Además, los inhibidores PARP de la presente invención se pueden usar en combinación con antibióticos aminoglicosidos, inhibidores CHK, drogas citotóxicas y/o inhibidores de la topoisomerasa.

EJEMPLOS

Preparación de Inhibidores de PARP

Se pueden desarrollar varios métodos para sintetizar los compuestos de acuerdo a la presente invención. Los métodos representativos para sintetizar estos compuestos se proporcionan en los Ejemplos. Se debe destacar, sin embargo, que los compuestos de la presente invención también se pueden sintetizar a través de otras rutas de síntesis que otros puedan diseñar.

Se reconocerá fácilmente que ciertos compuestos de acuerdo a la presente invención poseen átomos con uniones a otros átomos que les confieren una estequiometría particular a compuesto (*por ejemplo*, centros quirales). Se reconoce que la síntesis de los compuestos de acuerdo a la presente invención puede resultar en la creación de mezclas de estereoisómeros diferentes (*es decir*, enantiómeros y diastereómeros). A menos que se especifique una estequiometría particular, se pretende que la declaración de un compuesto abarque a todos los posibles estereoisómeros diferentes.

Varios métodos para separar las mezclas de estereoisómeros diferentes son conocidos en el arte. Por ejemplo, una mezcla racémica de un compuesto se puede hacer reaccionar con un agente de resolución ópticamente activo para formar un par de compuestos diastereoisoméricos. Los diastereómeros pueden entonce ser separados para poder recuperar los enantiómeros ópticamente puros. También se pueden utilizar complejos disociables para resolver los enantiómeros (*por ejemplo*, sales cristalinas diastereoisoméricas). Los diastereómeros en general poseen propiedades físicas suficientemente distintas (*por ejemplo*, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y pueden ser fácilmente separados aprovechando estas disimilaridades. Por ejemplo, los diastereómeros pueden ser generalmente separados mediante cromatografía o a través de técnicas de separación/resolución basadas en las diferencias en la

solubilidad. Una descripción más detallada de las técnicas que se pueden utilizar para resolver los estereoisómeros de compuestos a partir de su mezcla racémica se pueden encontrar en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Los compuestos de acuerdo a la presente invención también se pueden preparar cono una sal de adición de ácido farmacéuticamente aceptable haciendo reaccionar la forma de base libre del compuesto con un ácido inorgánico u orgánico farmacéuticamente aceptable. Alternativamente, una sal de adición de base farmacéuticamente aceptable de un compuesto se puede preparar haciendo reaccionar la forma de ácido libre del compuesto con una base inorgánica u orgánica farmacéuticamente aceptable. Las bases y ácidos inorgánicos u orgánicos adecuados para la preparación de las sales farmacéuticamente aceptables de los compuestos se definen más adelante en la sección de las definiciones de esta descripción. Alternativamente, las formas de saltes de los compuestos se pueden preparar utilizando sales de los materiales de partida o de sus intermediarios.

Las formas de ácido libre o base libre de los compuestos se pueden preparar a partir de la correspondiente forma de sal de adición de base o la sal de adición de ácido. Por ejemplo, un compuesto en una forma de sal de adición de ácido se puede convertir en la correspondiente base libre tratándolo con una base adecuada (*por ejemplo*, solución de hidróxido de amonio, hidróxido de sodio, y similares). Un compuesto en una forma de sal de adición de base se puede convertir en el correspondiente ácido libre tratándolo con un ácido adecuado (*por ejemplo*, ácido clorhídrico, etc).

Los N-óxidos de los compuestos de acuerdo a la presente invención se pueden preparar a través de métodos conocidos para aquellos que son personas expertas en el arte. Por ejemplo, los N-óxidos se pueden preparar tratando una forma no oxidada de el compuesto con un agente oxidante (*por ejemplo*, ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-cloroperoxibenzoico, o similares) en un solvente orgánico inerte adecuado (*por ejemplo*, un hidrocarburo

halogenado tal como diclorometano) aproximadamente a 0°C. Alternativamente, los N-óxidos de los compuestos se pueden preparar a partir del N-óxido de u material de partida adecuado.

Los compuestos en una forma no oxidada se pueden preparar a partir de N-óxidos de compuestos tratando con un agente reductor (*por ejemplo*, azufre, dióxido de azufre, trifenil fosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fósforo, tribromuro, o similares) en un solvente orgánico inerte adecuado (*por ejemplo*, acetonitrilo, etanol, dioxanos acuoso, o similares) a una temperatura de 0 a 80°C.

Los derivados prodroga de los compuestos se pueden preparar a través de métodos conocidos para aquellos que son personas expertas en el arte (*por ejemplo*, para detalles adicionales véase Saulnier et al.(1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, se pueden preparar prodrogas adecuadas haciendo reaccionar un compuesto no derivatizado con un agente carbamilante adecuado (*por ejemplo*, 1,1-aciloxialquilcarbonocloridato, para-nitrofenil carbonato, o similares).

Los derivados protegidos de los compuestos se pueden preparar a través de métodos conocidos para aquellos que son personas expertas en el arte. Una descripción detallada de las técnicas aplicables a la generación de grupos protectores y su eliminación se puede encontrar en T.W. Greene, Protecting Groups in Organic Synthesis, 3rd edition, John Wiley & Sons, Inc. 1999.

Los compuestos de acuerdo a la presente invención pueden ser preparados convenientemente, o formados durante el proceso de la invención, como solvatos (*por ejemplo*, hidratos). Los hidratos de los compuestos de la presente invención pueden ser preparados convenientemente mediante recristalización a partir de una mezcla de solvente acuoso/orgánico, utilizando solventes orgánicos tal como dioxina, tetrahidrofurano o metanol.

Los compuestos de acuerdo a la presente invención también se pueden preparar como sus estereoisómeros individuales mediante reacción de una mezcla racémica del compuesto con un agente de resolución ópticamente activo para formar un par de compuestos

diastereoisomérico, separando los diastereómeros y recuperando el enantiómero ópticamente puro. Mientras que la resolución de los enantiómeros se puede realizar utilizando derivados de compuestos covalentes diastereoméricos, son preferidos los complejos disociables (*por ejemplo*, sales cristalinas diastereoisoméricas). Los diastereómeros tienen distintas propiedades físicas (*por ejemplo*, puntos de fusión, puntos de ebullición, solubilidades, reactividad, etc.) y pueden ser fácilmente separados aprovechándose de éstas disimilitudes. Los diastereómeros se pueden separar por cromatografía ó, preferentemente, mediante técnicas de separación/resolución basadas sobre diferencias en la solubilidad. El enantiómero ópticamente puro es luego recuperado, junto con el agente de resolución, por cualquiera de los medios prácticos que podría no resultar en una racemización. Una descripción más detallada de las técnicas aplicables a la resolución de estereoisómeros de compuestos de su mezcla racémica se puede encontrar en Jean Jacques Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

Como se utiliza aquí los símbolos y las convenciones utilizadas en éstos procesos, esquemas y ejemplos son consistentes con aquellos utilizados en la literatura científica contemporánea, por ejemplo, el Journal of the American Chemical Society ó el Journal of Biological Chemistry. Abreviaciones con una única letra estándar ó tres letras estándar, generalmente son utilizadas para designar residuos de aminoácidos, los cuales se asumen que están en la configuración L a menos que se indique lo contrario. A menos que se indique de otra manera, todos los materiales de partida se obtuvieron de proveedores comerciales y se usaron sin posterior purificación. Específicamente, las siguientes abreviaciones se pueden utilizar en los ejemplos y en todas las especificaciones:

µL (microlitros)	Ac (acetilo)
atm (atmósfera)	ATP (Adenosina Trifofatasa)
BOC (ter-butiloxicarbonilo)	BOP cloruro de (bis(2-oxo-3-oxazolidinil)fosfínico)
BSA (Bovino sero albúmina)	CBZ (benciloxicarbonilo)

CDI (1,1-carbonildiimidazol)	DCC (diciclohexilcarbodiimida)
DCE (dicloroetano)	DCM (diclorometano)
DMAP (4-dimetilaminopiridina)	DME (1,2-dimetoxietano)
DMF (N,N-dimetilformamida)	DMPU (N,N'-dimetilpropilenurea)
DMSO (dimetilsulfóxido)	EDCI clorhidrato de(etilcarbodiimida
EDTA (ácido etilendiaminotetraacético)	Et (etil)
Et_2O (dietil éter)	EtOAc (acetato de etilo)
FMOC (9-fluorenilmetoxicarbonilo)	g (gramos)
h (horas)	HOAc ó AcOH (ácido acético)
HOBT (1-hidroxibenzotriazol)	HOSu (N-hidroxisuccinimida)
HPLC (cromatografía líquida de alta presión)	Hz (Hertz)
i.v. (intravenosa)	IBCF (isobutil cloroformiato)
i-PrOH (isopropanol)	L (litros)
M (molar)	mCPBA (ácido meta-cloroperbenzoico)
Me (metilo)	MeOH (metanol)
mg (miligramos)	MHz (megahertz)
min (minutos)	mL (mililitros)
mM (milimolar)	mmol (milimoles)
mol (moles)	MOPS (ácido morfolinpropano sulfónico)
mp (punto de fusión)	NaOAc (acetato de sodio)
OMe (metoxi)	psi (libras por pulgada cuadrada)
RP (fase reversa)	RT (temperatura ambiente)
SPA (Ensayo de proximidad por centelleo)	TBAF (fluoruro de tetra-n-butilamonio)
TBS (t-butildimetilsililo)	tBu (ter-butilo)
TEA (trietilamina)	TFA (ácido trifluoroacético)
TFAA (anhídrido trifluoroacético)	THF (tetrahidrofurano)
TIPS (triisopropilsililo)	TLC (cromatografía en capa

	fina)
TMS (trimetilsililo)	TMSE (2-(trimetilsilil)etilo)
Tr (tiempo de retención)	

Todas las referencias a éter ó Et_2O son para dietil éter; y salmuera se refiere a una solución acuosa saturada de NaCl. A menos que se indique de otra manera, todas las temperaturas son expresadas en °C (grados centígrados). Todas las reacciones son conducidas bajo una atmósfera inerte a temperatura ambiente a menos que se indique de otra manera.

El espectro ^1H NMR se registró en un Bruker Avance 400. Los corrimientos químicos son expresados en partes por millón (ppm). Los constantes de acoplamiento están en unidades de Hertz (Hz). Los patrones de desdoblamiento describen aparente multiplicidades y son designados como s (singulete), d (doblete), t (triplete), c (cuarteto), m (multiplete), br (ancho).

Los datos de la baja resolución del espectro de masas (MS) y pureza del compuesto se adquirieron en un Waters ZQ LC/MS sistema único de cuadrupolo equipado con una fuente de ionización con electrospray (ESI), detector UV (220 y 254 nm), y el detector de dispersión de luz evaporativa (ELSD). La cromatografía en capa fina se realizó en placas de sílica gel de 0.25 mm E. Merck (60F-254), visualizada con luz UV, 5% de ácido fosfomolíbdico etanólico, Ninhidrina ó solución de p-anisaldehído. La cromatografía en columna evaporativa se realizó sobre sílica gel (230-400 mesh, Merck).

Los materiales de partida y reactivos utilizados en preparar estos compuestos són ya sea de proveedores comerciales disponibles tales como Aldrich Chemical Company (Milwaukee, WI), Bachem (Torrance, CA), Sigma (St. Louis, MO), ó pueden ser preparados por métodos bien conocidos por personas expertas en el arte, siguiendo los procedimientos descritos en tales referencias estándar como Fieser and Fieser's Reagents for Organic Synthesis, vols. 1-17, John Wiley and Sons, New York, NY, 1991; Rodd's Chemistry of Carbon Compounds, vols. 1-5 and supps, Elsevier Science Publishers, 1989; Organic Reacciones, vols. 1-40, John Wiley and Sons, New York, NY, 1991; March J.: Advanced Organic Chemistry, 4th ed, John Wiley and

Sons, New York, NY; y Larock: Comprehensive Organic Transformations, VCH Publishers, New York, 1989.

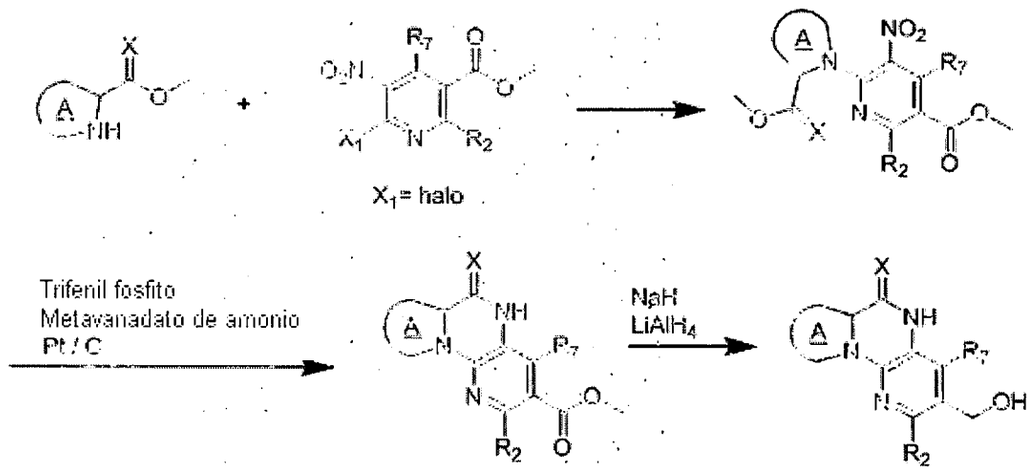
El descubrimiento total de todos los documentos citados a lo largo de ésta solicitud son incorporados aquí como referencia.

Esquemas sintéticos para compuestos de la presente invención

Los compuestos de acuerdo a la presente invención se pueden sintetizar de acuerdo a los esquemas de reacción a continuación mostrados. Otros esquemas de reacción pueden ser fácilmente diseñados por aquellos expertos en el arte. También se puede apreciar que una variedad de diferentes solventes, temperaturas y otras condiciones de reacción se pueden variar para optimizar los rendimientos de las reacciones.

En las reacciones descritas a continuación puede ser necesario proteger grupos funcionales reactivos, por ejemplo hidroxi, amino, imino, tio ó grupos carboxi, cuando estos son deseados en el producto final, para evitar su participación no deseada en las reacciones. Los grupos protectores convencionales se pueden utilizar de acuerdo con prácticas estándar, por ejemplo, véase T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

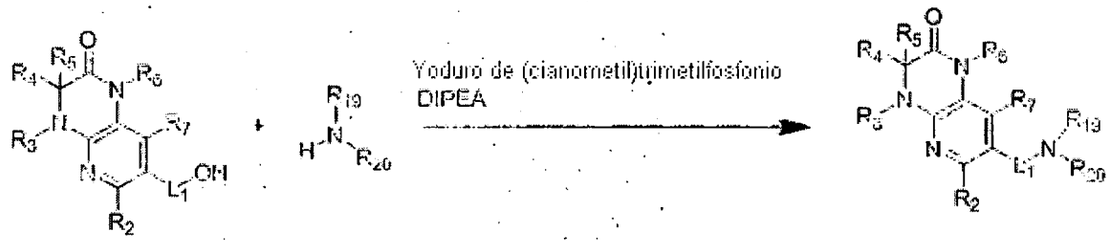
Esquema 1



Un α-aminoéster es condensado con una 2-halo-3-nitropiridina sustituida (alternativamente con o sin solvente ó

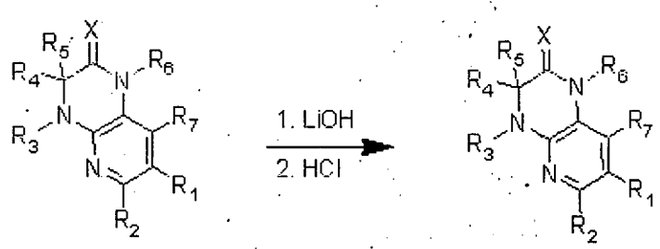
aplicación de calor) seguido por reducción del grupo nitro y cierre del anillo para proporcionar una piridopirazina sustituida Alternativamente la reducción y ciclación del nitro se puede realizar con polvo de hierro en AcOH con calentamiento. La reducción del metil éster en la posición 7 es acompañada con hidruro de aluminio y litio (u otros hidruros como agentes de reducción) después de la desprotonación de la amida N-H para proteger la amida.

Esquema 2



La sustitución nucleofílica del alcohol con aminas es acompañada después de la conversión del alcohol al yoduro. Otros métodos de la activación del alcohol se puede utilizar incluyendo condiciones de Mitsunobu condiciones entre otros.

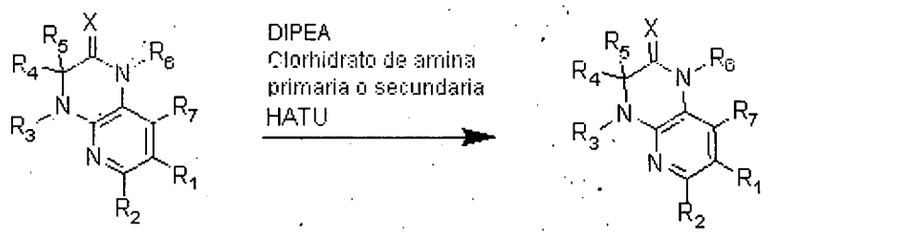
Esquema 3



donde R_1 posee un éster terminal donde R_1 posee un ácido carboxílico terminal

La hidrólisis de un éster terminal es acompañada con hidróxido de litio seguido por tratamiento con ácido para proporcionar un ácido carboxílico terminal. Alternativamente, otras condiciones de hidrólisis, ambas básicas y acídicas, se pueden utilizar, incluyendo hidróxido de sodio, hidróxido de potasio, ácido clorhídrico y otros.

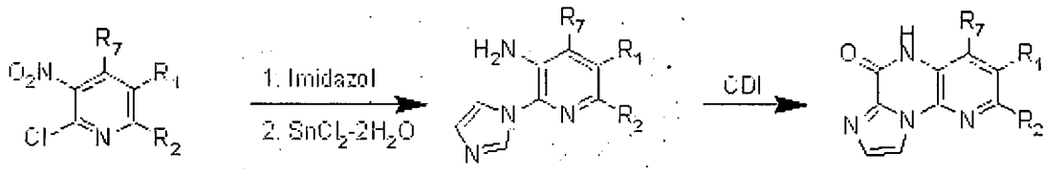
Esquema 4



donde R_1 posee un ácido carboxílico terminal donde R_1 posee una carboxamida terminal

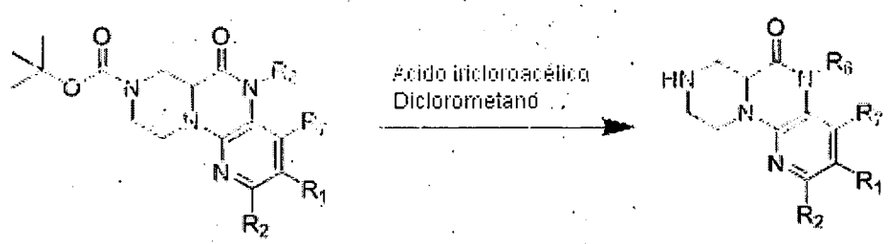
Los ácidos carboxílicos terminales son convertidos a carboxamidas terminales a través de la activación del ácido con HATU seguido por tratamiento con aminas primarias ó secundarias. Alternativamente, existen otros métodos para convertir los ácidos carboxílicos a carboxamidas incluyendo conversión a un intermediario de cloruro de ácido ó el uso de otros reactivos de activación tales como EDC, HOBt, EDAC, PyBOP, TATU y otros.

Esquema 5



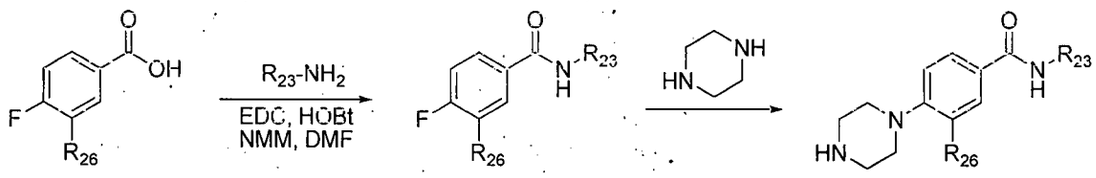
Se realiza La sustitución nucleofílica aromático de un 2-halo-3-nitropiridina con imidazol seguida por reducción del grupo nitro. El tratamiento con CDI forma la pirazinona.

Esquema 6



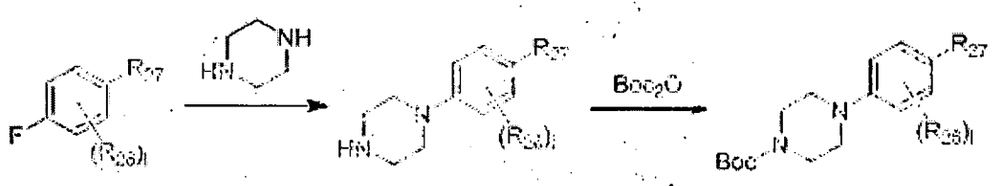
La desprotección del grupo Boc es acompañada por agitación con TFA en DCM. Alternativamente, otros ácidos fuertes y solventes se pueden utilizar incluyendo pero no limitado a HCl en EtOAc.

Esquema 7a: Procedimiento general para la síntesis de 4-piperazinilbenzamidas sustituidas



Los ácidos sustituidos 4-fluorobenzoico son convertidos a benzamidas utilizando varias aminas y un reactivo de acoplamiento tal como EDC con HOBt. Alternativamente, otros reactivos de acoplamiento se pueden utilizar para formar la amida. La subsiguiente sustitución nucleofílica aromática con piperazina proporciona las 4-piperazinilbenzamidas sustituidas requeridas.

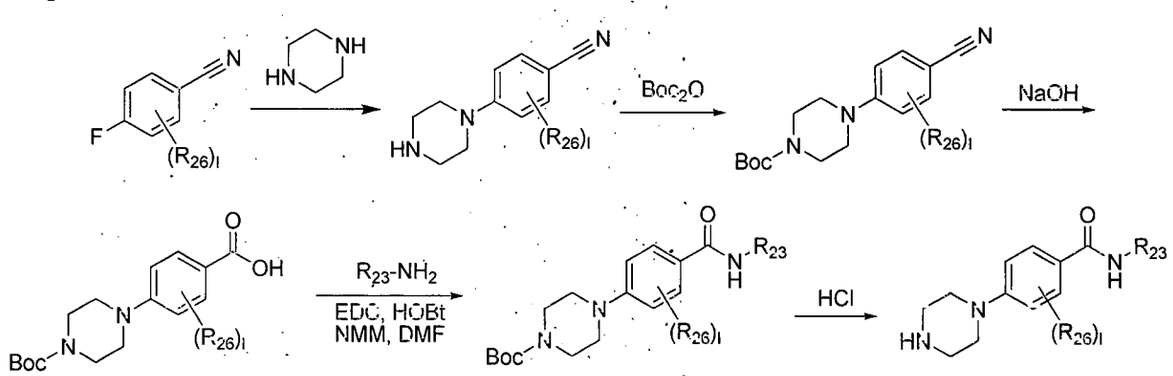
Esquema 7b: Procedimiento general alternativo para la síntesis de 4-piperazinilbenzamidas sustituidas



l= 0, 1, 2, 3 o 4

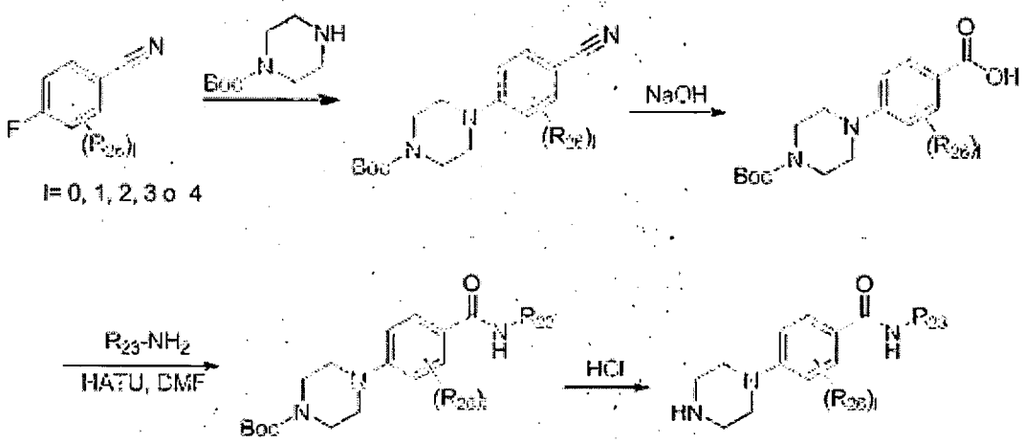
La sustitución nucleofílica aromática de fluoruros de arilo con piperazina proporciona N-arilpiperazinas las cuales pueden ser protegidas con un grupo Boc para permitir posteriormente la funcionalización de los sustituyentes del arilo. Alternativamente, además de Boc se pueden utilizar otros grupos protectores.

Esquema 8



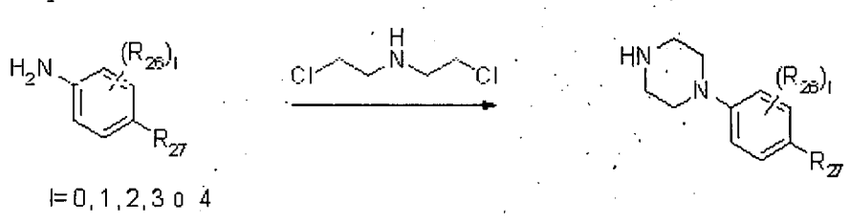
Los 4-fluorobenzonitrilos sustituidos se someten a sustitución nucleofílica aromático con piperazina seguido por protección utilizando anhídrido de Boc. El nitrilo es hidrolizado al correspondiente ácido carboxílico que es entonces acoplado con una amina para proporcionar la benzamida resultante. Finalmente el grupo protector Boc es eliminado por tratamiento con ácido para proporcionar las 4-piperazinilbenzamidas sustituidas.

Esquema 9



Los 4-fluorobenzonitrilos sustituidos se someten a sustitución nucleofílica aromático con Boc-piperazina. El nitrilo es hidrolizado al correspondiente ácido carboxílico el cual es entonces acoplado con una amina para proporcionar la benzamida resultante. Finalmente el grupo protector Boc es eliminado para proporcionar las 4-piperazinilbenzamidas sustituidas.

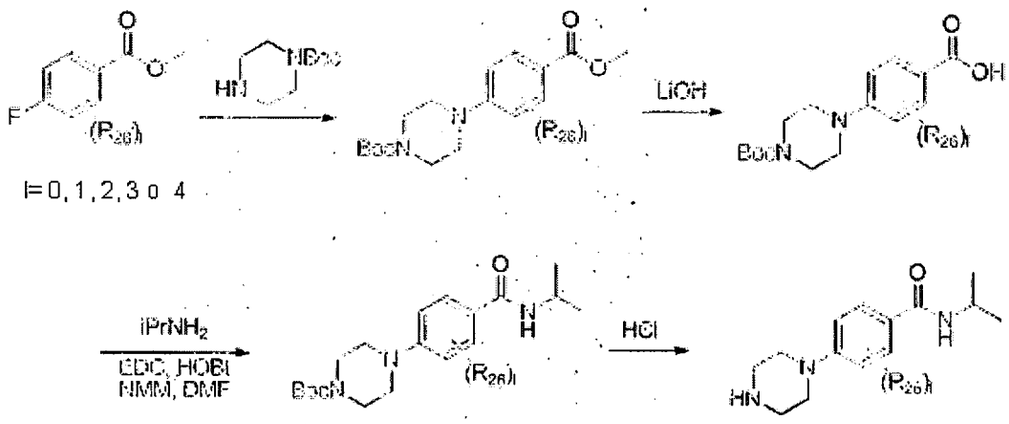
Esquema 10



Las anilinas sustituidas se pueden convertir a piperazinas sustituidas a través de una alquilación de la anilina con bis(2-cloroetil)amina. Alternativamente, otros halógenos grupos salientes

se pueden incorporar en la amina tal como bis(2-bromoetil)amina u otros.

Esquema 11



Los 4-fluorobenzoatos sustituidos se someten a sustitución nucleofílica aromático con N-Boc piperazina seguido por hidrólisis del éster con hidróxido de litio para proporcionar una 4-carboxifenil-N-piperazina protegida. Alternativamente, otras condiciones de hidrólisis ambas básicas y acídicas se pueden utilizar, incluyendo hidróxido de sodio, hidróxido de potasio, ácido clorhídrico y otros. La formación de amida del ácido benzoico con aminas es mediada con reactivos de acoplamiento tal como EDC con HOBt seguido por eliminación con HCl del grupo protector para proporcionar las 4-benzamidopiperazinas sustituidas deseadas. Alternativamente, existen otros métodos para convertir los ácidos carboxílicos a carboxamidas incluyendo conversión a un intermediario con ácido clorhídrico ó el uso de otros reactivos de activación tales como EDAC, PyBOP, TATU y otros.

Los componentes quirales se pueden separar y purificar utilizando cualesquiera de una variedad de técnicas conocidas para aquellos expertos en el arte. Por ejemplo, componentes quirales se pueden purificar utilizando cromatografía fluida supercrítica (SFC). En una variación particular, los análisis analíticos quirales SFC/MS son conducidos utilizando un sistema SFC analítico Berger (AutoChem, Newark, DE) el cual consiste de un módulo de control del fluido con

una bomba binaria Berger SFC, bomba de fluido supercrítica FCM 1100/1200 y una bomba de modificador de fluido FCM 1200, un horno Berger TCM 2000, y un autosampler Alcott 718. El sistema integrado se puede controlar por el programa Chemstation BI-SFC versión 3.4. La detección can be acompañado con un detector Watrers ZQ 2000 operado en modo positive con una interfase ESI y un rango de barrido de 200-800 Da con 0;5 segundos por barrido. Las separaciones cromatográficas se pueden realizar en una columna ChiralPak AD-H, ChiralPak AS-H, ChiralCel OD-H, o ChiralCel OJ-H de (5μ, 4,6 x 250 mm; Chiral Technologies, Inc. West Chester, PA) con 10 a 40% de metanol como el modificador y con ó sin acetato de amonio (10 mM). Cualesquiera de una variedad de tasas de flujo se pueden utilizar incluyendo, por ejemplo, 1,5 ó 3,5 mL/min con una presión de entrada establecida a 100 bar. Adicionalmente, una variedad de condiciones para inyectar la muestra se puede utilizar incluyendo, por ejemplo, inyecciones de muestra de ya sea 5 ó 10μL en metanol a 0,1 mg/mL en concentración.

En otra variación, las separaciones preparativas quirales son realizadas utilizando un sistema de purificación Berger MultiGram II SFC. Por ejemplo, las muestras pueden ser cargadas en una columna ChiralPak AD (21 x 250 mm, 10μ). Variaciones en particular, la tasa de flujo para la separación puede ser de 70 mL/min, el volumen de inyección de hasta 2 mL, y la presión de entrada establecida a 130 bar. Equipo de inyecciones se pueden aplicar para aumentar la eficiencia.

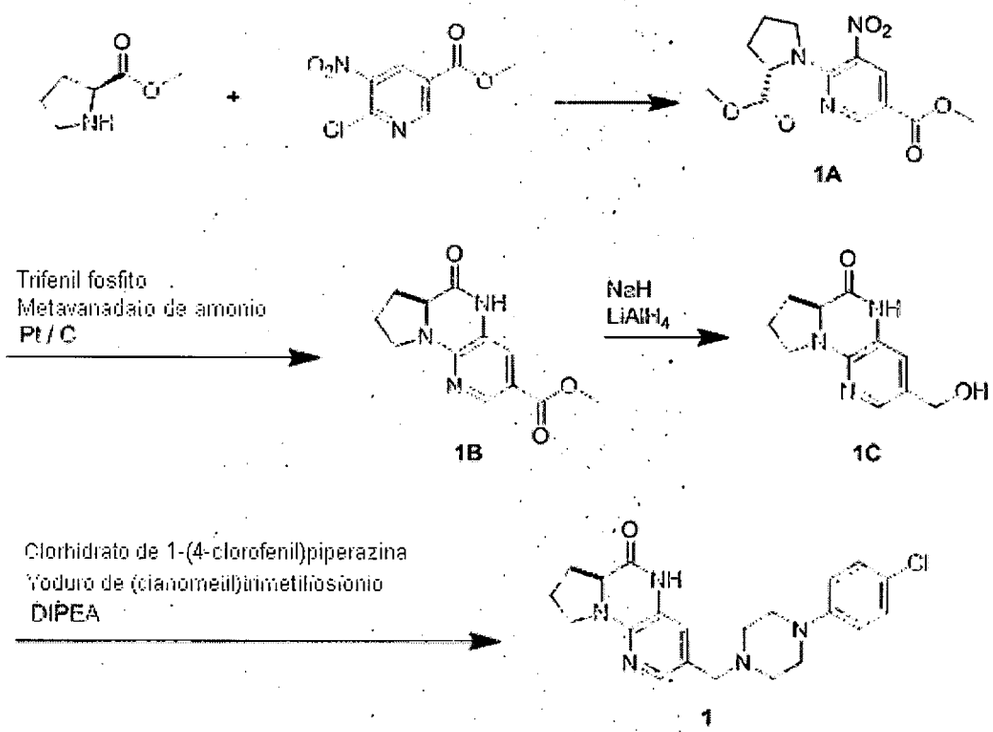
En cada uno de los procedimientos ó esquemas de las reacciones de más arriba, los diferentes sustituyentes se pueden seleccionar de entre los diferentes sustituyentes que de otra manera se enseñan aquí.

Las descripciones de la síntesis de compuestos particulares de acuerdo a la presente invención se basan en los esquemas de reacción de más arriba y son publicados aquí.

Ejemplos de inhibidores PARP

La presente invención es además ejemplificada, pero no limitada por, los siguientes ejemplos que describe la síntesis de compuestos particulares de acuerdo a la invención

Compuesto 1: (S)-3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



Compuesto 1A: 6-(2-(metoxicarbonil)pirrolidin-1-il)-5-nitronicotinato de (S)-metiló: Se agregó pirrolidin-2-carboxilato de (S)-metilo (6,56 g, 50,8 mmol) a 6-cloro-5-nitronicotinato de metil (5,00 g, 23,1 mmol) y la mezcla de reacción se agitó a 90°C por 10 minutos (reacción exotérmica). Se enfrió a temperatura ambiente, se diluyó con EtOAc (10 mL) y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (EtOAc en hexanos 20-30%) para proporcionar el compuesto del título como un aceite amarillo (6,70 g, 94%). [M+H] calculado para $C_{13}H_{15}N_3O_6$, 310; encontrado, 310.

Compuesto 1B: 6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]-pirrolo[1,2-a]pirazin-3-carboxilato de (S)-metilo: Se disolvieron 6-(2-(metoxicarbonil)pirrolidin-1-il)-5-nitro-nicotinato de (S)-metilo (1,45 g, 46,9 mmol) y trifenil fosfito (5,00 mg, 0,0161 mmol) en diclorometano (12 mL). Se agregó metavanadato de amonio (50 mg, 0,427 mmol) y Pt/C (5% en peso, 200 mg) y la mezcla de reacción se agitó bajo hidrógeno (80 psi) por 5 horas. La mezcla de reacción se filtró

a través de un pequeño tapón de celite y el precipitado se lavó muchas veces con diclorometano caliente hasta que estuvo libre de precipitado blanco. El filtrado se concentró al vacío y cristalizó con etil éter (15 mL). El sólido resultante se filtró y se secó al vacío para proporcionar el compuesto del título como un sólido blanquecino (0,930 g, 80%). [M+H] calculado para $C_{12}H_{13}N_3O_3$, 248; encontrado, 248.

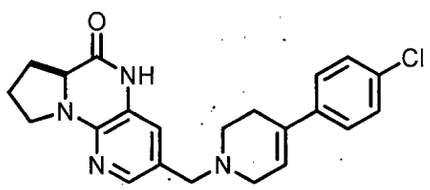
Compuesto 1C: (S)-3-(hidroximetil)-6a,7,8,9-tetrahidro-pirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: Se suspendió el 6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-carboxilato de (S)-metilo (3,00 g, 10,5 mmol) en THF y se agregó hidruro de sodio (suspensión en aceite mineral al 60%, 0,712 g, 17,8 mmol) bajo atmósfera de nitrógeno. La mezcla de reacción se agitó a temperatura ambiente por 1 hora y se enfrió a -8°C. Se agregó gota a gota $LiAlH_4$ (2M en THF, 12,5 mL, 25 mmol) durante 5 minutos y la mezcla de reacción se dejó enfriar a -40°C y se mantuvo a -40-(-20)°C por 3 horas. La mezcla de reacción se enfrió a -60°C y se detuvo con MeOH, agua y TFA hasta resultar en una mezcla transparente. Esta se purificó utilizando HPLC (acetonitrilo en agua 1-30%, solución tampón de TFA). Las fracciones que contienen el producto se concentraron al vacío y cristalizaron con etil éter. El sólido se filtró y se secó al vacío para proporcionar el compuesto del título como un sólido gris (2,60 g, 74%, sal de TFA). [M+H] calculado para $C_{11}H_{13}N_3O_2$, 220; encontrado, 220.

Compuesto 1: (S)-3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (200 mg, 0,912 mmol), clorhidrato de 1-(4-clorofenil)piperazina (200 mg, 0,858 mmol), N,N-diisopropiletilamina (DIPEA; 0,50 mL), y yoduro de (cianometil)trimetilfosfonio (220 mg, 1,08 mmol) en propionitrilo (2 mL) y se calentaron en un frasco cerrado a 90°C por 4 horas. La mezcla de reacción se diluyó con MeOH (2 mL) y se purificó utilizando HPLC a escala preparativa (acetonitrilo en agua 45-95%, solución

tampón con NH_4HCO_3). Las fracciones que contienen producto se concentraron al vacío y se diluyeron con agua (5 mL). El precipitado resultante se filtró y se secó al vacío para proporcionar el compuesto del título como un sólido blanquecino (135 mg, 40%).

^{1}H NMR (DMSO-d_6) δ (ppm): 10,43 (s, 1H), 7,61 (d, J = 1,8 Hz, 1H), 7,21 (d, J = 8,8 Hz, 2H), 6,98 (d, J = 1,8 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 3,91 - 4,06 (m, 1H), 3,51 - 3,66 (m, 1H), 3,37 - 3,47 (m, 1H), 3,10 (br. s., 4H), 2,46 (d, J = 4,3 Hz, 4H), 2,09 - 2,26 (m, 1H), 1,80 - 2,03 (m, 3H); [M+H] calculado para $C_{21}H_{24}ClN_5O$, 398; encontrado, 398; punto de fusión 265-268°C.

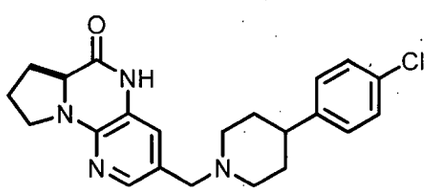
Compuesto 2: (S)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo-[1,2-a]pirazin-6(5H)-ona



Se preparó el compuesto 2 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina en lugar de clorhidrato de 1-(4-clorofenil)piperazina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,77 (d, J = 2,0 Hz, 1H), 7,52 (s, 1H), 7,29 - 7,33 (m, 2H), 7,26 - 7,29 (m, 2H), 7,01 (d, J = 1,8 Hz, 1H), 6,01 - 6,08 (m, 1H), 4,07 (dd, J = 9,2, 6,4 Hz, 1H), 3,72 - 3,83 (m, 1H), 3,57 - 3,66 (m, 1H), 3,44 - 3,55 (m, 2H), 3,15 (q, J = 2,8 Hz, 2H), 2,65 - 2,76 (m, 2H), 2,47 - 2,57 (m, 2H), 2,34 - 2,46 (m, 1H), 1,94 - 2,26 (m, 3H): [M+H] calculado para $C_{22}H_{23}ClN_4O$, 395; encontrado, 395; punto de fusión 234-235°C.

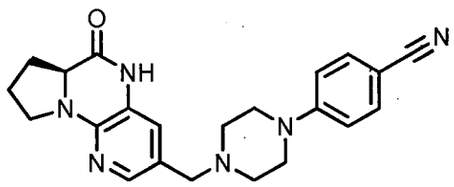
Compuesto 3: (S)-3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6-(5H)-ona



Se preparó el compuesto 3 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó clorhidrato de 4-(4-clorofenil)piperidina en lugar de clorhidrato de 1-(4-clorofenil)piperazina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,92 (br. s., 1H), 7,74 (d, J = 1,5 Hz, 1H), 7,26 (d, J = 8,3 Hz, 2H), 7,15 (d, J = 8,3 Hz, 2H), 6,99 (d, J = 1,5 Hz, 1H), 4,07 (dd, J = 9,5, 6,4 Hz, 1H), 3,69 - 3,82 (m, 1H), 3,54 - 3,66 (m, 1H), 3,33 - 3,49 (m, 2H), 3,00 (d, J = 11,4 Hz, 2H), 2,33 - 2,55 (m, 2H), 1,95 - 2,25 (m, 5H), 1,74 - 1,85 (m, 3H); [M+H] calculado para $C_{22}H_{25}ClN_4O$, 397; encontrado, 397.

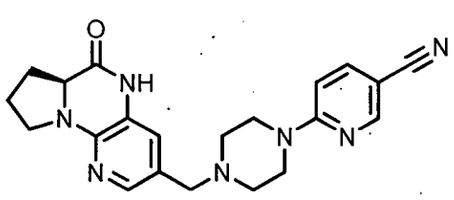
Compuesto 4: (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzonitrilo



Se preparó el compuesto 4 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó 4-(piperazin-1-il)benzonitrilo en lugar de clorhidrato 1-(4-clorofenil)piperazina.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,44 (s, 1H), 7,59 (dd, J = 16,9, 5,3 Hz, 3H), 6,99 (dd, J = 9,3, 5,3 Hz, 3H), 3,91 - 4,07 (m, 1H), 3,51 - 3,65 (m, 1H), 3,31-3,46 (m, 7H), 2,37 - 2,47 (m, 4H), 2,10 - 2,25 (m, 1H), 1,82 - 2,01 (m, 3H); [M+H] calculado para $C_{22}H_{24}N_6O$, 389; encontrado, 389; punto de fusión 252°C.

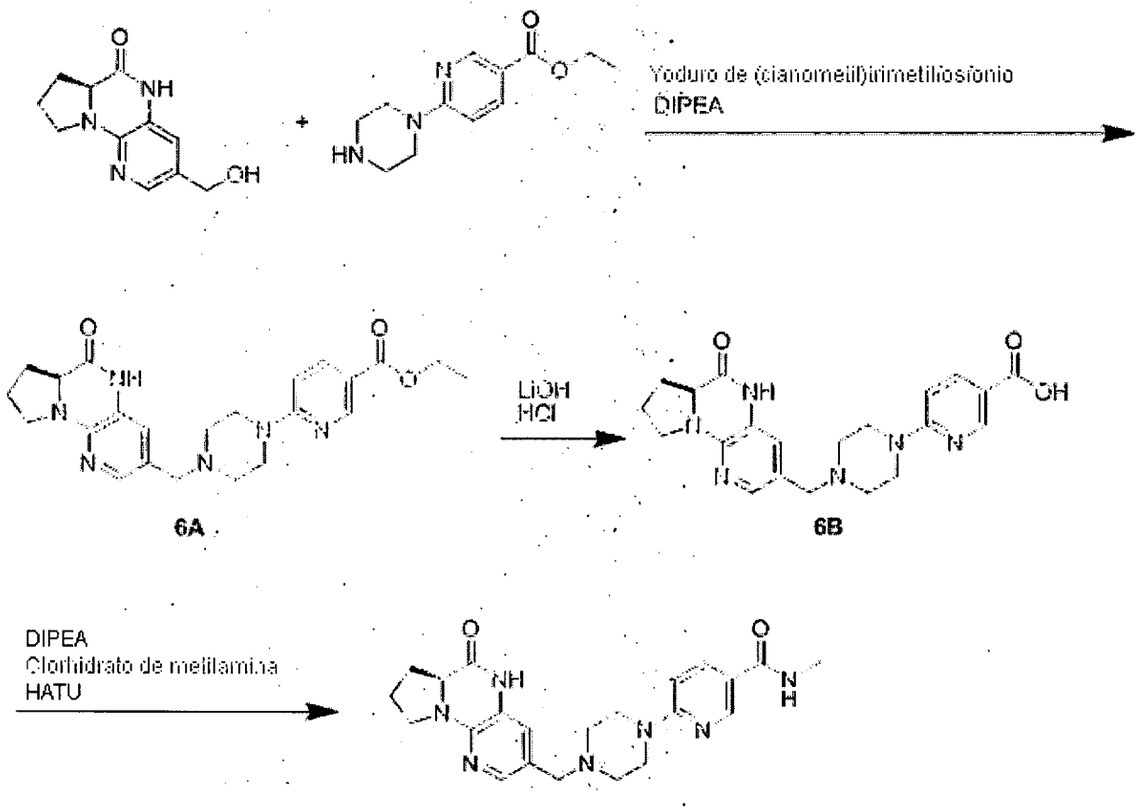
Compuesto 5: (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidro-pirido-[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo



Se preparó el compuesto 5 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó 6-(piperazin-1-il)nicotinonitrilo en lugar de clorhidrato de 1-(4-clorofenil)piperazina.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,44 (s, 1H), 8,47 (d, J = 2,3 Hz, 1H), 7,84 (dd, J = 9,1, 2,3 Hz, 1H), 7,60 (d, J = 1,5 Hz, 1H), 6,98 (d, J = 1,8 Hz, 1H), 6,91 (d, J = 9,1 Hz, 1H), 3,92 - 4,06 (m, 1H), 3,57 - 3,71 (m, 5H), 3,27 - 3,48 (m, 3H), 2,40 (t, J = 4,5 Hz, 4H), 2,10 - 2,24 (m, 1H), 1,81 - 2,01 (m, 3H); [M+H] calculado para $C_{21}H_{23}N_7O$, 390; encontrado, 390; punto de fusión 252-256°C.

Compuesto 6: (S)-N-metil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)nicotinamida



6A

6B

6

Compuesto 6A: 6-(4-((6-oxo-5,6,6a,7,8,9-hexahidro-pirido-[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)-nicotinato de (S)-etilo: Se suspendieron (S)-3-(hidroxi-metil)-6a,7,8,9-tetrahidro-

pirido[3,2-e]pirrolo[1,2-a]-pirazin-6(5H)-ona (233 mg, 1,06 mmol), 6-(piperazin-1-il)nicotinato de etilo (270 mg, 0,1,15 mmol), DIPEA (0,80 mL), y yoduro de (cianometil)trimetilfosfonio (369 mg, 01,82 mmol) en propionitriló (3 mL) y se calentaron en un frasco cerrado a 90°C por 5 horas. La mezcla se enfrió, se diluyó con una solución de K_2CO_3 (2,50 g) en agua (15 mL) y se extrajo con diclorometano (2 × 10 mL). Los extractos orgánicos combinados se secaron con ($MgSO_4$) y se concentraron al vacío. El aceite resultante se cristalizó con etil éter-etanol (10:1, 22 mL) para proporcionar el compuesto del título como un sólido color tostado (0,355 mg, 77%). [M+H] calculado para $C_{23}H_{28}N_6O_3$, 437; encontrado, 437.

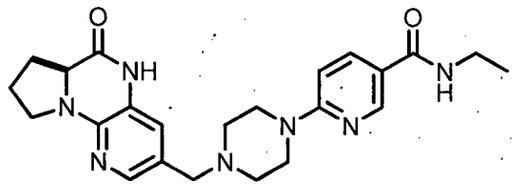
Compuesto 6B: ácido (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)nicotínico: Se suspendió 6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo (0,355 mg, 0,813 mmol) en dioxano (4 mL) y se trató con LiOH (1N, 4,00 mL, 4,00 mmol). La solución resultante se agitó a temperatura ambiente por 3 horas y se concentró al vacío hasta que la mayor parte del solvente orgánico se eliminó. La solución se acidificó con HCl (4,5N) a pH = 3 y el precipitado resultante se recogió por filtración, se lavó con etil éter (5 mL) y se secó al vacío para proporcionar el compuesto del título como un sólido café (0,260 g, 78%). [M+H] calculado para $C_{21}H_{24}N_6O_3$, 409; encontrado, 409.

Compuesto 6: (S)-N-metil-6-(4-((6-oxo-5,6,6a,7,8,9-hexa-hidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)nicotinamida: el ácido Se suspendió (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo [1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotínico (100 mg, 0,245 mmol) en DMF (1,5 mL) y se agregó DIPEA (0,3 mL) seguido por clorhidrato de metilamina (27 mg, 0,400 mmol) y HATU (200 mg, 0,526 mmol). La mezcla de reacción se agitó a temperatura ambiente por 4 horas y se diluyó con MeOH (2 mL). La solución se purificó utilizando HPCL (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3). Las fracciones se concentraron al vacío

y el residuo resultante se cristalizó con MeOH-agua (1:5, 15 mL) para proporcionar el compuesto del título como un sólido blanquecino (52,3 mg, 51%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1,80 - 2,03 (m, 3 H) 2,09 - 2,25 (m, 1 H) 2,41 (br. s., 4 H) 2,74 (d, *J*=4,29 Hz, 3 H) 3,34 - 3,44 (m, 3 H) 3,46 - 3,64 (m, 5 H) 3,92 - 4,05 (m, 1 H) 6,82 (d, *J*=9,09 Hz, 1 H) 6,99 (d, 1 H) 6,93 - 7,04 (m, 1 H) 7,61 (s, 1 H) 7,91 (dd, *J*=8,97, 2,15 Hz, 1 H) 8,17-8,23 (m, 1H) 8,56 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{22}H_{27}N_7O_2$, 422; encontrado, 422.

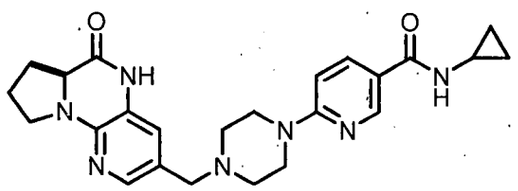
Compuesto 7: (S)-N-etil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)nicotinamida



Se suspendieron el ácido (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotínico (87 mg, 0,213 mmol) y el clorhidrato de etanamina (17,4 mg, 0,213 mmol) en DMF (1,065 mL) y se trató con DIPEA (0,186 mL, 1,065 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (162 mg, 0,426 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 horas y se purificó utilizando HPLC (acetonitrilo en agua 10-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-etil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)nicotinamida (26,4 mg, 0,061 mmol, rindiendo 28,5%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1,09 (t, *J*=7,20 Hz, 3 H) 1,82 - 2,02 (m, 3 H) 2,18 (d, *J*=2,27 Hz, 1 H) 2,41 (t, *J*=4,80 Hz, 5 H) 3,20 - 3,29 (m, 2 H) 3,34 - 3,44 (m, 3 H) 3,51 - 3,63 (m, 5 H) 3,95 - 4,03 (m, 1 H) 6,82 (d, *J*=9,09 Hz, 1 H) 6,99 (d, *J*=1,77 Hz, 1 H) 7,61 (d, *J*=1,77 Hz, 1 H) 7,93 (dd, *J*=9,09, 2,53 Hz, 1 H) 8,23 (t, *J*=5,31 Hz, 1 H) 8,57 (d, *J*=2,27 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{23}H_{29}N_7O_2$, 422; encontrado, 422.

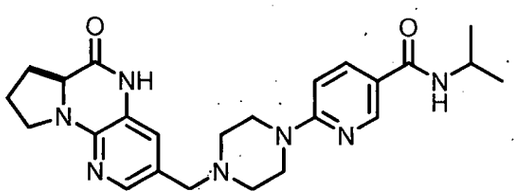
Compuesto 8: (S)-N-ciclopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)nicotinamida



Se suspendieron el ácido (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)nicotínico (87 mg, 0,213 mmol) y la ciclopropanamina (18,24 mg, 0,319 mmol) en DMF (1 ml) y se trataron con DIPEA (0,186 ml, 1,065 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (162 mg, 0,426 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 horas y se purificó utilizando HPLC (acetonitrilo en agua 10-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-ciclopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida (70,3 mg, 0,157 mmol, rindiendo 73,7%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 0,49 - 0,56 (m, 2 H) 0,62 - 0,70 (m, 2 H) 1,82 - 2,02 (m, 3 H) 2,11 - 2,22 (m, 1 H) 2,40 (t, *J*=4,93 Hz, 4 H) 2,78 (tq, *J*=7,34, 3,86 Hz, 1 H) 3,34 (br. s., 2 H) 3,36 - 3,44 (m, 1 H) 3,49 - 3,64 (m, 5 H) 3,94 - 4,03 (m, 1 H) 6,81 (d, *J*=8,59 Hz, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,61 (d, *J*=1,77 Hz, 1 H) 7,90 (dd, *J*=9,09, 2,53 Hz, 1 H) 8,20 (d, *J*=4,04 Hz, 1 H) 8,54 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{24}H_{29}N_7O_2$, 448; encontrado, 448.

Compuesto 9: (S)-N-isopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)nicotinamida

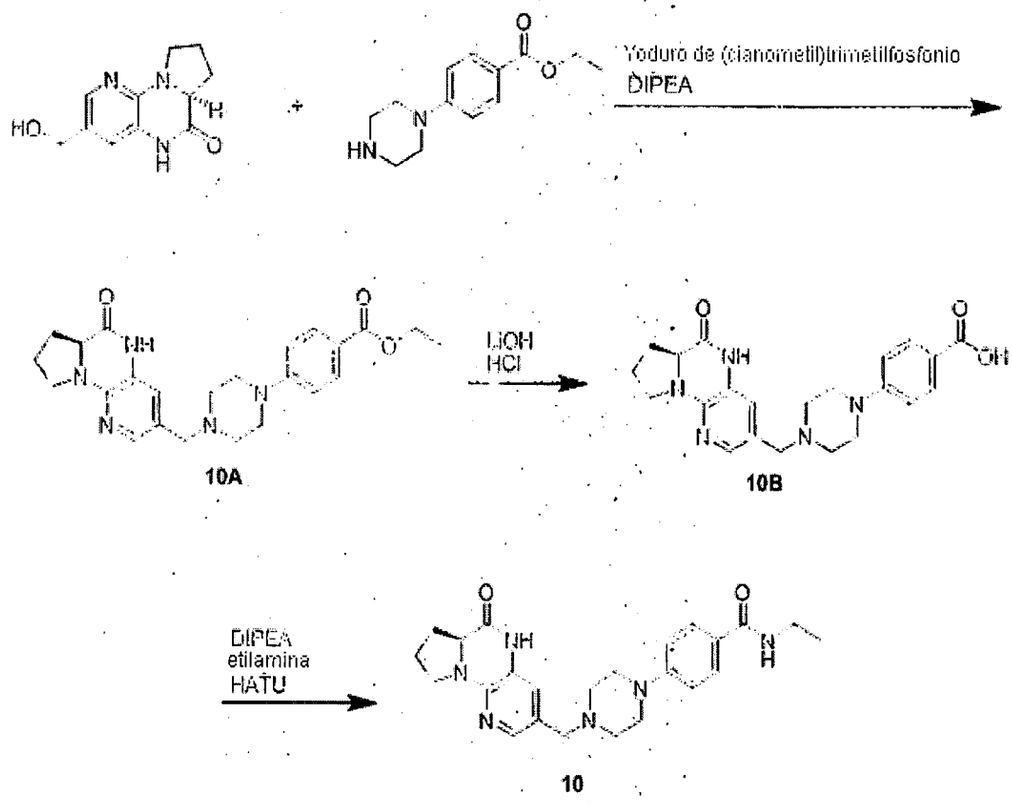


Se suspendió el ácido (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)- nicotínico (87,0 mg, 0,213 mmol) y propan-2-amina (18,89 mg, 0,319 mmol) en DMF (1 ml) y se trató con DIPEA (0,186 ml, 1,065 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (162 mg, 0,426 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 horas y se purificó utilizando HPLC (acetonitrilo en agua 10-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-isopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida (62,1 mg, 0,138 mmol, rindiendo 64,9%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,13 (d, *J*=6,57 Hz, 6 H) 1,84 - 2,01 (m, 3 H) 2,12 - 2,22 (m, 1 H) 2,41 (d, *J*=4,29 Hz, 4 H) 3,36 - 3,47 (m, 1H) 3,49 - 3,64 (m, 5 H) 3,95 - 4,10 (m, 2 H) 6,81 (d, *J*=8,84 Hz, 1 H) 6,99 (d, *J*=2,02 Hz, 1 H) 7,61 (d, *J*=1,77 Hz, 1 H) 7,94 (dd, *J*=9,09, 2,53 Hz, 1H) 7,97 (d, *J*=7,83 Hz, 1 H) 8,57 (d, *J*=2,53 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{24}H_{31}N_7O_2$, 450; encontrado, 450.

Compuesto 10: (S)-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzamida

Método A



10A

10B

10

Compuesto 10A: 4-(4-((6-oxo-5,6,6a,7,8,9-hexahidro-pirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzoato de (S)-etilo: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo- [1,2-a]pirazin-6(5H)-ona (187 mg, 0,854 mmol), 4-(piperazin-1-il)benzoato de etilo (200 mg, 0,854 mmol), yoduro de (cianometil)trimetilfosfonio (311 mg, 1,280 mmol) y N,N-diisopropiletilamina (0,745 ml, 4,27 mmol) en propionitrilo (2 ml) y se calentaron en un frasco cerrado a 90°C por 2 horas. La mezcla de reacción se volvió una solución transparente café oscura. La mezcla se enfrió a temperatura ambiente, se diluyó con MeOH (2 mL), se filtró, los sólidos retenidos, y se purificó utilizando HPLC preparativa. Las fracciones que contienen producto se concentraron al vacío y se cristalizaron de agua (3 mL). El precipitado se filtró y se secó al vacío para proporcionar el producto como un sólido café claro (18,3 mg). El sólido de la filtración anterior se recristalizó de éter-MeOH (10 mL, 5:1). Los productos combinados se secaron al vacío para proporcionar 4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-

il)benzoato de (S)-etilo (283 mg, 0,650 mmol, rindiendo 76%) como un sólido cafesoso. [M+H] calculado para $C_{24}H_{29}N_5O_3$, 436; encontrado, 436; punto de fusión 242°C.

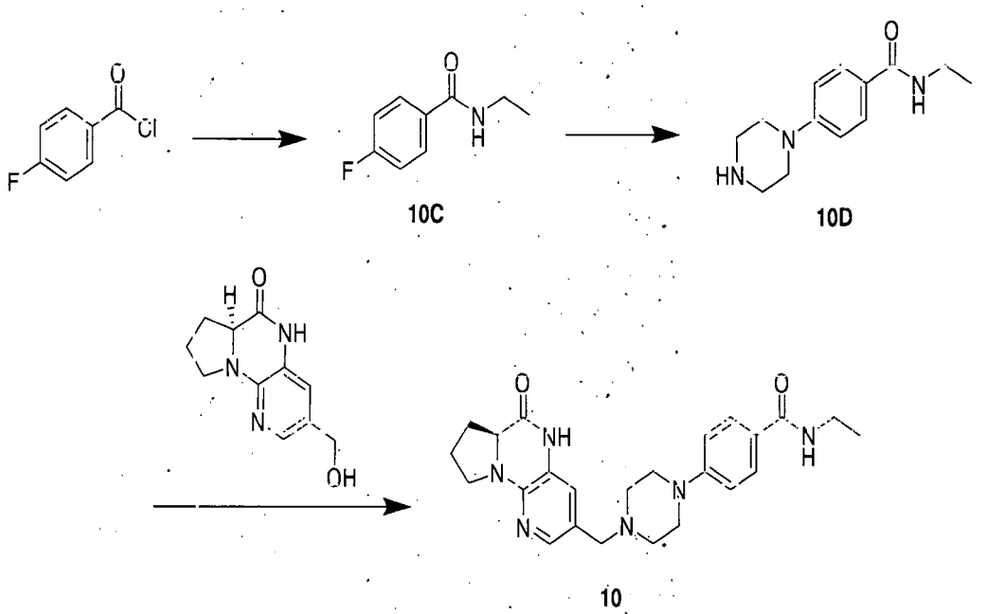
Compuesto 10B: ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzoico: Se suspendió 4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo (280 mg, 0,643 mmol) en 1,4-Dioxano (3,22 mL) y se trató con LiOH 1N (3,215 mL, 3,22 mmol). La mezcla de reacción se agitó a temperatura ambiente por 23 horas. La mezcla de reacción se concentró al vacío hasta que la mayor parte del dioxano se eliminó y se acidificó con HCl (4,5 N) hasta que resultó un precipitado grueso. Se recogió por filtración, se lavó con agua y se secó al vacío para proporcionar el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo- [1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoico (225 mg, 0,552 mmol, rindiendo 86%) como un sólido café. [M+H] calculado para $C_{22}H_{25}N_5O_3$, 408; encontrado, 408.

Compuesto 10: (S)-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexa-hidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida: Se suspendió el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoico (75,0 mg, 0,184 mmol) en DMF (1,0 mL) y se agregó DIPEA (0,15 mL) seguido por etilamina (30 mg, 0,665 mmol) y HATU (85,0 mg, 0,224 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 horas y se agregó otra porción de HATU (60,0 mg, 0,158 mmol). La mezcla de reacción se agitó durante la noche y se purificó utilizando HPCL (acetonitrilo en agua 10-75%, solución tampón de NH_4HCO_3). Las fracciones se concentraron al vacío y el resíduo resultante se cristalizó con MeOH - agua (1:10, 5 mL) para proporcionar el compuesto del título como un sólido verde claro (24,0 mg, 30%).

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1,09 (t, J=7,20 Hz, 3 H) 1,85 - 2,01 (m, 3 H) 2,18 (dt, J=5,37, 2,75 Hz, 1 H) 2,43 - 2,48 (m, 4 H)

3,18 - 3,28 (m, 6 H) 3,35 (s, 2 H) 3,37 - 3,45 (m, 1 H) 3,54 - 3,67 (m, 1 H) 3,94 - 4,05 (m, 1 H) 6,92 (d, *J*=9,09 Hz, 2 H) 6,99 (d, *J*=2,02 Hz, 1 H) 7,62 (d, *J*=2,02 Hz, 1 H) 7,71 (d, *J*=9,09 Hz, 2 H) 8,17 (t, *J*=5,56 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{24}H_{30}N_6O_2$, 435; encontrado, 435.

Método B



Compuesto 10C: N-etil-4-fluorobenzamida: Una solución de etilamina (69,4 mL, 139 mmol) y trietilamina (21,10 mL, 151 mmol) en DCM (Volumen: 150 mL) se agregó cloruro de p-fluorobenzoilo (15,13 mL, 126 mmol) a 0°C. La reacción se agitó a 0°C por 1 hora y luego se enfrió lentamente a temperatura ambiente. La mezcla de reacción se diluyó con agua. Las capas se separaron y la capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y la fase orgánica se removió a sequedad mediante evaporación rotatoria. El extracto orgánico se secó al vacío para proporcionar N-etil-4-fluorobenzamida (21 g, rindiendo 100%) como un sólido color tostado.

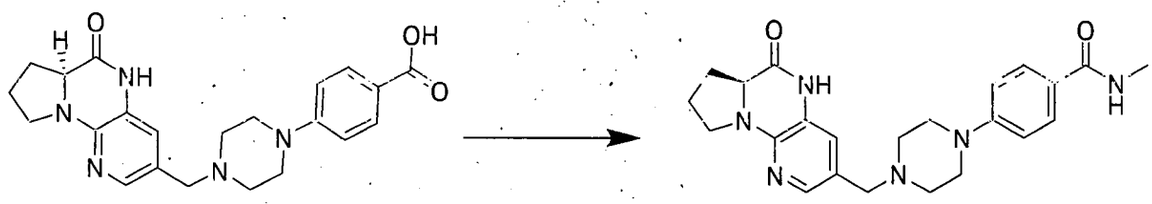
Compuesto 10D: N-etil-4-(piperazin-1-il)benzamida: Utilizando N-etil-4-fluorobenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática con piperazina, se obtuvo el compuesto del título (rindiendo 77%) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,10 (t, J=7,07 Hz, 3 H) 2,25 (br. s., 1 H) 2,76 - 2,86 (m, 4 H) 3,09 - 3,18 (m, 4 H) 3,21 - 3,28 (m, 2 H) 6,90 (m, J=8,84 Hz, 2 H) 7,67 - 7,75 (m, 2 H) 8,11 (t, J=5,31 Hz, 1 H). ESI-MS: m/z 234,2 $(M+H)^+$. mp=131,3-134,4°C.

Compuesto 10: (S)-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida: A una suspensión de (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (0,8 g, 3,65 mmol)) en propiononitrilo (Volumen: 27,4 ml) se agregó yoduro de (cianometil)trimetilfosfonio (1,064 g, 4,38 mmol), N-etil-4-(piperazin-1-il)benzamida (0,851 g, 3,65 mmol) y DIEA (1,912 ml, 10,95 mmol). Se calentó el frasco a 90°C durante 16 horas. La reacción cruda se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y la mezcla se purificó mediante HPLC (55-90, básico) para proporcionar el producto como un sólido blanco.

Compuesto 11: (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida

Método A



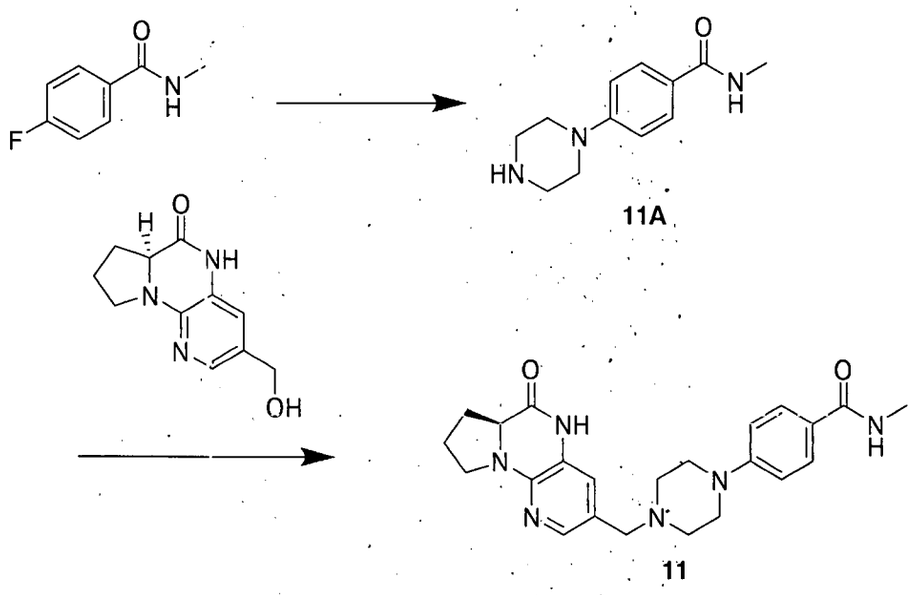
11

Se suspendieron el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzoico (87 mg, 0,214 mmol) y el clorhidrato de metanamina (21,62 mg, 0,320 mmol) en DMF (1 ml) y se trató con DIPEA (0,186 ml, 1,068 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b] piridin-3-il)-1,1,3,3-tetrametilisouronio (162 mg, 0,427 mmol). La mezcla de reacción se agitó a temperatura ambiente por 23 horas y se purificó utilizando HPLC (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-

il)benzamida (42,4 mg, 0,101 mmol, rindiendo 47,2%) como un sólido amarillo claro.

^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 1,83 - 2,01 (m, 3 H) 2,11 - 2,25 (m, 1 H) 2,39 - 2,48 (m, 4 H) 2,73 (d, *J*=4,55 Hz, 3 H) 3,13 - 3,27 (m, 4 H) 3,34 - 3,44 (m, 3 H) 3,52 - 3,64 (m, 1 H) 3,96 - 4,02 (m, 1 H) 6,92 (d, *J*=9,09 Hz, 2 H) 6,98 (d, *J*=2,02 Hz, 1 H) 7,62 (d, *J*=1,77 Hz, 1 H) 7,69 (d, *J*=9,09 Hz, 2 H) 8,13 (q, *J*=4,29 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{23}H_{28}N_6O_2$, 421; encontrado, 421.

Método B



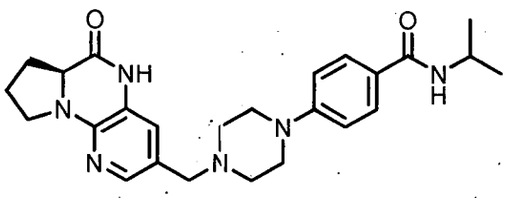
Compuesto 11A: N-metil-4-(piperazin-1-il)benzamida: A una solución de 4-fluoro-N-metilbenzamida (6 g, 39,2 mmol) en DMSO (Volumen: 24,0 mL) se agregó piperazina (16,87 g, 196 mmol) a 23°C. La reacción se agitó a 120°C por 68 horas. La mezcla de reacción se vertió en hielo (261 g) y la reacción en el matraz se lavó con H_2O (~50 mL). A continuación, se agregó celite (30 g) para ayudar a la filtración. La suspensión resultante se calentó a 100°C, se enfrió a ~40°C, se filtró, y se lavó con H_2O caliente (4 x 50 mL). El sólido resultante se secó *al vacío*. El filtrado se agitó a temperatura ambiente durante la noche proporcionando una suspensión. La suspensión se filtró, se lavó con H_2O (3 x 25 mL), y el sólido resultante se secó *al vacío*. El filtrado turbio se filtró una vez más a través de un medio de embudo fritado y se lavó con H_2O (3 x 10 mL). Al filtrado se agregó NaCl

(200,1 g), se enfrío en hielo, se filtró, se lavó con H_2O fría (3 x 25 mL), y se secó el sólido resultante *al vacío*. El producto purificado se volvió a suspender en H_2O (30 mL), se agitó por 30 minutos a 23°C, se filtró, se lavó con H_2O (3 x 5 mL), y se secó el sólido resultante *al vacío*. El producto purificado se resuspendió en ACN (25 mL), se agitó por 10 minutos, y se secó *al vacío*. Este procedimiento se repitió tres veces para proporcionar el N-metil-4-(piperazin-1-il)benzamida (5,64 g, 25,7 mmol, rindiendo 65,7%) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,29 (br. s., 1 H) 2,74 (d, *J*=4,55 Hz, 3 H) 2,77 - 2,86 (m, 4 H) 3,08 - 3,18 (m, 4 H) 6,91 (m, 2 H) 7,69 (m, 2 H) 8,13 (q, *J*=4,04 Hz, 1 H). ESI-MS: m/z 220,2 $(M+H)^+$. mp=153,9-156,5°C.

Compuesto 11: (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (1,500 g, 6,84 mmol), N-metil-4-(piperazin-1-il)benzamida (1,500 g, 6,84 mmol), yoduro de (cianometil)trimetilfosfonio (2,494 g, 10,26 mmol) y N,N-diisopropiletilamina (5,97 ml, 34,2 mmol) en propiononitrilo (Volumen: 27,4 ml) y se calentaron en un frasco cerrado a 90°C. La reacción cruda se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y la mezcla se purificó mediante HPLC (55-90, básico) para proporcionar el producto como un sólido blanco.

Compuesto 12: (S)-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida



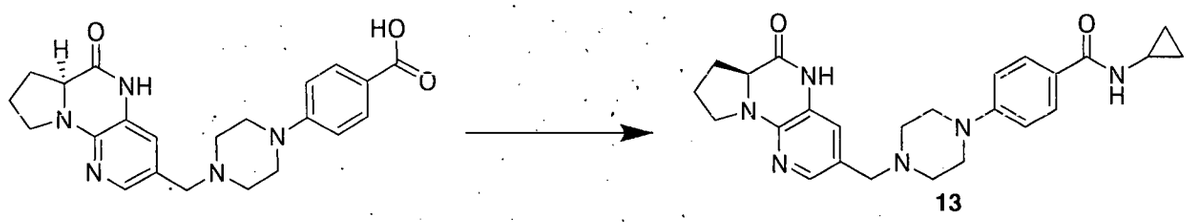
Se suspendieron el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-

il)benzoico (87,0 mg, 0,214 mmol) y el propan-2-amina (18,93 mg, 0,320 mmol) en DMF (1 ml) y se trató con DIPEA (0,186 ml, 1,068 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametil- isouronio (162 mg, 0,427 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 horas y se purificó utilizando HPLC (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-3-il)metil)piperazin-1-il)benzamida (39,6 mg, 0,088 mmol, rindiendo 41,3%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,13 (d, *J*=6,57 Hz, 6 H) 1,85 - 2,00 (m, 3 H) 2,11 - 2,24 (m, 1 H) 2,41 - 2,48 (m, 4 H) 3,17 - 3,27 (m, 4 H) 3,34 - 3,44 (m, 3 H) 3,53 - 3,65 (m, 1 H) 3,93 - 4,13 (m, 2 H) 6,91 (d, *J*=9,09 Hz, 2 H) 6,99 (d, *J*=2,02 Hz, 1 H) 7,62 (d, *J*=2,02 Hz, 1 H) 7,72 (d, *J*=9,09 Hz, 2 H) 7,89 (d, *J*=7,83 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{25}H_{32}N_6O_2$, 449; encontrado, 449.

Compuesto 13: (S)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida

Método A



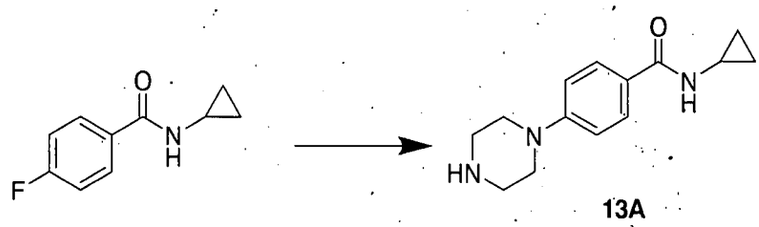
13

Se suspendieron el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoico (87 mg, 0,214 mmol) y la ciclopropanamina (18,29 mg, 0,320 mmol) en DMF (1 ml) y se trató con DIPEA (0,186 ml, 1,068 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]-piridin-3-il)-1,1,3,3-tetra-metil isouronio (162 mg, 0,427 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 horas y se purificó utilizando HPLC (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3) para proporcionar (S)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-

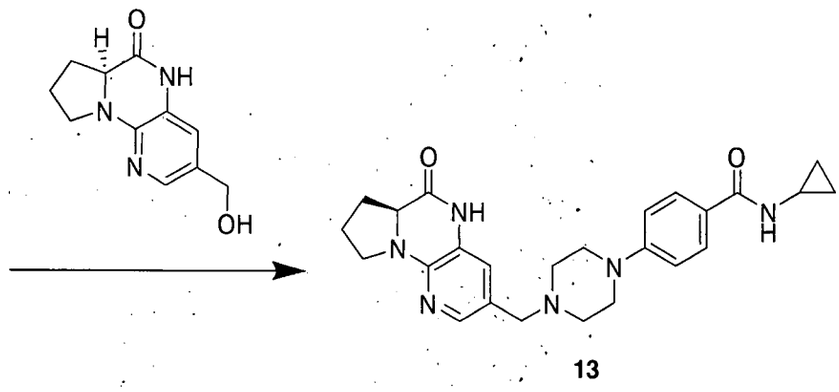
il)metil)piperazin-1-il)benzamida (43,0 mg, 0,096 mmol, rindiendo 45,1%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 0,46 - 0,59 (m, 2 H) 0,59 - 0,71 (m, 2 H) 1,82 - 2,02 (m, 3 H) 2,10 - 2,25 (m, 1 H) 2,46 (br. s., 4 H) 2,74 - 2,83 (m, 1 H) 3,21 (br. s., 4 H) 3,34 - 3,46 (m, 3 H) 3,53 - 3,64 (m, 1 H) 3,94 - 4,02 (m, 1 H) 6,91 (d, *J*=8,84 Hz, 2 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,61 (d, *J*=1,26 Hz, 1 H) 7,68 (d, *J*=8,84 Hz, 2 H) 8,13 (d, *J*=4,04 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{25}H_{30}N_6O_2$, 447; encontrado, 447; punto de fusión 265-268°C.

Método B



13A



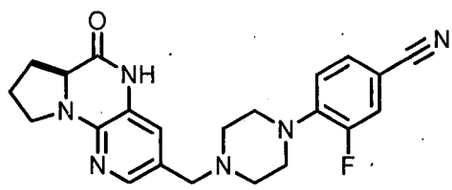
13

Compuesto 13A: N-ciclopropil-4-(piperazin-1-il)benzamida: Utilizando N-ciclopropil-4-fluorobenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, el compuesto del título se obtuvo (rindiendo 15%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,47 - 0,58 (m, 2 H) 0,58 - 0,73 (m, 2 H) 2,28 (br. s., 1 H) 2,70 - 2,88 (m, 5 H) 3,04 - 3,21 (m, 4 H) 6,90 (m, *J*=9,09 Hz, 2 H) 7,69 (m, *J*=8,84 Hz, 2 H) 8,12 (d, *J*=3,79 Hz, 1 H). ESI-MS: m/z 246,2 $(M+H)^+$. mp=175,1-177,2°C.

Compuesto 13: (S)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (300 mg, 1,368 mmol), N-ciclopropil-4-(piperazin-1-il)benzamida (336 mg, 1,368 mmol), yoduro de (cianometil)trimetilfosfonio (499 mg, 2,053 mmol) y N,N-diisopropiletilamina (1.195 µl, 6,84 mmol) en propionitrilo (Volumen: 4109 µl) y se calentó en un frasco cerrado a 120°C por 2 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (solución tampón de NH_4HCO_3, ACN en agua 20-70%). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (1:1, 15 mL), y luego de MeOH:EtOH:agua (1:1:1, 10 mL), se lavó con agua (3 mL) y se secó al vacío para proporcionar un sólido verde transparente.

Compuesto 14: (S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzonitrilo

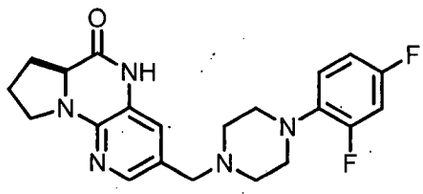


Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (150 mg, 0,684 mmol), 3-fluoro-4-(piperazin-1-il)benzonitrilo (140 mg, 0,684 mmol), yoduro de (cianometil)trimetilfosfonio (249 mg, 1,026 mmol) Y N,N-diisopropiletilamina (0,597 ml, 3,42 mmol) en propionitrilo (2 ml) y se calentó en un frasco cerrado a 90°C por 2 horas. La mezcla de reacción se volvió una solución transparente café oscura. Se enfrió a temperatura ambiente, se diluyó con DMSO (2 mL) y se purificó utilizando HPLC preparativa (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3). Las fracciones que contienen el producto se concentraron al vacío y cristalizaron con agua (3 mL). El precipitado se filtró y se secó al vacío para proporcionar (S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-

il)metil)piperazin-1-il)- benzonitrilo (60,2 mg, 0,148 mmol, rindiendo 21,65%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,83 - 2,03 (m, 3 H) 2,11 - 2,24 (m, 1 H) 2,44 - 2,49 (m, 4 H) 3,07 - 3,22 (m, 4 H) 3,34 - 3,42 (m, 3 H) 3,53 - 3,65 (m, 1 H) 3,93 - 4,03 (m, 1 H) 6,97 (d, *J*=2,02 Hz, 1 H) 7,11 (t, *J*=8,72 Hz, 1 H) 7,56 (dd, *J*=8,46, 1,64 Hz, 1 H) 7,61 (d, *J*=2,02 Hz, 1 H) 7,69 (dd, *J*=13,39, 2,02 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{22}H_{22}FN_6O$, 407; encontrado, 407; punto de fusión 226°C.

Compuesto 15: (S)-3-((4-(2,4-difluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]-pirazin-6(5H)-ona

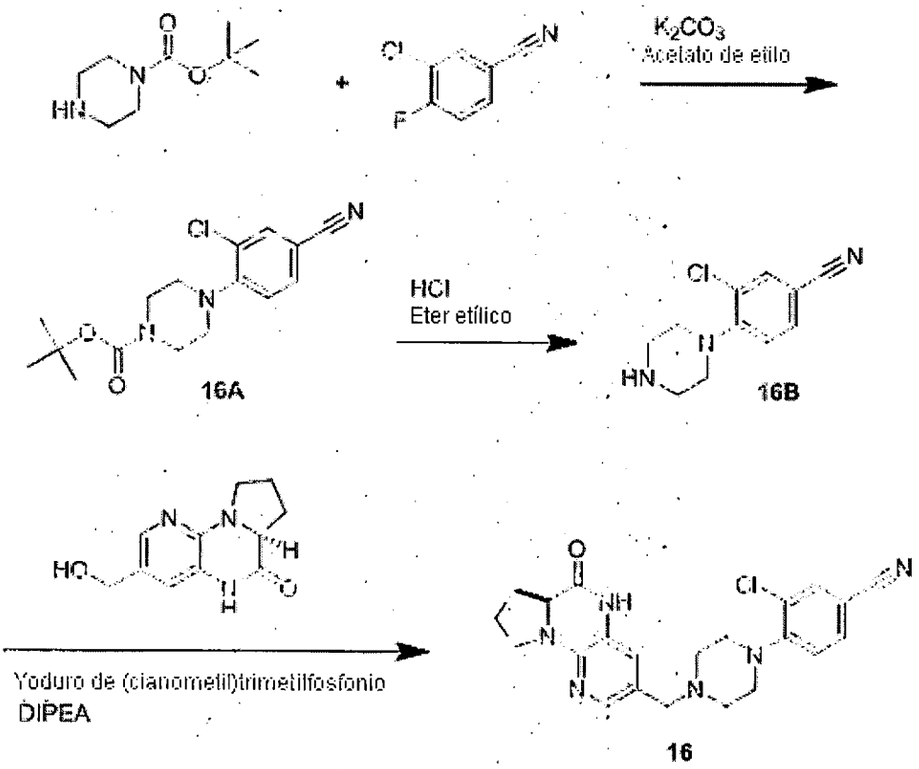


Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (150 mg, 0,684 mmol), 1-(2,4-difluorofenil)piperazina (136 mg, 0,684 mmol), yoduro de (cianometil)trimetilfosfonio (249 mg, 1,026 mmol) y N,N-diisopropiletilamina (0,597 ml, 3,42 mmol) en propionitrilo (2 ml) y se calentó en un frasco cerrado a 90°C por 2 horas. La mezcla de reacción se volvió una solución transparente café oscura. Se enfrió a temperatura ambiente, se diluyó con DMSO (2 mL) y se purificó utilizando HPLC preparativa (acetonitrilo en agua 25-95%, solución tampón de NH_4HCO_3). Las fracciones que contienen producto se concentraron al vacío y cristalizaron de agua (3 mL). El precipitado se filtró y se secó al vacío para proporcionar (S)-3-((4-(2,4-difluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona (63,2 mg, 0,158 mmol, rindiendo 23,13%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,84 - 2,03 (m, 3 H) 2,09 - 2,26 (m, 1 H) 2,41 - 2,49 (m, 4 H) 2,88 - 2,99 (m, 4 H) 3,34 - 3,43 (m, 3 H) 3,54 - 3,63 (m, 1 H) 3,94 - 4,02 (m, 1 H) 6,93 - 7,09 (m, 3 H)

7,18 (ddd, *J*=12,44, 9,16, 2,91 Hz, 1 H) 7,61 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{21}H_{23}F_2N_5O$, 400; encontrado, 400.

Compuesto 16: (S)-3-cloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzonitrilo



Compuesto 16A: 4-(2-cloro-4-cianofenil)piperazina-1-carboxilato de ter-butilo: Se combinaron piperazina-1-carboxilato de ter-butilo (0,931 g, 5 mmol) y 3-cloro-4-fluorobenzonitrilo (0,785 g, 5,00 mmol), se agregó K_2CO_3 (0,898 g, 6,50 mmol) y la mezcla de reacción se agitó a 90°C por 1 día. La mezcla se trituró con acetato de etilo (3 × 5 mL) y los extractos orgánicos combinados se filtraron. Ésta se concentró hasta alrededor de 5-10 mL y se sometió a cromatografía de columna evaporativa sobre sílica gel (SiO_2 120 g, hexanos:acetato de etilo 1:0 a 4:1) para proporcionar 4-(2-cloro-4-cianofenil)piperazina-1-carboxilato de ter-butilo (1,264 g, 3,93 mmol, rindiendo 79%) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,42 (s, 9 H) 3,00 - 3,09 (m, 4 H) 3,42 - 3,53 (m, 4 H) 7,25 (d, *J*=8,59 Hz, 1 H) 7,77 (dd, *J*=8,34, 2,02

Hz, 1 H) 7,97 (d, *J*=2,02 Hz, 1 H); [M+H] calculado para $C_{16}H_{20}ClN_3O_2$, 322; encontrado, 322.

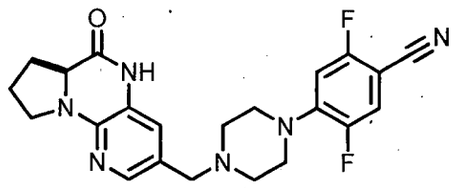
Compuesto 16B: clorhidrato de 3-cloro-4-(piperazin-1-il)-benzonitrilo: Se diluyó el 4-(2-cloro-4-cianofenil)piperazina-1-carboxilato de ter-butilo (0,322 g, 1 mmol) con HCl 4,0M en dioxano (3 mL) y se agitó por 30 minutos. El precipitado blanco grueso que se formó se diluyó con etil éter (10 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró bajo nitrógeno y se secó al vacío para proporcionar clorhidrato de 3-cloro-4-(piperazin-1-il)benzonitrilo (0,242 g, 0,937 mmol, rindiendo 94%) como un sólido blanco.

^{1}H NMR (400 MHz, DMSO-*d6*) δ (ppm): 3,14 - 3,29 (m, 4 H) 3,27 - 3,38 (m, 4 H) 7,33 (d, *J*=8,34 Hz, 1 H) 7,80 (dd, *J*=8,46, 1,89 Hz, 1 H) 8,02 (d, *J*=2,02 Hz, 1 H) 9,37 (br. s., 2 H); 4 H) 7,25 (d, *J*=8,59 Hz, 1 H) 7,77 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,97 (d, *J*=2,02 Hz, 1 H); [M+H] calculado para $C_{11}H_{12}ClN_3$, 222; encontrado, 222.

Compuesto 16: (S)-3-cloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de 3-cloro-4-(piperazin-1-il)benzonitrilo (118 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propionitrilo (2 ml) y se calentaron en un frasco cerrado a 90°C por 2 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (80g SiO_2, diclorometano-metanol 100:0-95:5). El sólido resultante se suspendió en éter (7 mL), se agitó hasta que resultó una suspensión fina, se filtró y el sólido se secó al vacío para proporcionar (S)-3-cloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo (135,4 mg, 0,320 mmol, rindiendo 70,2%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,80 - 2,03 (m, 3 H) 2,10 - 2,25 (m, 1 H) 2,39 - 2,61 (m, 4 H) 2,94 - 3,19 (m, 4 H) 3,35 - 3,46 (m, 3 H) 3,51 - 3,65 (m, 1 H) 3,91 - 4,05 (m, 1 H) 6,97 (d, *J*=1,77 Hz, 1 H) 7,22 (d, *J*=8,59 Hz, 1 H) 7,62 (d, *J*=1,52 Hz, 1 H) 7,74 (dd, *J*=8,46, 1,89 Hz, 1 H) 7,93 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H); [M+H] calculado para $C_{22}H_{23}ClN_6O$, 423; encontrado, 423; punto de fusión 213-215°C.

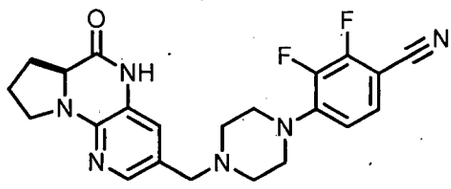
Compuesto 17: (S)-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo



El compuesto 17 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 2,4,5-trifluorobenzonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,81 - 2,01 (m, 3 H) 2,11 - 2,25 (m, 1 H) 2,47 (br. s., 4 H) 3,22 (br. s., 4 H) 3,34 - 3,44 (m, 3 H) 3,52 - 3,65 (m, 1 H) 3,92 - 4,05 (m, 1 H) 6,97 (d, *J*=1,52 Hz, 1 H) 7,08 (dd, *J*=12,00, 7,20 Hz, 1 H) 7,61 (d, *J*=1,52 Hz, 1 H) 7,77 (dd, *J*=13,14, 6,32 Hz, 1 H) 10,45 (s, 1 H); [M+H] calculado para $C_{22}H_{22}F_2N_6O$, 425; encontrado, 425; punto de fusión 224-227°C.

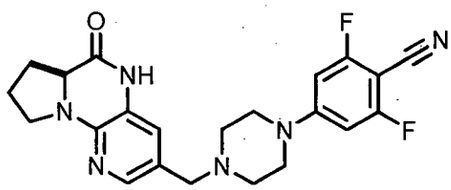
Compuesto 18: (S)-2,3-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo



El compuesto 18 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 2,3,4-trifluorobenzonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,82 - 2,03 (m, 3 H) 2,09 - 2,28 (m, 1 H) 2,38 - 2,49 (m, 4 H) 3,24 (br. s., 4 H) 3,34 - 3,45 (m, 3 H) 3,52 - 3,63 (m, 1 H) 3,93 - 4,03 (m, 1 H) 6,88 - 6,99 (m, 2 H) 7,52 - 7,63 (m, 2 H) 10,45 (s, 1 H); [M+H] calculado para $C_{22}H_{22}F_2N_6O$, 425; encontrado, 425.

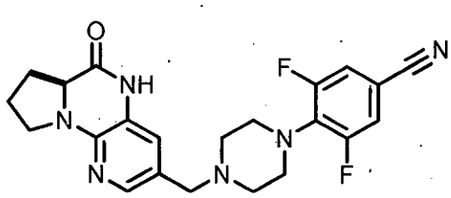
Compuesto 19: (S)-2,6-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo



El compuesto 19 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 2,4,6-trifluorobenzonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,83 - 2,04 (m, 3 H) 2,09 - 2,26 (m, 1 H) 2,33 - 2,47 (m, 4 H) 3,35 (s, 2 H) 3,37 - 3,49 (m, 5 H) 3,53 - 3,66 (m, 1 H) 3,94 - 4,06 (m, 1 H) 6,86 (d, *J*=12,63 Hz, 2 H) 6,97 (d, *J*=1,77 Hz, 1 H) 7,61 (d, *J*=1,52 Hz, 1 H) 10,45 (s, 1 H); [M+H] calculado para $C_{22}H_{22}F_2N_6O$, 425; encontrado, 425.

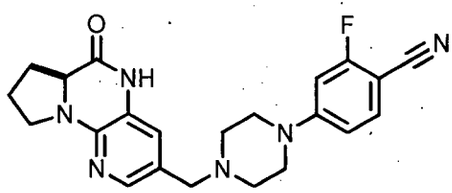
Compuesto 20: (S)-3,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo



El compuesto 20 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 3,4,5-trifluorobenzonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,81 - 2,04 (m, 3 H) 2,11 - 2,25 (m, 1 H) 2,43 (br. s., 4 H) 3,23 (br. s., 4 H) 3,34 - 3,47 (m, 3 H) 3,53 - 3,64 (m, 1 H) 3,94 - 4,01 (m, 1 H) 6,98 (d, *J*=1,52 Hz, 1 H) 7,61 (d, *J*=1,77 Hz, 1 H) 7,62 - 7,72 (m, 2 H) 10,43 (s, 1 H); [M+H] calculado para $C_{22}H_{22}F_2N_6O$, 425; encontrado, 425.

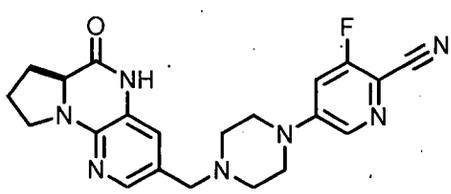
Compuesto 21: (S)-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzonitrilo



El compuesto 21 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 2,4-difluorobenzonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,84 - 2,01 (m, 3 H) 2,10 - 2,23 (m, 1 H) 2,36 - 2,47 (m, 4 H) 3,34 - 3,44 (m, 7 H) 3,54 - 3,63 (m, 1 H) 6,83 (dd, *J*=9,09, 2,53 Hz, 1 H) 6,93 (dd, *J*=14,27, 2,40 Hz, 1 H) 6,97 (d, *J*=2,02 Hz, 1 H) 7,55 - 7,62 (m, 2 H) 10,44 (s, 1 H); [M+H] calculado para $C_{22}H_{23}FN_6O$, 407; encontrado, 407; punto de fusión 251-255°C.

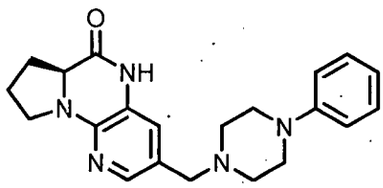
Compuesto 22: (S)-3-fluoro-5-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)picolinonitrilo



El compuesto 22 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 16, excepto que 3,5-difluoropicolinonitrilo se utilizó en lugar de 3-cloro-4-fluorobenzonitrilo.

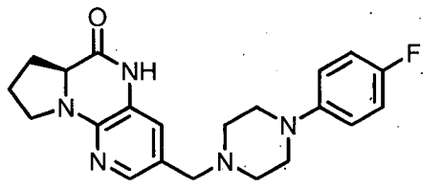
^{1}H NMR (400 MHz, DMSO-*d*6) δ (ppm): 1,83 - 2,02 (m, 3 H) 2,10 - 2,24 (m, 1 H) 2,35 - 2,47 (m, 4 H) 3,34 - 3,51 (m, 7 H) 3,52 - 3,65 (m, 1 H) 3,94 - 4,03 (m, 1 H) 6,97 (d, *J*=1,77 Hz, 1 H) 7,38 (dd, *J*=13,52, 2,15 Hz, 1 H) 7,61 (d, *J*=1,52 Hz, 1 H) 8,29 (s, 1 H) 10,45 (s, 1 H); [M+H] calculado para $C_{21}H_{22}FN_7O$, 408; encontrado, 408.

Compuesto 23: (S)-3-((4-fenilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



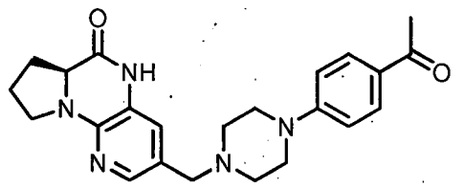
Se diluyeron el clorhidrato de 1-fenilpiperazina (11,9 mg, 0,060 mmol), yoduro de (cianometil)trimetilfosfonio (0,025 g, 0,102 mmoles), y (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (0,014 g, 0,063 mmoles) con propionitrilo (0,5 ml) y se trataron con DIPEA (0,017 ml, 0,100 mmol). La mezcla de reacción se agitó a 90°C durante la noche. La mezcla de reacción se lavó con agua (1 mL) y se concentró. El resíduo se disolvió en DMSO (1 mL) y se purificó utilizando HPLC (acetonitrilo-agua, solución tampón de NH_4HCO_3). Las fracciones se concentraron al vacío, se disolvieron en dioxano-agua (1:1:, 2 mL) y el liofilizado proporcionó el compuesto del título como un sólido blanco (5,1 mg, 23%). [M+H] calculado para $C_{21}H_{25}N_5O$ 364; encontrado, 364.

Compuesto 24: (S)-3-((4-(4-fluorofenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



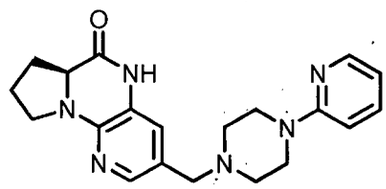
Se preparó el compuesto 24 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{24}FN_5O$ 382; encontrado, 382.

Compuesto 25: (S)-3-((4-(4-acetilfenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



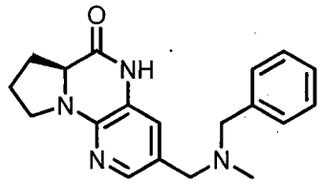
Se preparó el compuesto 25 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{23}H_{27}N_5O_2$ 406; encontrado, 406.

Compuesto 26: (S)-3-((4-(piridin-2-il)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



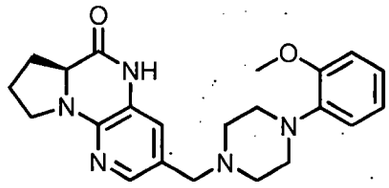
Se preparó el compuesto 26 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{20}H_{24}N_6O$ 365; encontrado, 365.

Compuesto 27: (S)-3-((bencil(metil)amino)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



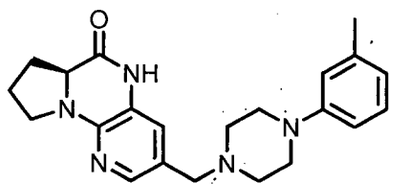
Se preparó el compuesto 27 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{19}H_{22}N_4O$ 323; encontrado, 323.

Compuesto 28: (S)-3-((4-(3-metoxifenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



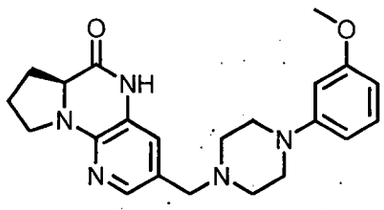
Se preparó el compuesto 28 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{27}N_5O_2$ 394; encontrado, 394.

Compuesto 29: (S)-3-((4-m-tolilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



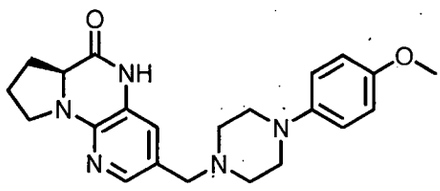
Se preparó el compuesto 29 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{27}N_5O$ 378; encontrado, 378.

Compuesto 30: (S)-3-((4-(3-metoxifenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



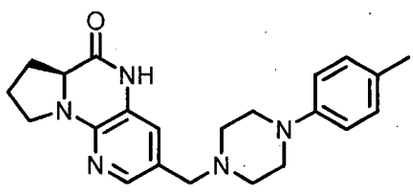
Se preparó el compuesto 30 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{27}N_5O_2$ 394; encontrado, 394.

Compuesto 31: (S)-3-((4-(4-metoxifenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



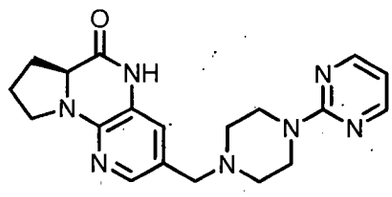
Se preparó el compuesto 31 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{27}N_5O_2$ 394; encontrado, 394.

Compuesto 32: (S)-3-((4-p-tolilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



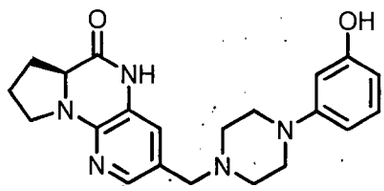
Se preparó el compuesto 32 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{27}N_5O$ 378; encontrado, 378.

Compuesto 33: (S)-3-((4-(pirimidin-2-il)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



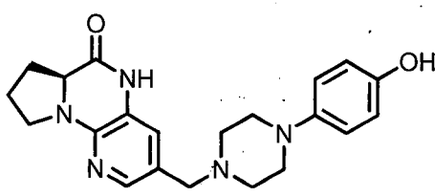
Se preparó el compuesto 33 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{19}H_{23}N_7O$ 366; encontrado, 366.

Compuesto 34: (S)-3-((4-(3-hidroxifenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



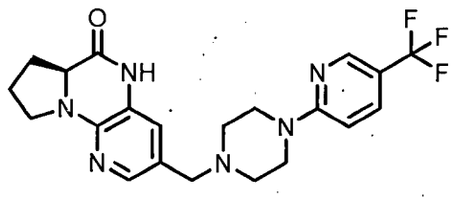
Se preparó el compuesto 34 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{25}N_5O_2$ 380; encontrado, 380.

Compuesto 35: (S)-3-((4-(4-hidroxifenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



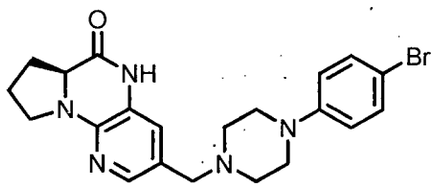
Se preparó el compuesto 35 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{25}N_5O_2$ 380; encontrado, 380.

Compuesto 36: (S)-3-((4-(5-(trifluorometil)piridin-2-il)-piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]- pirrolo[1,2-a]pirazin-6(5H)-ona



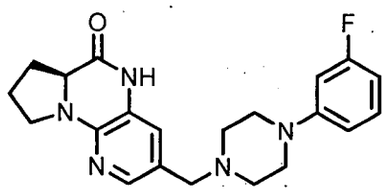
Se preparó el compuesto 36 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{23}F_3N_6O$ 433; encontrado, 433.

Compuesto 37: (S)-3-((4-(4-bromofenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]-pirazin-6(5H)-ona



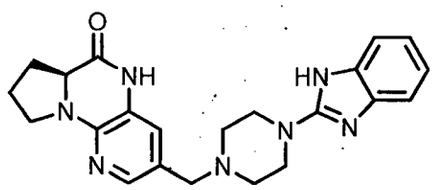
Se preparó el compuesto 37 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{24}BrN_5O$ 444; encontrado, 444.

Compuesto 38: (S)-3-((4-(3-fluorofenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



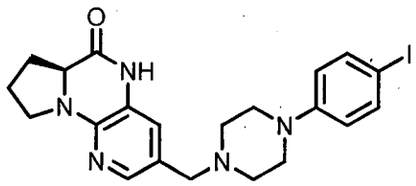
Se preparó el compuesto 38 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{24}FN_5O$ 382; encontrado, 382.

Compuesto 39: (S)-3-((4-(1H-benzo[d]imidazol-2-il)-piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]- pirrolo[1,2-a]pirazin-6(5H)-ona



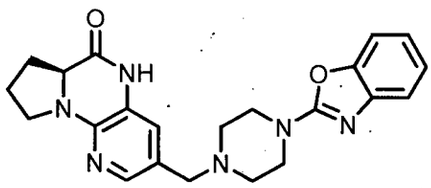
Se preparó el compuesto 39 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{25}N_7O$ 404; encontrado, 404.

Compuesto 40: (S)-3-((4-(4-yodofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



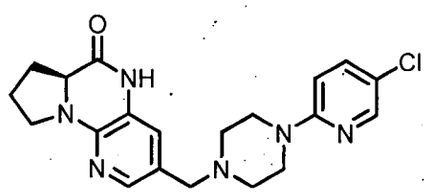
Se preparó el compuesto 40 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{24}IN_5O$ 490; encontrado, 490.

Compuesto 41: (S)-3-((4-(benzo[d]oxazol-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



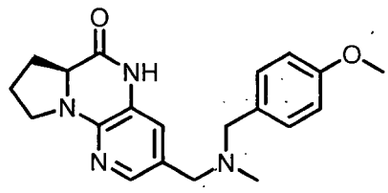
Se preparó el compuesto 41 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{24}N_6O_2$ 405; encontrado, 405.

Compuesto 42: (S)-3-((4-(5-cloropiridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



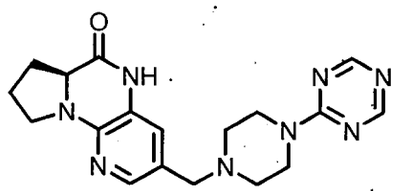
Se preparó el compuesto 42 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{20}H_{23}ClN_6O$ 399; encontrado, 399.

Compuesto 43: (S)-3-(((4-metoxibencil)(metil)amino)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



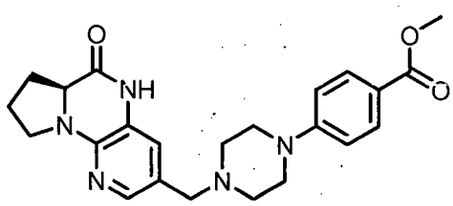
Se preparó el compuesto 43 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{20}H_{24}N_4O_2$ 353; encontrado, 353.

Compuesto 44: (S)-3-((4-(1,3,5-triazin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



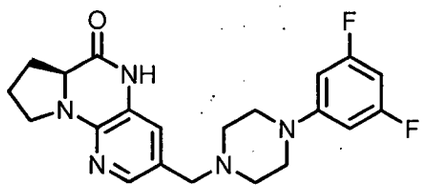
Se preparó el compuesto 44 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{18}H_{22}N_8O$ 367; encontrado, 367.

Compuesto 45: (S)-metil 4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzoato



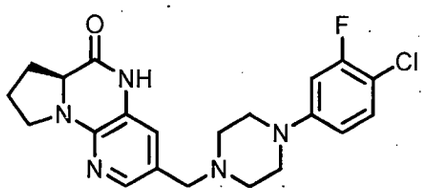
Se preparó el compuesto 45 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{23}H_{27}N_5O_3$ 422; encontrado, 422.

Compuesto 46: (S)-3-((4-(3,5-difluorofenil)piperazin-1-il)-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



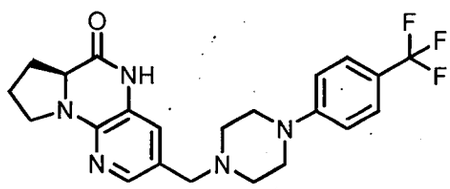
Se preparó el compuesto 46 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{23}F_2N_5O$ 400; encontrado, 400.

Compuesto 47: (S)-3-((4-(4-cloro-3-fluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



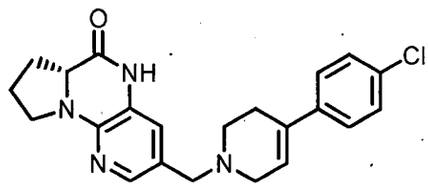
Se preparó el compuesto 47 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{21}H_{23}ClFN_5O$ 416; encontrado, 416.

Compuesto 48: (S)-3-((4-(4-(trifluorometil)fenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



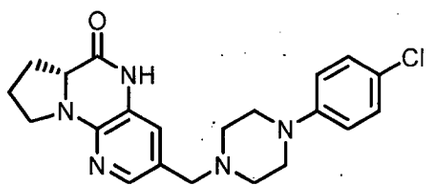
Se preparó El compuesto 48 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{22}H_{24}F_3N_5O$ 432; encontrado, 432.

Compuesto 49: (R)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo- [1,2-a]pirazin-6(5H)-ona



Se preparó el compuesto 49 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 2, excepto que se utilizó el pirrolidin-2-carboxilato de (R)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,43 (s, 1H), 7,62 (d, J = 1,8 Hz, 1H), 7,40 - 7,48 (m, 2H), 7,29 - 7,40 (m, 2H), 6,99 (d, J = 1,8 Hz, 1H), 6,18 (br. s., 1H), 3,91 - 4,06 (m, 1H), 3,52 - 3,67 (m, 1H), 3,40 - 3,49 (m, 3H), 3,01 (d, J = 2,3 Hz, 2H), 2,56 - 2,65 (m, 2H), 2,43 (br. s., 2H), 2,10 - 2,24 (m, 1H), 1,77 - 2,01 (m, 3H); [M+H] calculado para $C_{22}H_{23}ClN_4O$, 395; encontrado, 395.

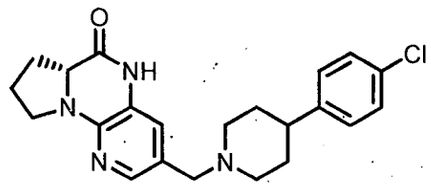
Compuesto 50: (R)-3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



Se preparó el compuesto 50 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el pirrolidin-2-carboxilato de (R)-metilo en lugar de (S)-metil pirrolidin-2-carboxilato.

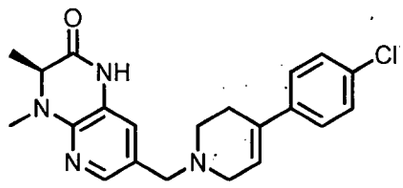
^{1}H NMR (DMSO-d_6) δ (ppm): 10,43 (s, 1H), 7,61 (d, J = 1,5 Hz, 1H), 7,21 (d, J = 8,8 Hz, 2H), 6,98 (d, J = 1,8 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 3,89 - 4,05 (m, 1H), 3,52 - 3,66 (m, 1H), 3,37 - 3,48 (m, 3H), 3,10 (br. s., 4H), 2,46 (d, J = 4,5 Hz, 4H), 2,07 - 2,25 (m, 1H), 1,78 - 2,04 (m, 3H); [M+H] calculado para $C_{21}H_{24}ClN_5O$, 398; encontrado, 398.

Compuesto 51: (R)-3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]- pirazin-6(5H)-ona



Se preparó el compuesto 51 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 3, excepto que se utilizó el pirrolidin-2-carboxilato de (R)-metilo en lugar de pirrolidin-2-carboxilato (S)-metilo. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,42 (s, 1H), 7,60 (d, J = 1,8 Hz, 1H), 7,29 - 7,37 (m, 2H), 7,19 - 7,29 (m, 2H), 6,97 (d, J = 1,8 Hz, 1H), 3,90 - 4,05 (m, 1H), 3,51 - 3,65 (m, 1H), 3,35 - 3,45 (m, 1H), 2,88 (d, J = 10,9 Hz, 2H), 2,08 - 2,25 (m, 1H), 1,82 - 2,05 (m, 5H), 1,64 - 1,78 (m, 2H), 1,48 - 1,64 (m, 2H); [M+H] calculado para $C_{22}H_{25}ClN_4O$, 397; encontrado, 397.

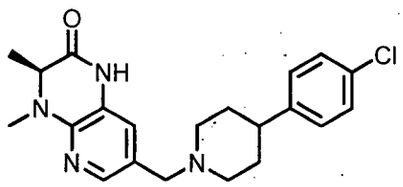
Compuesto 52: (S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]- pirazin-2(1H)-ona



Se preparó el compuesto 52 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 2, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de (S)-metil pirrolidin-2-carboxilato de (S)-metilo.

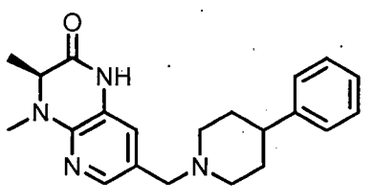
^{1}H NMR (CLOROFORMo-d) δ (ppm): 7,80 (d, J = 1,8 Hz, 1H), 7,60 (br. s., 1H), 7,28 - 7,33 (m, 4H), 6,96 - 7,06 (m, 1H), 6,01 - 6,08 (m, 1H), 4,13 (q, J = 6,6 Hz, 1H), 3,47 - 3,58 (m, J = 3,3 Hz, 2H), 3,18 (d, J = 2,3 Hz, 2H), 3,08 (s, 3H), 2,69 - 2,79 (m, 2H), 2,55 (br. s., 2H), 1,36 (d, J = 7,1 Hz, 3H); [M+H] calculado para $C_{21}H_{23}ClN_4O$, 383; encontrado, 383.

Compuesto 53: (S)-7-((4-(4-clorofenil)piperidin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona



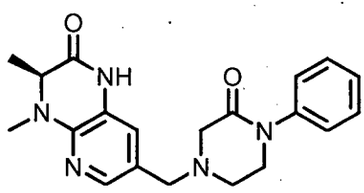
Se preparó el compuesto 53 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 3, excepto que se utilizó el 2-(metilámino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de(S)-metilo. ^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,82 - 7,94 (m, 1H), 7,78 (d, J = 1,8 Hz, 1H), 7,27 (d, J = 8,6 Hz, 2H), 7,15 (d, J = 8,3 Hz, 2H), 7,00 (br. s., 1H), 4,13 (q, J = 7,0 Hz, 1H), 3,48 (br. s., 2H), 3,08 (s, 5H), 2,51 (br. s., 1H), 2,14 (d, J = 2,0 Hz, 2H), 1,81 (br. s., 4H), 1,37 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{21}H_{25}ClN_4O$, 385; encontrado, 385.

Compuesto 54: (S)-3,4-dimetil-7-((4-fenilpiperidin-1-il)metil)-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona



Se preparó el compuesto 54 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo y 4-fenilpiperidina se utilizó en lugar de 1-(4-clorofenil)piperazina.
^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1,23 (d, *J*=6,82 Hz, 3 H) 1,82 (m, *J*=13,89 Hz, 2 H) 2,00 (d, *J*=12,88 Hz, 2 H) 2,74 - 2,85 (m, 1 H) 2,94 - 3,11 (m, 5 H) 3,47 (t, *J*=13,77 Hz, 2 H) 4,22 (d, *J*=5,05 Hz, 2 H) 7,06 (d, *J*=2,27 Hz, 1 H) 7,18 - 7,26 (m, 3 H) 7,29 - 7,36 (m, 2 H) 7,85 (d, *J*=2,02 Hz, 1 H) 9,30 (br. s., 1 H) 10,83 (s, 1 H); [M+H] calculado para $C_{21}H_{26}N_4O$, 351; encontrado, 351.

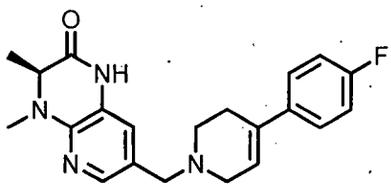
Compuesto 55: (S)-3,4-dimetil-7-((3-oxo-4-fenilpiperazin-1-il)metil)-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona



Se preparó el compuesto 55 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo y se utilizó 1-fenilpiperazin-2-ona en lugar de 1-(4-clorofenil)piperazina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,81 (d, J = 1,8 Hz, 1H), 7,68 (s, 1H), 7,37 - 7,45 (m, 2H), 7,29 (d, J = 8,1 Hz, 3H), 6,93 (d, J = 1,8 Hz, 1H), 4,14 (q, J = 6,8 Hz, 1H), 3,70 (t, J = 5,3 Hz, 2H), 3,51 (s, 2H), 3,26 - 3,38 (m, 2H), 3,08 (s, 3H), 2,83 (t, J = 5,4 Hz, 2H), 1,38 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{20}H_{23}N_5O_2$, 366; encontrado, 366.

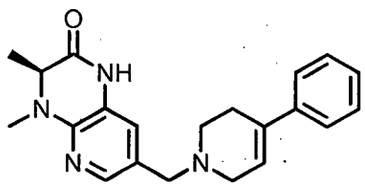
Compuesto 56: (S)-7-((4-(4-fluorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]- pirazin-2(1H)-ona



Se preparó el compuesto 56 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo y se utilizó 4-(4-fluorofenil)-1,2,3,6-tetrahidropiridina en lugar de 1-(4-clorofenil)piperazina.

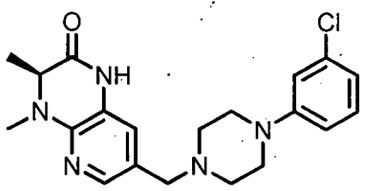
^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,26 (s, 1H), 7,80 (d, J = 2,0 Hz, 1H), 7,29 - 7,38 (m, 2H), 6,93 - 7,05 (m, 3H), 5,95 - 6,03 (m, 1H), 4,08 - 4,17 (m, 1H), 3,46 - 3,55 (m, 2H), 3,14 (d, J = 2,8 Hz, 2H), 3,07 (s, 3H), 2,66 - 2,75 (m, 2H), 2,48 - 2,57 (m, 2H), 1,35 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{21}H_{23}FN_4O$, 367; encontrado, 367.

Compuesto 57: (S)-3,4-dimetil-7-((4-fenil5,6-dihidro piridin-1(2H)-il)metil)-3,4-dihidropirido[3,2-b]-pirazin-2(1H)-ona



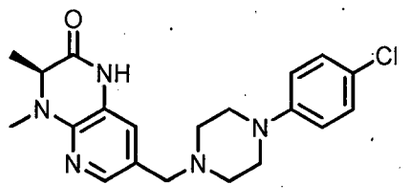
Se preparó el compuesto 57 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo y 4-fenil-1,2,3,6-tetrahidropiridina se utilizó en lugar de 1-(4-clorofenil)piperazina. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,49 (s, 1H), 7,68 (d, J = 1,5 Hz, 1H), 7,41 (d, J = 7,3 Hz, 2H), 7,32 (t, J = 7,6 Hz, 2H), 7,17 - 7,27 (m, 1H), 7,00 (d, J = 1,8 Hz, 1H), 6,13 (br. s., 1H), 4,05 (q, J = 6,8 Hz, 1H), 3,43 (q, J = 12,9 Hz, 2H), 3,02 (d, J = 2,5 Hz, 2H), 2,94 (s, 3H), 2,57 - 2,65 (m, 2H), 2,47 (br. s., 2H), 1,17 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{21}H_{24}N_4O$, 349; encontrado, 349.

Compuesto 58: (S)-7-((4-(3-clorofenil)piperazin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona



Se preparó el compuesto 58 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carboxilato de (S)-metilo y se utilizó 1-(3-clorofenil)piperazina en lugar de 1-(4-clorofenil)piperazina. ^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,79 (d, J = 1,5 Hz, 1H), 7,68 (br. s., 1H), 7,17 (t, J = 8,1 Hz, 1H), 6,89 - 7,06 (m, 1H), 6,87 (d, J = 2,0 Hz, 1H), 6,82 (d, J = 7,8 Hz, 1H), 6,78 (dd, J = 8,3, 2,0 Hz, 1H), 4,13 (q, J = 6,8 Hz, 1H), 3,45 (br. s., 2H), 3,21 (br. s., 4H), 3,08 (s, 3H), 2,60 (br. s., 4H), 1,37 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{20}H_{24}ClN_5O$, 386; encontrado, 386.

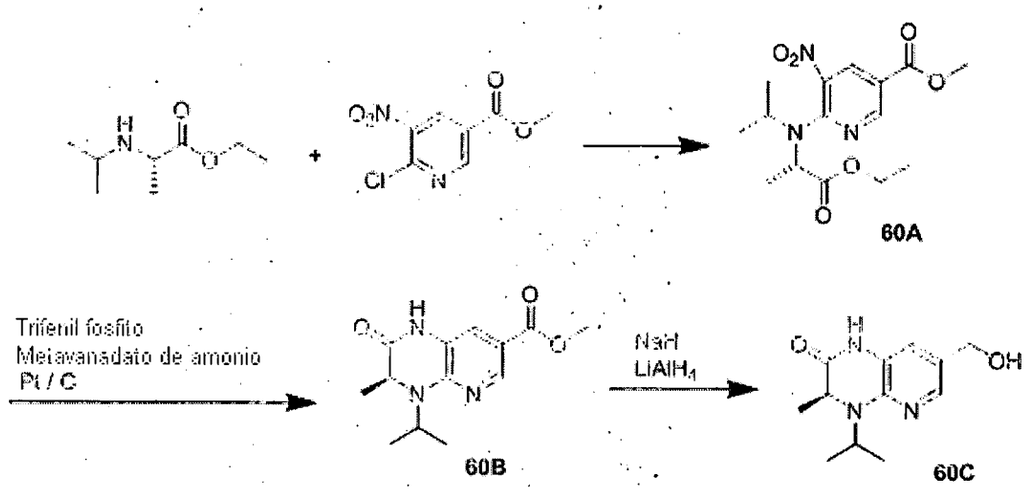
Compuesto 59: (S)-7-((4-(4-clorofenil)piperazin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona

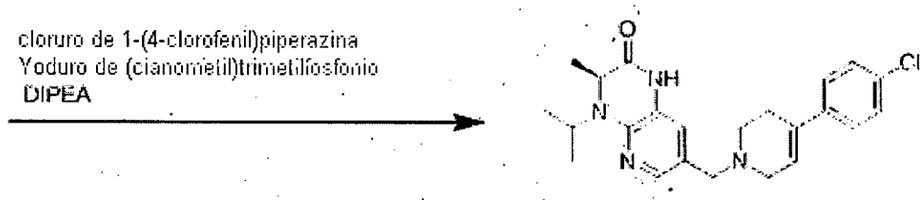


se preparó el compuesto 59 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó el 2-(metilamino)propanoato de (S)-metilo en lugar de pirrolidin-2-carbonilato de (S)-metilo y 1-(4-clorofenil)piperazina se utilizó en lugar de 1-(4-clorofenil)piperazina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,79 (d, J = 1,8 Hz, 1H), 7,72 - 7,78 (m, 1H), 7,17 - 7,24 (m, 2H), 6,89 - 7,02 (m, 1H), 6,79 - 6,88 (m, 2H), 4,13 (q, J = 7,0 Hz, 1H), 3,45 (br. s., 2H), 3,17 (br. s., 4H), 3,08 (s, 3H), 2,60 (br. s., 4H), 1,37 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{20}H_{24}ClN_5O$, 386; encontrado, 386.

Compuesto 60: (S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona





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Compuesto 60A: 6-((1-etoxi-1-oxopropan-2-il)(isopropil)- amino)-5-nitronicotinato de (S)-metilo: Se agregó 2-(isopropilamino)propanoato de (S)-etilo (2,83 g, 17,8 mmol) a 6-cloro-5-nitronicotinato de metilo (1,72 g, 7,94 mmol) y la mezcla de reacción se agitó en un frasco cerrado a 90°C por 20 horas. Se enfrió y se diluyó con EtOAc (25 mL). El precipitado resultante se recoge de la filtración, el filtrado se concentró al vacío y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (SiO_2 220 g, hexanos:acetato de etilo 4:1) para proporcionar el compuesto del título como un aceite amarillo (1,12 g, 42%). ^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ (ppm): 1,18 (t, *J*=7,07 Hz, 3 H) 1,30 (d, *J*=6,32 Hz, 3 H) 1,36 (d, *J*=6,57 Hz, 3 H) 1,66 (d, *J*=6,82 Hz, 3 H) 3,48 - 3,62 (m, 1 H) 3,90 (s, 3 H) 4,03 (q, *J*=6,65 Hz, 1 H) 4,06 - 4,21 (m, 2 H) 8,54 (d, *J*=2,02 Hz, 1 H) 8,70 (d, *J*=2,02 Hz, 1 H); [M+H] calculado para $C_{15}H_{21}N_3O_6$, 340; encontrado, 340.

Compuesto 60B: 4-isopropil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[3,2-b]pirazin-7-carboxilato de (S)-metilo: Se disolvió 6-((1-etoxi-1-oxopropan-2-il)(isopropil)amino)-5-nitronicotinato de (S)-metilo (0,900 g, 2,65 mmol) en diclorometano (10 mL). A ésta solución se agregó trifenil fosfito (3,0 mg, 9,7 umol), metavanadato de amonio (30 mg, 0,265 mmol) y Pt/C (5% en peso, 0,120 g). La mezcla de reacción se hidrogenó a 80 psi a 25°C por 6 horas. La mezcla se filtró a través de un pequeño lecho de celite y el lecho se lavó con diclorometano (20 mL). Los filtrados combinados se concentraron al vacío y cristalizaron con etil éter para proporcionar el compuesto del título como un sólido blanco (0,658 g, 94%).

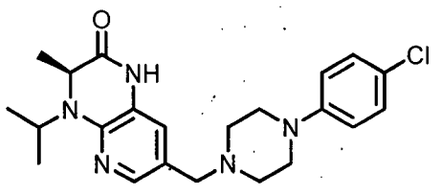
^{1}H NMR (400 MHz, CLOROFORMO-*d*) δ (ppm): 1,33 (d, *J*=6,82 Hz, 3 H) 1,36 - 1,41 (m, 6 H) 3,90 (s, 3 H) 4,34 (q, *J*=6,65 Hz, 1 H) 4,86 (m, 1 H) 7,52 (d, *J*=1,77 Hz, 1 H) 8,59 (d, *J*=1,77 Hz, 1 H) 8,73 (br. s., 1 H); [M+H] calculado para $C_{13}H_{17}N_3O_3$, 264; encontrado, 264.

Compuesto 60C: (S)-7-(hidroximetil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona: Se disolvió 4-isopropil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[3,2-b]pirazin-7-carboxilato de (S)-metilo (0,649 g, 2,46 mmol) en THF (8 mL) y se enfrió a 0°C bajo atmósfera de nitrógeno. Se agregó en una porción hidruro de sodio (suspensión en aceite mineral al 60%, 0,112 g, 2,80 mmol). La mezcla de reacción se dejó enfriar a temperatura ambiente y se agitó por 30 minutos. Luego se enfrió a -0°C y se agregó gota a gota $LiAlH_4$ (1M en THF, 9,80 mL, 9,80 mmol) durante 10 minutos. La mezcla de reacción se mantuvo a -30-(-20)°C por 1 hora, se enfrió por debajo de -50°C y lentamente se detuvo con MeOH (5 mL). La solución resultante se calentó a temperatura ambiente y se sometió a HPLC preparativa (acetonitrilo en agua 1-30%, solución tamponada de TFA) para proporcionar el compuesto del título como un sólido gris (sal de TFA, 450 mg, 52%). [M+H] calculado para $C_{12}H_{17}N_3O_2$, 236; encontrado, 236.

Compuesto 60: (S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona: El compuesto 60 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1D, excepto que se utilizó el (S)-7-(hidroximetil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona en lugar de (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona y se utilizó 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina en lugar de 1-(4-clorofenil)piperazina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,33 (s, 1H), 7,84 (d, J = 1,8 Hz, 1H), 7,21 - 7,36 (m, 4H), 7,04 (d, J = 1,5 Hz, 1H), 6,06 (br. s., 1H), 4,64 - 4,84 (m, 1H), 4,28 (q, J = 6,7 Hz, 1H), 3,52 (s, 2H), 3,05 - 3,27 (m, 2H), 2,65 - 2,79 (m, 2H), 2,54 (br. s., 2H), 1,37 (d, J = 6,8 Hz, 3H), 1,25 - 1,33 (m, 6H); [M+H] calculado para $C_{23}H_{27}ClN_4O$, 411; encontrado, 411.

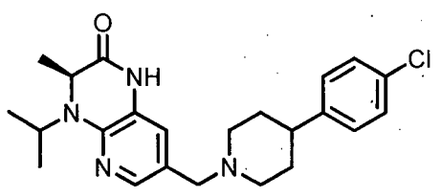
Compuesto 61: (S)-7-((4-(4-clorofenil)piperazin-1-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]- pirazin-2(1H)-ona



Se preparó el compuesto 61 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 60, excepto que se utilizó el 1-(4-clorofenil)piperazina en lugar de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,58 (s, 1H), 7,83 (d, J = 2,0 Hz, 1H), 7,17 - 7,23 (m, 2H), 7,00 (d, J = 2,0 Hz, 1H), 6,80 - 6,86 (m, 2H), 4,67 - 4,81 (m, 1H), 4,28 (q, J = 6,7 Hz, 1H), 3,45 (s, 2H), 3,12 - 3,21 (m, 4H), 2,54 - 2,66 (m, 4H), 1,37 (d, J = 6,8 Hz, 3H), 1,32 (d, J = 6,8 Hz, 3H), 1,29 (d, J = 7,1 Hz, 3H); [M+H] calculado para $C_{22}H_{28}ClN_5O$, 414; encontrado, 414.

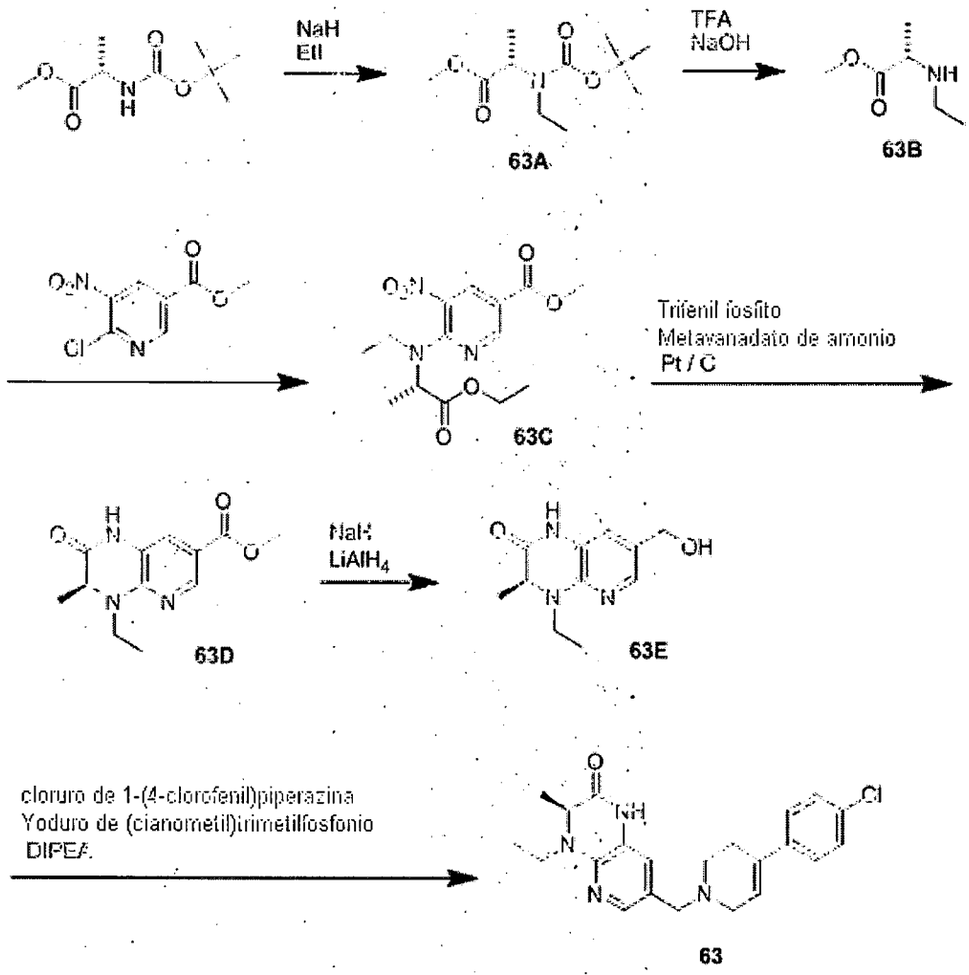
Compuesto 62: (S)-7-((4-(4-clorofenil)piperidin-1-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]- pirazin-2(1H)-ona



Se preparó el compuesto 62 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 60, excepto que se utilizó el 4-(4-clorofenil)piperidina en lugar de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,15 (s, 1H), 7,82 (d, J = 2,0 Hz, 1H), 7,22 - 7,30 (m, 2H), 7,13 - 7,19 (m, 2H), 7,00 (s, 1H), 4,66 - 4,82 (m, 1H), 4,28 (q, J = 6,8 Hz, 1H), 3,43 (s, 2H), 3,01 (br. s., 2H), 2,41 - 2,56 (m, 1H), 2,08 (t, J = 11,4 Hz, 2H), 1,57 - 1,87 (m, 4H), 1,36 (d, J = 6,8 Hz, 3H), 1,31 (d, J = 6,8 Hz, 3H), 1,29 (d, J = 6,8 Hz, 3H); [M+H] calculado para $C_{23}H_{29}ClN_4O$, 413; encontrado, 413.

Compuesto 63: (S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-etil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona



El compuesto 63A: 2-(ter-butoxicarbonil(etil)amino) propanoato de (S)-metilo: Se disolvió 2-(ter-butoxicarbonilamino)-propanoato de (S)-metilo (10,0 g, 49,2 mmol) en THF (100 mL) y se enfrió a 0°C bajo nitrógeno. Se agregó el hidruro de sodio en porciones (suspensión en aceite mineral al 60%, 3,00 g, 75,1 mmol) durante dos minutos. La mezcla de reacción se agitó por 5 minutos a 0°C y se agregó EtI (4,80 mL, 59,5 mmol). Se dejó enfriar a temperatura ambiente durante el periodo de 1 hora, se agitó a temperatura ambiente durante la noche y a 70°C por 7 días. La mezcla de reacción se enfrió, se filtró y se concentró al vacío. El sólido se trituró con hexanos (2 × 70 mL), los triturados se concentraron al vacío y el resíduo se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (SiO_2 330 g, hexanos:acetato de etilo 19:1-9:1) para proporcionar el compuesto del título como un aceite (4,40 g, 39%). [M+H] calculado para $C_{11}H_{21}NO_4$, 232; encontrado, 232.

Compuesto 63B: 2-(etilamino)propanoato de (S)-metilo: Se disolvió el 2-(ter-butoxicarbonil(etil)amino)propanoato de (S)-metilo (4,40 g, 19,0 mmol) en diclorometano y se trató con TFA (10 mL). La mezcla de reacción se agitó por 2 horas a temperatura ambiente y se concentró al vacío. El resíduo se diluyó con salmuera y NaOH (50% acuoso) se agregó gota a gota hasta pH = 12,5. Esto se extrajo con EtOAc (3 × 30 mL). Los extractos orgánicos combinados se secaron con ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar el compuesto del título como un líquido no transparente (1,85 g, 74%). [M+H] calculado para $C_6H_{13}NO_2$, 132; encontrado, 132.

Compuesto 63C: 6-((1-etoxi-1-oxopropan-2-il)(etil)amino)-5-nitronicotinato de (S)-metilo: Se agregó 2-(etilamino)propanoato de (S)-metilo (1,83 g, 14,0 mmol) a 6-cloro-5-nitronicotinato de metilo (1,30 g, 6,00 mmol) y la mezcla de reacción se agitó en un frasco cerrado a 90°C por 1 hora. Se enfrió y se diluyó con EtOAc (25 mL). El precipitado resultante se recogió por filtración, el filtrado se concentró al vacío y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (SiO_2 220 g, acetato de etilo en hexanos 0-50%) para proporcionar el compuesto del título como un aceite amarillo (1,23 g, 66%). [M+H] calculado para $C_{14}H_{19}N_3O_6$, 326; encontrado, 326.

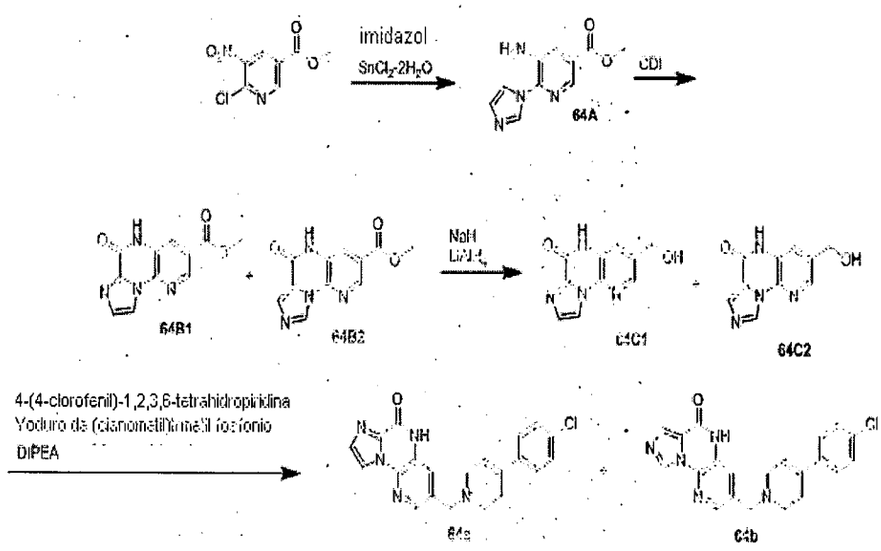
Compuesto 63D: 4-etil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de (S)-metilo: Se disolvió el 6-((1-etoxi-1-oxopropan-2-il)(etil)amino)-5-nitronicotinato de (S)-metilo (1,22 g, 3,92 mmol) en diclorometano (12 mL). A ésta solución se agregaron trifenil fosfito (5,0 mg, 16 umol), metavanadato de amonio (50,0 mg, 0,427 mmol) y Pt/C (5% en peso, 0,200 g). La mezcla de reacción se hidrogenó a 100 psi a 25°C por 18 horas. La mezcla se filtró a través de un pequeño lecho de celite y el lecho se lavó con diclorometano (20 mL). Los filtrados combinados se concentraron al vacío y se cristalizaron con etil éter (50 mL) para proporcionar el compuesto del título como un sólido blanco (0,560 g, 57%). [M+H] calculado para $C_{12}H_{15}N_3O_3$, 250; encontrado, 250.

Compuesto 63E: (S)-4-etil-7-(hidroximetil)-3-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se disolvió el 4-etil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de (S)-metilo (0,560 g, 2,25 mmol) en THF (5 mL) y se enfrió a 0°C bajo atmósfera de nitrógeno. Se agregó hidruro de sodio en una porción (suspensión en aceite mineral al 60%, 0,135 g, 3,38 mmol). La mezcla de reacción se dejó enfriar a temperatura ambiente y se agitó por 30 minutos. Luego se enfrió a -50°C y se agregó gota a gota $LiAlH_4$ (2M en THF, 3,40 mL, 6,80 mmol) durante 10 minutos. La mezcla de reacción se mantuvo a -30-(-20)°C por 1 hora, se enfrió por debajo de -50°C y lentamente se detuvo con MeOH (5 mL). La solución resultante se calentó a temperatura ambiente y se sometió a HPLC preparativa (acetonitrilo en agua 1-30%, solución tampón de TFA) para proporcionar el compuesto del título como un aceite oscuro (sal de TFA, 0,587 mg, 78%). [M+H] calculado para $C_{11}H_{15}N_3O_2$, 222; encontrado, 222.

Compuesto 63: (S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-etil-3-metil-3,4-dihidropirido[3,2-b]- pirazin-2(1H)-ona: Se preparó el compuesto 63 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1D, excepto que se utilizó el (S)-4-etil-7-(hidroximetil)-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona en lugar de (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona y se utilizó 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina en lugar de 1-(4-clorofenil)piperazina.
^1H NMR (CLOROFORMO-d) δ (ppm): 7,79 (d, J = 1,5 Hz, 1H), 7,68 (br. s., 1H), 7,27 - 7,34 (m, 4H), 7,02 (s, 1H), 6,06 (br. s., 1H), 4,21 (q, J = 6,8 Hz, 1H), 3,98 - 4,12 (m, 1H), 3,44 - 3,61 (m, 2H), 3,07 - 3,26 (m, 3H), 2,75 (t, J = 5,2 Hz, 2H), 2,55 (br. s., 2H), 1,36 (d, J = 6,8 Hz, 3H), 1,26 (t, J = 7,2 Hz, 3H); [M+H] calculado para $C_{22}H_{25}ClN_4O$, 397; encontrado, 397.

Compuestos 64a y 64b: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)imidazo[1,2-a]pirido[3,2-e]pirazin-6(5H)-ona y 3-((4-(4-

clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-imidazo[1,5-a]pirido[3,2-e]pirazin-6(5H)-ona



Compuesto 64A: 5-amino-6-(1H-imidazol-1-il)nicotinato de metilo: Se disolvió el 6-cloro-5-nitronicotinato de metilo (2,17 g, 10,0 mmol) en acetato de etilo (55 mL) y se agregó imidazol (4,09 g, 60 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 horas y se trató con $SnCl_2$-$2H_2O$ (13,5 g, 60,0 mmol). Se calentó a 70°C por 2 horas, se diluyó con carbonato de potasio (saturado, acuoso) y se extrajo con acetato de etilo (5 × 20 mL). Los extractos orgánicos combinados se secaron con ($MgSO_4$), se filtraron y se concentraron al vacío para proporcionar el compuesto del título como un sólido amarillo crudo, el cual se utilizó en la siguiente etapa sin posterior purificación. [M+H] calculado para $C_{10}H_{10}N_4O_2$, 219; encontrado, 219.

Compuestos 64B1 y 64B2: 6-oxo-5,6-dihidroimidazo[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de metilo y 6-oxo-5,6-dihidroimidazo[1,5-a]pirido[3,2-e]pirazin-3-carboxilato de metilo: Se suspendió el 5-amino-6-(1H-imidazol-1-il)nicotinato de metilo crudo de la etapa anterior (máximo 10,0 mmol) en 1,2-diclorobenceno 90 mL y se agregó N,N'-carbonil diimidazol (CDI; 2,43 g, 15,0 mmol). La mezcla de reacción se calentó en un frasco cerrado a 170°C por 2 horas. La

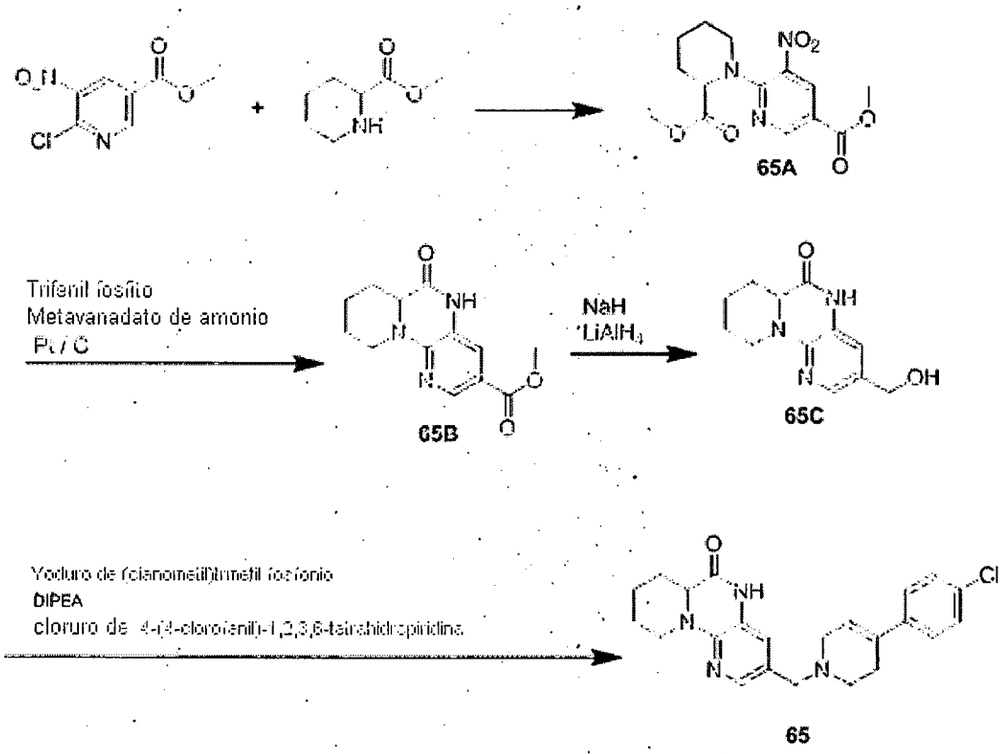
mezcla de reacción se enfrió, se vertió en etil éter:hexanos (1:1, 300 mL) y el sólido resultante se filtró y se sometió a columna cromatográfica evaporativa sobre sílica gel (SiO_2 330 g, diclorometano:metanol 19:1-6:1). El sólido se suspendió en etil éter (30 mL), se recogió por filtración y se secó al vacío para proporcionar el compuesto del título como un sólido amarillo (mezcla de regioisómeros de imidazol ~2:10, 467 g, 19%). [M+H] calculado para $C_{11}H_8N_4O_3$, 245; encontrado, 245.

Compuestos 64C1 y 64C2: 3-(Hidroximetil)imidazo[1,2-a]pirido[3,2-e]pirazin-6(5H)-ona y 3-(Hidroximetil)imidazo[1,5-a]pirido[3,2-e]pirazin-6(5H)-ona: Se suspendió el 6-oxo-5,6-dihidroimidazo[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de metilo (0,410 g, 1,68 mmol) en THF (20 mL) y se agregó hidruro de sodio (suspensión en aceite mineral al 60%, 0,112 g, 2,80 mmol) en una porción. La mezcla de reacción se agitó a temperatura ambiente por 1 hora, se enfrió a -50°C y se agregó gota a gota $LiAlH_4$ (2M en THF, 1,7 mL, 3,4 mmol) durante dos minutos. La mezcla de reacción se mantuvo a -30-(-10)°C por 3 horas y se agregó más $LiAlH_4$ (2M en THF, 0,7 mL y 1,0 mL, 3,4 mmol combinados). La mezcla de reacción se enfrió a -60°C y lentamente se detuvo con MeOH, se calentó a temperatura ambiente y se agregaron TFA y agua hasta una solución transparente como resultado. La solución se sometió a HPLC preparativa (acetonitrilo en agua 1-30%, solución tampón de TFA) para proporcionar el compuesto del título como un sólido gris (mezcla de regioisómeros de imidazol~2:1, 147 mg, 40%;). [M+H] calculado para $C_{10}H_8N_4O_2$, 217; encontrado, 217.

Compuestos 64a y 64b: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)imidazo[1,2-a]pirido[3,2-e]pirazin-6(5H)-ona y 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)imidazo[1,5-a]pirido[3,2-e]pirazin-6(5H)-ona: Se preparó el compuesto 64 como una mezcla, utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1D, excepto que se utilizó una mezcla de 3-(hidroximetil)imidazo[1,2-a]pirido[3,2-e]pirazin-6(5H)-ona y 3-(hidroximetil)imidazo- [1,5-a]pirido[3,2-e]pirazin-6(5H)-ona en lugar de (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-

a]pirazin-6(5H)-ona y se utilizó 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina en lugar de 1-(4-clorofenil)piperazina. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2,51 - 2,53 (m, 2 H) 2,63 - 2,76 (m, 2 H) 3,12 (br. s., 2 H) 3,72 (br. s., 2 H) 6,20 - 6,23 (m, 1 H) 7,37 - 7,40 (m, 2 H) 7,45 - 7,48 (m, 2 H) 7,61 (d, *J*=1,26 Hz, 1 H) 7,76 (d, *J*=2,02 Hz, 1 H) 7,91 (s, 1 H) 8,27 (d, *J*=1,77 Hz, 1 H) 8,38 (d, *J*=1,26 Hz, 1 H); [M+H] calculado para $C_{21}H_{18}ClN_5O$, 392; encontrado, 392. Regioisómero invertido: ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2,50 - 2,53 (m, 2 H) 2,63 - 2,76 (m, 2 H) 3,12 (br. s., 2 H) 3,70 (br. s., 2 H) 6,20 - 6,23 (m, 1 H) 7,37 - 7,40 (m, 2 H) 7,45 - 7,48 (m, 2 H) 7,70 (d, *J*=1,77 Hz, 1 H) 7,91 (d, *J*= 0,76 Hz, 1 H) 8,21 (d, *J*=1,77 Hz, 1 H) 8,91 (d, *J*= 0,76 Hz, 1 H); [M+H] calculado para $C_{21}H_{18}ClN_5O$, 392; encontrado, 392.

Compuesto 65: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Compuesto 65A: 6-(2-(metoxicarbonil)piperidin-1-il)-5-nitronicotinato de metilo: El 6-cloro-5-nitronicotinato de metilo (2,0 g, 9,23 mmol)

se agregó a piperidina-2-carboxilato de metilo (5,2 g, 36,92 mmol) mientras se agita a temperatura ambiente. La reacción amarilla viscosa se calentó a 90°C por una hora y luego de vuelta se dejó enfriar a temperatura ambiente. La reacción se diluyó con diclorometano (20 mL) y se purificó mediante columna cromatográfica (SiO_2 220 g, acetato de etilo en hexanos gradiente 20-30%,) para rendir el compuesto del título (2,95 g, rindiendo 99%) como un aceite amarillo. [M+H] calculado para C14H17N3O6, 324; encontrado, 324.

Compuesto 65B: 6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de metilo: Se disolvió el 6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e] pirazin-3-carboxilato de metilo (2,95 g, 9,12 mmol) en diclorometano (20 mL). A la solución amarilla se agregó metavanadato de amonio (20,0 mg, 0,171 mmol), trifenil fosfito (aproximadamente 30 ul, 0,097 mmol), y Pt/C (300 mg, 5% w/w). La mezcla de reacción se presurizó con gas hidrógeno (110 psi) y se agitó a temperatura ambiente por 16 horas. La reacción luego se despresurizó y se diluyó con diclorometano (100 mL) la cual se calentó a reflujo por 30 minutos. La solución caliente se filtró a través de un lecho de celite y se lavó con diclorometano caliente (3 x 20 mL). El filtrado se concentró para rendir el compuesto del título (1,91 g, 80%) como un sólido blanco. [M+H] calculado para C13H15N3O3, 262; encontrado, 262.

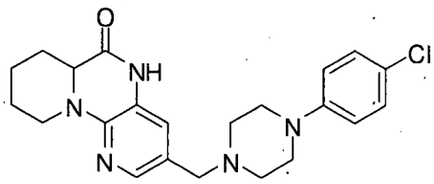
Compuesto 65C: 3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: Se resuspendió 6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de metilo (500 mg, 1,91 mmol) en tetrahidrofurano (23 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 114,7 mg, 2,87 mmol) y se agitó 30 minutos. La reacción luego se enfrió a -45°C y se agregó hidruro de aluminio y litio (2M en THF, 1,91 mL, 3,82 mmol). La reacción se agitó a una temperatura entre -20 y -10°C por 1 hora. La reacción nuevamente se enfrió a -60°C y se agregó MeOH (1 mL) seguido por agua (1 mL). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (300 mL) y agua (200 mL). La

mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (3 x 100 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron con sulfato de sodio y se concentraron para rendir el compuesto del título (429,4 mg, 96%) como un sólido blanco. [M+H] calculado para C12H15N3O2, 234; encontrado, 234.

Compuesto 65: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: Se suspendió el 3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,43 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (103 mg, 0,41 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (94,0 mg, 0,41 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión luego de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (31,8 mg, 18%) como un sólido blanco.

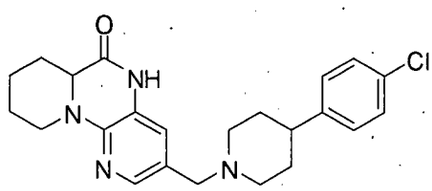
^{1}H NMR (DMSO-d_6) δ (ppm): 10,47 (s, 1H), 7,66 (d, J = 2,0 Hz, 1H), 7,41 - 7,48 (m, 2H), 7,33 - 7,40 (m, 2H), 6,98 (d, J = 2,0 Hz, 1H), 6,18 (s, 1H), 4,43 - 4,57 (m, 1H), 3,84 (d, J = 11,4 Hz, 1H), 3,42 (s, 2H), 3,01 (d, J = 2,8 Hz, 2H), 2,55 - 2,66 (m, 3H), 2,44 (br. s., 2H), 1,98 - 2,09 (m, 1H), 1,78 - 1,92 (m, 1H), 1,57 - 1,70 (m, 1H), 1,33 - 1,56 (m, 3H). [M+H] calculado para C23H25ClN4O, 409; encontrado, 409.

Compuesto 66: 3-((4-(4-clorofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se suspendió el 3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,43 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (103 mg, 0,41 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-clorofenil)piperazina (94,0 mg, 0,41 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión se enfrió de nuevo a temperatura ambiente y se filtró. Los sólidos se recolectaron para proporcionar el compuesto del título (69,9 mg, 39%) como un sólido blanco. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,47 (s, 1H), 7,65 (d, J = 1,8 Hz, 1H), 7,21 (d, J = 9,1 Hz, 2H), 6,97 (d, J = 1,8 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 4,50 (d, J = 12,9 Hz, 1H), 3,83 (dd, J = 11,2, 2,7 Hz, 1H), 3,34 (d, J = 5,6 Hz, 2H), 3,01 - 3,17 (m, 4H), 2,55 - 2,65 (m, 1H), 2,37 - 2,48 (m, 4H), 1,98 - 2,08 (m, 1H), 1,85 (d, J = 12,4 Hz, 1H), 1,63 (d, J = 12,6 Hz, 1H), 1,32 - 1,56 (m, 3H). [M+H] calculado para C22H26ClN5O, 412; encontrado, 412.

Compuesto 67: 3-((4-(4-clorofenil)piperidin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona

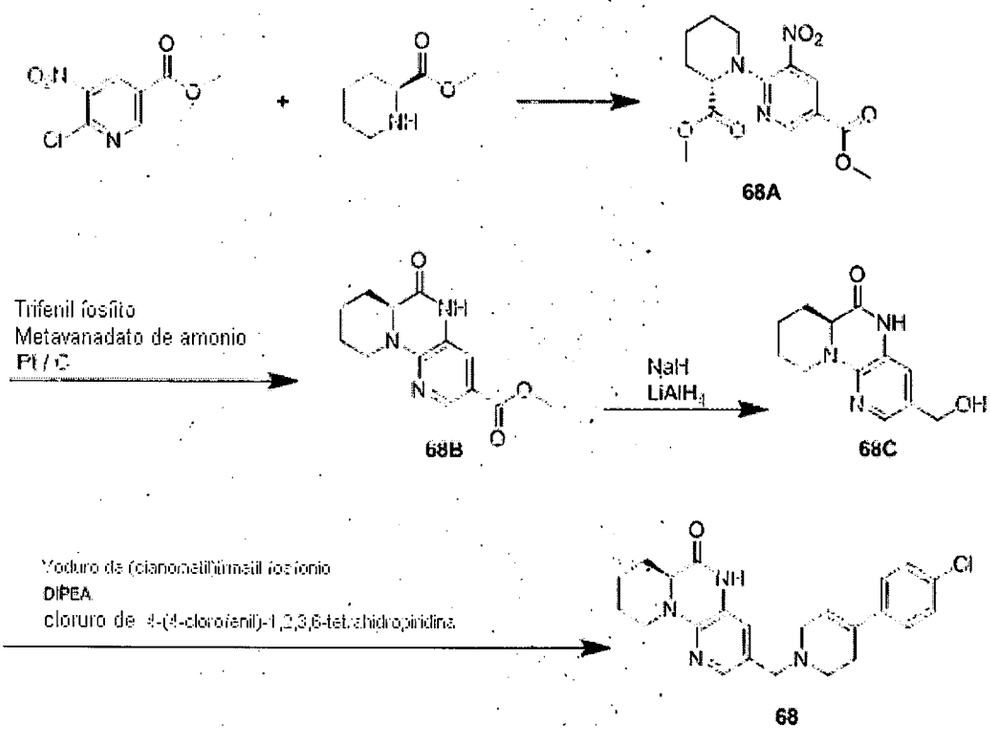


Se suspendió el 3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,43 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (103 mg, 0,41 mmol) seguido por N-etil-

N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)piperidina (95,0 mg, 0,41 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción se enfrió a temperatura ambiente y se purificó mediante HPLC (MeCN/H_2O 10-80, solución tampón de TFA). Las fracciones se recolectaron y liofilizaron para rendir el compuesto del título (57,3 mg, 32%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) □: 13,44 (br. s., 1H), 10,82 (s, 1H), 9,52 (br. s., 1H), 7,84 (d, J = 2,0 Hz, 1H), 7,36 - 7,42 (m, 2H), 7,24 (d, J = 8,3 Hz, 2H), 7,06 (d, J = 2,0 Hz, 1H), 4,58 (d, J = 13,1 Hz, 1H), 4,21 (d, J = 4,5 Hz, 2H), 3,97 (dd, J = 11,6, 2,8 Hz, 1H), 3,46 (d, J = 11,6 Hz, 2H), 2,96 - 3,07 (m, 2H), 2,79 - 2,85 (m, 1H), 2,67 (td, J = 12,8, 2,7 Hz, 1H), 2,06 - 2,10 (m, 1H), 1,95 - 2,02 (m, 2H), 1,72 - 1,91 (m, 3H), 1,64 - 1,67 (m, 1H), 1,33 - 1,58 (m, 3H). [M+H] calculado para C23H27ClN4O, 411; encontrado, 411.

Compuesto 68: (S)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Compuesto 68A: 6-(2-(metoxicarbonil)piperidin-1-il)-5-nitronicotinato de (S)-metilo: Se agregó 6-cloro-5-nitronicotinato de metilo (2,333 g, 10,77 mmol) a la piperidina-2-carboxilato de (S)-metilo pura (2,93 g, 20,46 mmol) mientras se agita. La reacción se agitó 1 hora a 90°C, se enfrió a temperatura ambiente y se resuspendió en acetato de etilo (10 mL). La mezcla se purificó por SiO_2 (330 g, EA en hexanos 20-30%) para rendir 3,4 g (98%) del compuesto del título como un aceite amarillo. [M+H] calculado para C14H17N3O6, 324; encontrado, 324.

Compuesto 68B: 6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de (S)-metilo: En una bomba de hidrogenadora, el 6-(2-(metoxicarbonil)piperidin-1-il)-5-nitronicotinato de (S)-metilo (1,95 g, 6,03 mmol), trifenil fosfito (0,019 ml, 0,060 mmol), vanadato de amonio (0,056 g, 0,483 mmol) y platino (5% sobre carbono, 0,235 g, 0,060 mmol) se mezclaron en diclorometano (Volumen: 30,2 ml) para proporcionar una suspensión. La bomba se selló y presurizó a 110 psi con gas hidrógeno. La reacción se agitó a 110 psi por 16 horas, se despresurizó, se diluyó con DCM (100 mL) y se calentó a reflujo por 10 minutos. La mezcla caliente se filtró a través de celite y se lavó con DCM (50 mL). El filtrado se concentró al vacío para rendir 1,4 g (89%) del producto como un sólido blanco y se usó sin posterior purificación. [M+H] calculado para C13H15N3O3, 262; encontrado, 262.

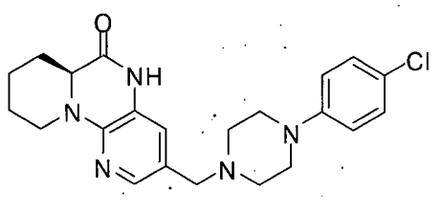
Compuesto 68C: (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: En un matraz de fondo redondo, el 6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de (S)-metilo (860 mg, 3,29 mmol) se disolvió en tetrahidrofurano (Volumen: 41 mL) para proporcionar una solución transparente. La solución se enfrió a 0°C y se agregó NaH (197 mg, 4,94 mmol). La reacción se dejó agitar a temperatura ambiente por 0,5 hora. La solución transparente luego se enfrió a -78°C y se agregó LAH durante 2 minutos. La temperatura de reacción se mantuvo entre -30°C y -20°C por 3 horas mientras se agita, luego se enfrió a -78°C. Se agregaron metanol (3ml, evolución de gas) y agua (1 ml). La reacción se agitó a temperatura ambiente por 30 minutos. El producto crudo se agregó a 400 ml de acetato de etilo. Se agregó agua (100 ml)

y la mezcla se agitó por 1 hora. La mezcla se filtró a través de un medio de frita para retirar los sólidos tostados los cuales fueron descartados. La capa acuosa se extrajo con acetato de etilo (1 X 100 mL). Las fracciones orgánicas se combinaron, se lavaron una vez con salmuera y se secaron con sulfato de sodio y se concentraron para rendir 743 mg (97%) del producto como un resíduo blanco. [M+H] calculado para C12H15N3O2, 234; encontrado, 234.

Compuesto 68: (S)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (125,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (225 ul, 1,3 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (109 mg, 0,472 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción luego se enfrió a temperatura ambiente, se diluyó con EtOH (3 ml) y agua (~ 300 ul), luego se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 2 horas. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (75,1 mg, 43%) como un sólido blanco.

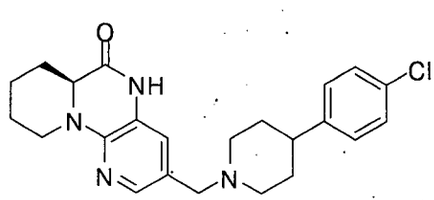
^{1}H NMR (DMSO-d_6) δ (ppm): 10,47 (s, 1H), 7,66 (d, J = 1,8 Hz, 1H), 7,40 - 7,48 (m, 2H), 7,34 - 7,40 (m, 2H), 6,98 (d, J = 2,0 Hz, 1H), 6,18 (s, 1H), 4,45 - 4,55 (m, 1H), 3,84 (d, J = 11,4 Hz, 1H), 3,42 (s, 2H), 3,01 (d, J = 2,8 Hz, 2H), 2,56 - 2,66 (m, 3H), 2,44 (br. s., 2H), 1,98 - 2,08 (m, 1H), 1,80 - 1,89 (m, 1H), 1,59 - 1,68 (m, 1H), 1,34 - 1,57 (m, 3H). [M+H] calculado para C23H25ClN4O, 409; encontrado, 409. MP: 201,6 °C

Compuesto 69: (S)-3-((4-(4-clorofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]- pirazin-6(6aH)-ona



Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido [1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (125,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (225 ul, 1,3 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-clorofenil) piperazina (110 mg, 0,472 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción luego se enfrió a temperatura ambiente, se diluyó con EtOH (3 ml) y agua (~ 300 ul), luego se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 2 horas. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (67,3 mg, 43%) como un sólido blanco. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,47 (s, 1H), 7,65 (d, J = 2,0 Hz, 1H), 7,21 (d, J = 9,1 Hz, 2H), 6,97 (d, J = 2,0 Hz, 1H), 6,88 - 6,95 (m, 2H), 4,45 - 4,55 (m, 1H), 3,83 (dd, J = 11,4, 2,8 Hz, 1H), 3,35 (s, 2H), 3,05 - 3,16 (m, 5H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,38 - 2,48 (m, 3H), 2,03 (d, J = 12,6 Hz, 1H), 1,77 - 1,91 (m, 1H), 1,63 (d, J = 12,6 Hz, 1H), 1,33 - 1,56 (m, 3H). [M+H] calculado para C22H26ClN5O, 412; encontrado, 412.

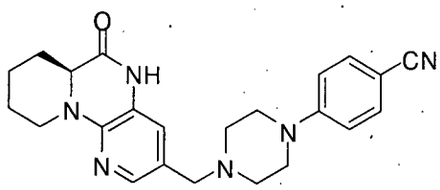
Compuesto 70: (S)-3-((4-(4-clorofenil)piperidin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol) en propionitrilo (1 mL) y se agregó yoduro de

(cianometil)trimetilfosfonio (125,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (225 ul, 1,3 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)piperidina (109 mg, 0,472 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción cruda se enfrió a temperatura ambiente y se concentró a un resíduo, luego se resuspendió en 3mL de DMSO y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (22,1 mg, 12,5%) como un sólido blanco.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,46 (s, 1H), 7,64 (d, J = 2,0 Hz, 1H), 7,29 - 7,37 (m, 2H), 7,21 - 7,28 (m, 2H), 6,96 (d, J = 2,0 Hz, 1H), 4,42 - 4,58 (m, 1H), 3,83 (dd, J = 11,4, 2,8 Hz, 1H), 3,32 (s, 2H), 2,80 - 2,95 (m, 2H), 2,54 - 2,66 (m, 1H), 1,92 - 2,08 (m, 3H), 1,83 (br. s., 1H), 1,66 - 1,77 (m, 2H), 1,33 - 1,66 (m, 6H). [M+H] calculado para C23H27ClN4O, 411; encontrado, 411.

Compuesto 71: (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]piracin-3-il)metil)piperacin-1-il)benconitrilo

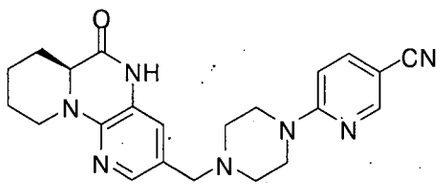


Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]piracin-6(6aH)-ona (86,0 mg, 0,369 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (108,0 mg, 0,442 mmol) seguido por N-etil-N-isopropilpropan-2-amina (193 ul, 1,1 mmol). A la mezcla agitada se agregó luego 4-(piperacin-1-il)benconitrilo (76 mg, 0,406 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción cruda se enfrió a temperatura ambiente y se concentró a un resíduo, luego se resuspendió en 3mL de DMSO y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y

se secó al vacío para proporcionar el compuesto del título (29,7 mg, 20,0%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (s, 1H), 7,65 (s, 1H), 7,57 (d, J = 8,8 Hz, 2H), 6,94 - 7,04 (m, 3H), 4,44 - 4,55 (m, 1H), 3,79 - 3,88 (m, 1H), 3,35 (br. s., 2H), 3,30 (br. s., 4H), 2,54 - 2,69 (m, 1H), 2,45 (br. s., 4H), 1,97 - 2,09 (m, 1H), 1,80 - 1,90 (m, 1H), 1,57 - 1,69 (m, 1H), 1,32 - 1,56 (m, 3H). [M+H] calculado para C23H26N6O, 403; encontrado, 403. MP: 212,2 °C

Compuesto 72: (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo



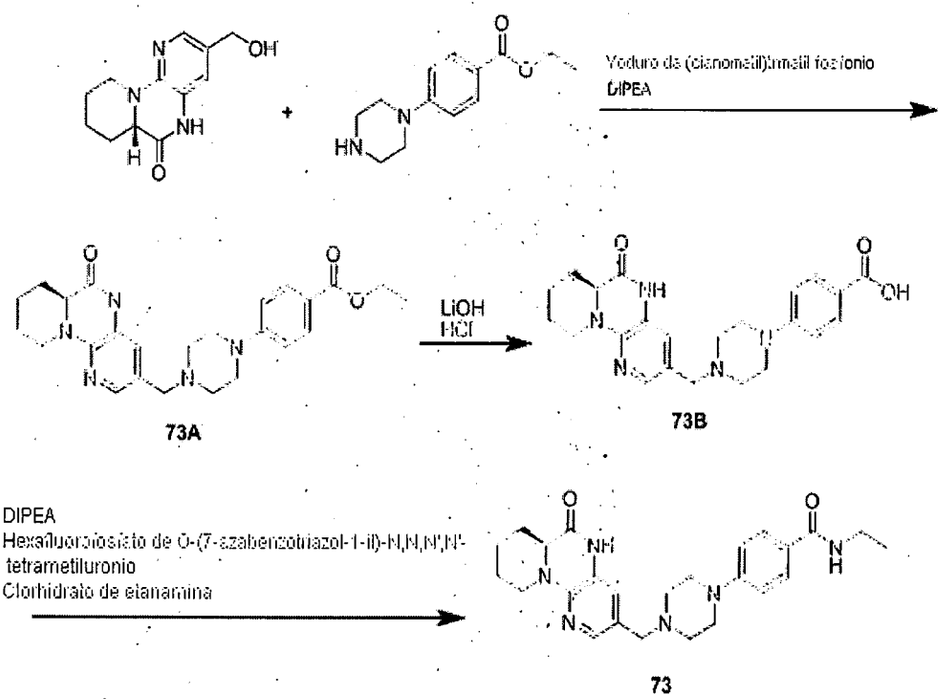
Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (89,0 mg, 0,382 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (111,0 mg, 0,458 mmol) seguido por N-etil-N-isopropilpropan-2-amina (200 ul, 1,1 mmol). A la mezcla agitada se agregó luego 6-(piperazin-1-il)nicotinonitrilo (79 mg, 0,420 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción cruda se enfrió a temperatura ambiente y se concentró a un residuo, luego se resuspendió en 3mL de DMSO y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (54,2 mg, 35,2%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (br. s., 1H), 8,46 (d, J = 2,3 Hz, 1H), 7,83 (dd, J = 9,1, 2,5 Hz, 1H), 7,64 (d, J = 2,0 Hz, 1H), 6,97 (d, J = 1,8 Hz, 1H), 6,90 (d, J = 9,1 Hz, 1H), 4,50 (d, J = 12,9 Hz, 1H), 3,83 (dd, J = 11,4, 2,8 Hz, 1H), 3,55 - 3,70 (m, 4H), 3,34 (s, 2H), 2,59 (td, J = 12,6, 2,4 Hz, 1H), 2,40 (t, J = 4,8 Hz, 4H), 2,03

(d, J = 12,6 Hz, 1H), 1,84 (d, J = 12,1 Hz, 1H), 1,63 (d, J = 13,6 Hz, 1H), 1,29 - 1,56 (m, 3H). [M+H] calculado para C22H25N7O, 404; encontrado, 404.

Compuesto 73: (S)-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzamida

Método A



Compuesto 73A: 4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo: Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (400 mg, 1,715 mmol) en propionitrilo (4,3 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (500,0 mg, 2,06 mmol) seguido por N-etil-N-isopropilpropan-2-amina (898 ul, 5,1 mmol). A la mezcla agitada se agregó luego etil 4-(piperazin-1-il)benzoato de etilo (402 mg, 1,715 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción luego se enfrió a temperatura ambiente, se diluyó con EtOH (8 ml) y agua (1 mL), luego se filtró. El precipitado se

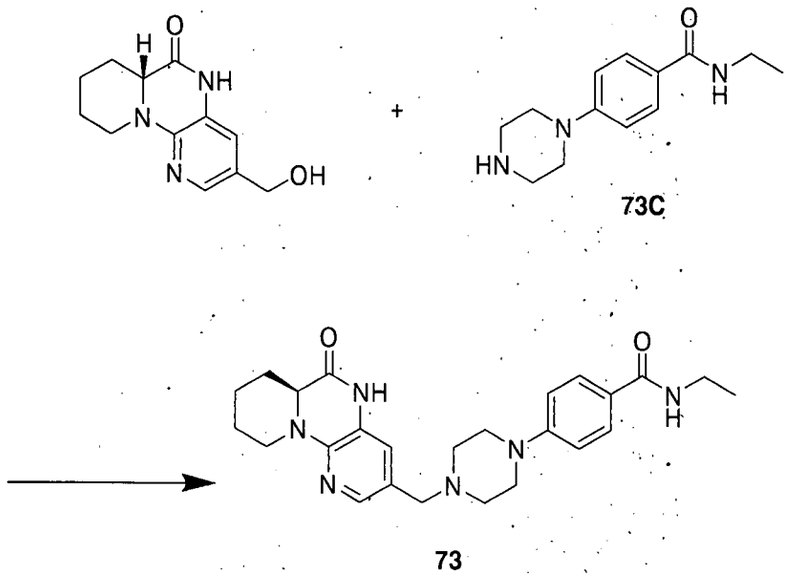
recogió por filtración y se secó al vacío para proporcionar el compuesto del título (508 mg, 65,9%) como un sólido café.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (s, 1H), 7,77 (d, J = 9,1 Hz, 2H), 7,65 (d, J = 2,0 Hz, 1H), 6,90 - 7,01 (m, 3H), 4,50 (d, J = 12,9 Hz, 1H), 4,23 (q, J = 7,1 Hz, 2H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,35 (s, 2H), 3,28 (br. s., 4H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,40 - 2,47 (m, 4H), 2,03 (d, J = 12,9 Hz, 1H), 1,80 - 1,89 (m, 1H), 1,64 (d, J = 12,6 Hz, 1H), 1,33 - 1,57 (m, 3H), 1,28 (t, J = 7,1 Hz, 3H). [M+H] calculado para C25H31N5O3, 450; encontrado, 450.

Compuesto 73B: ácido (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzoico: Se resuspendió el 4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-metilo (152 mg, 0,349 mmol) en dioxano (2 ml) y se agregó LiOH (1N, 2 ml, 2,000 mmol). La reacción se agitó 16 horas a temperatura ambiente. La reacción se concentró en vacío y el resíduo se suspendió en agua (5 mL) y se acidificó (HCl 4,5N) a pH 4. Se formó un precipitado blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (122,8 mg, 83%) como un sólido blanco. [M+H] calculado para C23H27N5O3, 422; encontrado, 422.

Compuesto 73: (S)-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: Se resuspendió el ácido (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]- pirazin-3-il)metil)piperazin-1-il)benzoico (122 mg, 0,29 mmol) en DMF (2,9 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (152 µl, 0,87 mmol), hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (165 mg, 0,434 mmol), y clorhidrato de etanamina (26,0 mg, 0,318 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (MeCN/H_2O 10-80, solución tampón de TFA). Las fracciones se recolectaron y liofilizaron para rendir 135 mg (85%) del producto como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,82 (s, 1H), 9,83 (br. s., 1H), 8,25 (t, J = 5,6 Hz, 1H), 7,84 (d, J = 2,0 Hz, 1H), 7,77 (d, J = 8,8 Hz, 2H), 6,94 - 7,12 (m, 3H), 4,59 (d, J = 13,1 Hz, 1H), 4,27 (br. s., 2H), 3,85 - 4,10 (m, 3H), 3,43 (d, J = 10,4 Hz, 2H), 3,21 - 3,30 (m, 2H), 2,95 - 3,19 (m, 4H), 2,61 - 2,72 (m, 1H), 2,05 (d, J = 11,8 Hz, 1H), 1,87 (d, J = 12,4 Hz, 1H), 1,66 (d, J = 12,1 Hz, 1H), 1,31 - 1,62 (m, 3H), 1,09 (t, J = 7,2 Hz, 3H). [M+H] calculado para C23H27N5O3, 449; encontrado, 449. MP: 232,6 °C.

Método B

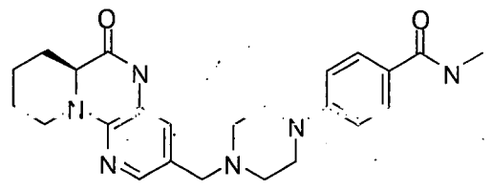


73C

73

Compuesto 73: (S)-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzamida: A una suspensión de (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (800 mg, 3,43 mmol) se agregó yoduro de (cianometil)trimetilfosfonio (1.000 mg, 4,12 mmol) y DIEA (1.797 µl, 10,29 mmol) y N-etil-4-(piperazin-1-il)benzamida (800 mg, 3,43 mmol)). Se calentó el frasco a 90°C durante 16 horas. La reacción cruda se enfrió a temperatura ambiente y se filtró. El sólido resultante se recolectó y suspendió en EtOH (24 mL), se calentó a reflujo, luego se enfrió a temperatura ambiente y se filtró. El material resultante se lavó con EtOH para proporcionar un sólido blanco.

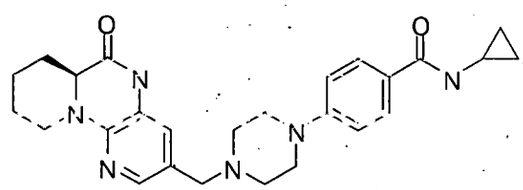
Compuesto 74: (S)-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Se resuspendió el ácido (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzoico (50 mg, 0,119 mmol) en DMF (0,5 mL). A la mezcla se agregó clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (34,1mg, 0,178 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hidrato (27,2 mg, 0,178 mmol), 4-metilmorfolina (0,065 mL, 0,593 mmol) y clorhidrato de metanamina (8,01 mg, 0,119 mmol). La reacción se agitó a temperatura ambiente durante la noche. A la solución agitada se agregó agua (2 mL) y el precipitado se filtró, recolectó, y se secó al vacío para proporcionar el compuesto del título (23,8 mg, 46,2%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,49 (s, 1H), 8,14 (q, J = 4,5 Hz, 1H), 7,58 - 7,80 (m, 3H), 6,82 - 7,04 (m, 3H), 4,51 (d, J = 12,9 Hz, 1H), 3,84 (dd, J = 11,2, 2,7 Hz, 1H), 3,30 - 3,51 (m, 3H), 3,23 (br. s., 4H), 2,74 (d, J = 4,5 Hz, 3H), 2,61 (td, J = 12,7, 2,7 Hz, 1H), 2,49 (br. s., 3H), 2,04 (d, J = 12,6 Hz, 1H), 1,85 (d, J = 12,1 Hz, 1H), 1,64 (d, J = 12,6 Hz, 1H), 1,33 - 1,59 (m, 3H). [M+H] calculado para C24H30N6O2, 435; encontrado, 435.

Compuesto 75: (S)-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzamida

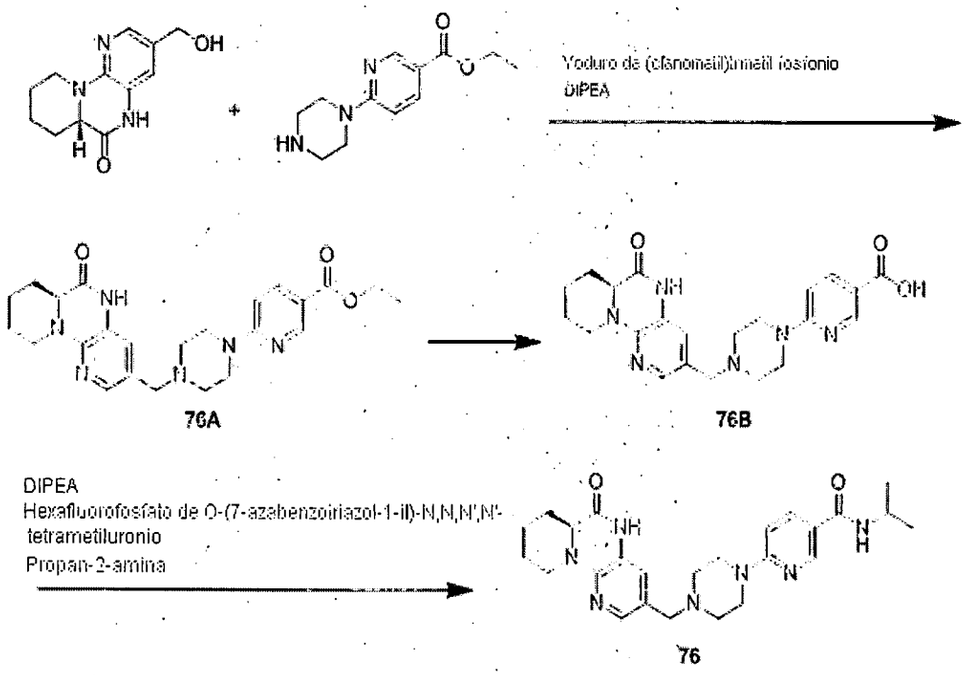


Se resuspendió el ácido (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzoico (50 mg, 0,119 mmol) en DMF (0,5 mL). A la mezcla se

agregó clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (34,1mg, 0,178 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hidrato (27,2 mg, 0,178 mmol), 4-metilmorfolina (0,065 mL, 0,593 mmol) y ciclopropanamina (6,77 mg, 0,119 mmol). La reacción se agitó a temperatura ambiente durante la noche. A la solución agitada se agregó agua (2 mL) y el precipitado se filtró, recolectó, y se secó al vacío para proporcionar el compuesto del título (41,2 mg, 75,0%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (s, 1H), 8,13 (d, J = 4,0 Hz, 1H), 7,57 - 7,76 (m, 3H), 6,80 - 7,02 (m, 3H), 4,50 (d, J = 13,1 Hz, 1H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,35 (br. s., 2H), 3,22 (br. s., 4H), 2,79 (td, J = 7,3, 3,9 Hz, 1H), 2,60 (td, J = 12,6, 2,7 Hz, 1H), 2,46 (br. s., 4H), 2,03 (d, J = 12,9 Hz, 1H), 1,83 (br. s., 1H), 1,64 (d, J = 12,9 Hz, 1H), 1,31 - 1,57 (m, 3H), 0,61 - 0,69 (m, 2H), 0,48 - 0,56 (m, 2H). [M+H] calculado para C26H32N6O2, 461; encontrado, 461.

Compuesto 76: (S)-N-isopropil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)-piperazin-1-il)nicotinamida



Compuesto 76A: 6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)- nicotinato de (S)-etilo: Se suspendió el (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (330 mg, 1,415 mmol) en propionitrilo (3,5 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (413,0 mg, 1,70 mmol) seguido por N-etil-N-isopropilpropan-2-amina (741 ul, 4,2 mmol). A la mezcla agitada se agregó luego 6-(piperazin-1-il)nicotinato de etilo (366 mg, 1,56 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción luego se enfrió a temperatura ambiente, se diluyó con EtOH (8 ml) y agua (1 mL), luego se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (567 mg, 89%) como un sólido café.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (s, 1H), 8,63 (d, J = 2,0 Hz, 1H), 7,93 (dd, J = 9,1, 2,3 Hz, 1H), 7,65 (d, J = 1,8 Hz, 1H), 6,97 (d, J = 2,0 Hz, 1H), 6,85 (d, J = 9,1 Hz, 1H), 4,44 - 4,56 (m, 1H), 4,24 (q, J = 7,1 Hz, 2H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,53 - 3,73 (m, 4H), 3,35 (s, 2H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,41 (t, J = 4,8 Hz, 4H), 2,05 (br. s., 1H), 1,85 (d, J = 12,4 Hz, 1H), 1,64 (d, J = 12,4 Hz, 1H), 1,34 - 1,57 (m, 3H), 1,28 (t, 3H) [M+H] calculado para C24H30N6O3, 451; encontrado, 451.

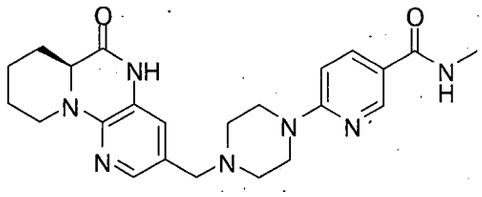
Compuesto 76B: ácido (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotínico: El compuesto 76B se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 73B excepto que se utilizó 6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido-[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo en lugar de 4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo para rendir el compuesto del título como un sólido blanco. [M+H] calculado para C22H26N6O3, 423; encontrado, 423.

Compuesto 76: (S)-N-isopropil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotinamida: Se resuspendió el ácido (S)-6-(4-((6-oxo-

6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotínico (75 mg, 0,178 mmol) en DMF (0,9 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (93 µl, 0,53 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (101 mg, 0,266 mmol), y propan-2-amina (11,5 mg, 0,195 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (MeCN/H_2O 10-80, solución tampón de TFA). Las fracciones se recolectaron y liofilizaron para rendir 64,8 mg (65%) de producto como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,84 (s, 1H), 9,93 (br. s., 1H), 8,64 (d, J = 2,0 Hz, 1H), 8,02 - 8,11 (m, 2H), 7,82 (d, J = 2,0 Hz, 1H), 7,05 (d, J = 2,0 Hz, 1H), 6,96 (d, J = 9,1 Hz, 1H), 4,43 - 4,63 (m, 3H), 4,25 (s, 2H), 4,07 (dd, J = 14,1, 6,6 Hz, 1H), 3,93 - 4,02 (m, 1H), 3,37 - 3,55 (m, 1H), 2,96 - 3,25 (m, 4H), 2,68 (td, J = 12,9, 2,5 Hz, 1H), 2,02 - 2,11 (m, 1H), 1,87 (d, J = 12,4 Hz, 1H), 1,33 - 1,72 (m, 4H), 1,14 (d, J = 6,8 Hz, 6H). [M+H] calculado para C25H33N7O2, 464; encontrado, 464.

Compuesto 77: (S)-N-metil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)-piperazin-1-il)nicotinamida

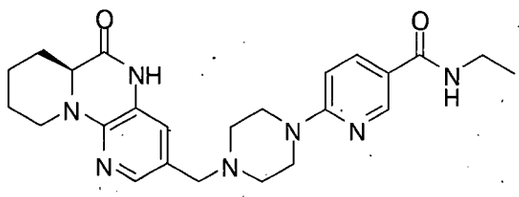


Se resuspendió el ácido (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotínico (75 mg, 0,178 mmol) en DMF (0,9 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (93 µl, 0,53 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (101 mg, 0,266 mmol), y clorhidrato de metanamina (13,2 mg, 0,195 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (MeCN/H_2O 10-80, solución tampón de TFA). Las fracciones se recolectaron y

liofilizaron para rendir 23,8 mg (30%) del producto como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,48 (s, 1H), 8,56 (d, J = 2,3 Hz, 1H), 8,20 (d, J = 4,5 Hz, 1H), 7,92 (dd, J = 9,0, 2,1 Hz, 1H), 7,65 (s, 1H), 6,98 (d, J = 1,5 Hz, 1H), 6,82 (d, J = 8,8 Hz, 1H), 4,50 (d, J = 12,9 Hz, 1H), 3,77 - 3,94 (m, 1H), 3,56 (d, J = 2,3 Hz, 4H), 3,34 (s, 2H), 2,74 (d, J = 4,5 Hz, 3H), 2,53 - 2,69 (m, 1H), 2,41 (br. s., 4H), 1,99 - 2,08 (m, 1H), 1,84 (br. s., 1H), 1,59 - 1,69 (m, 1H), 1,31 - 1,57 (m, 3H). [M+H] calculado para C25H33N7O2, 436; encontrado, 436.

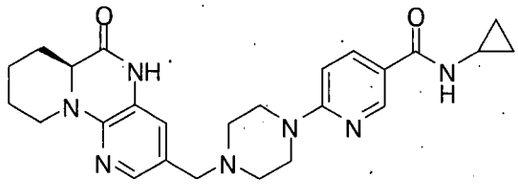
Compuesto 78: (S)-N-etil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotinamida



Se resuspendió el ácido (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotínico (75 mg, 0,178 mmol) en DMF (0,9 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (93 µl, 0,53 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (101 mg, 0,266 mmol), y clorhidrato de etanamina (15,9 mg, 0,195 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (MeCN/H_2O 10-80, solución tampón de TFA). Las fracciones se recolectaron y liofilizaron para rendir 27,4 mg (34%) del compuesto del título como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,84 (s, 1H), 10,03 (br. s., 1H), 8,64 (s, 1H), 8,35 (t, J = 5,2 Hz, 1H), 8,04 (d, J = 9,1 Hz, 1H), 7,83 (s, 1H), 6,90 - 7,11 (m, 2H), 4,40 - 4,71 (m, 3H), 4,26 (s, 2H), 3,98 (d, J = 11,1 Hz, 1H), 2,96 - 3,57 (m, 8H), 2,61 - 2,74 (m, 1H), 2,08 (d, J = 11,9 Hz, 1H), 1,87 (d, J = 12,4 Hz, 1H), 1,33 - 1,73 (m, 4H), 1,11 (t, 3H). [M+H] calculado para C24H31N7O2, 450; encontrado, 450.

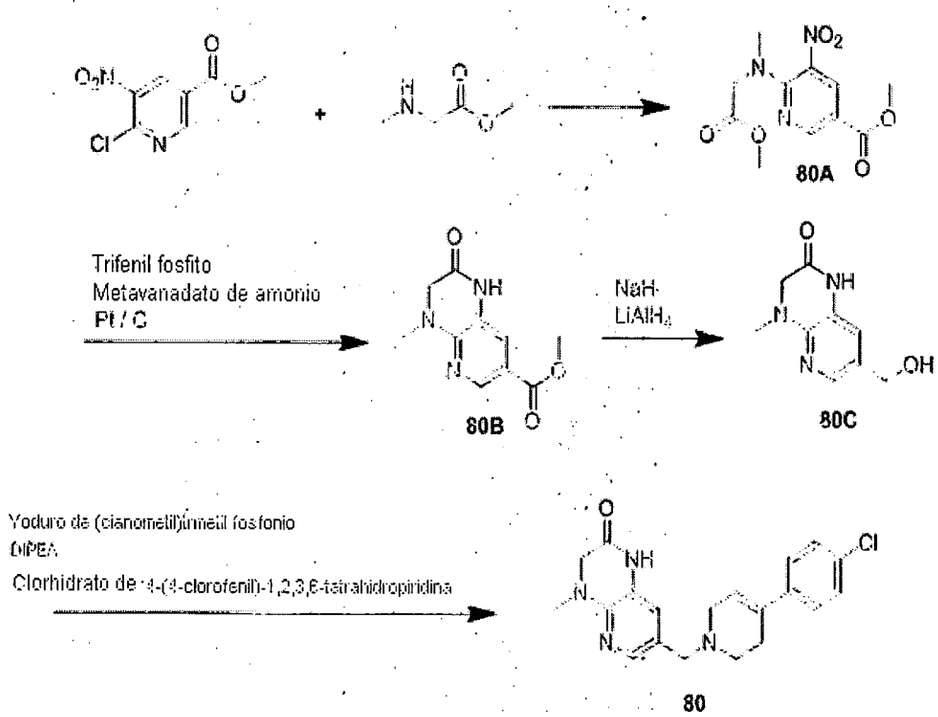
Compuesto 79: (S)-N-ciclopropil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotinamida



Se resuspendió el ácido (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)nicotínico (75 mg, 0,178 mmol) en DMF (0,9 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (93 µl, 0,53 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (101 mg, 0,266 mmol), y ciclopropanamina (11,15 mg, 0,195 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC ($MeCN/H_2O$ 10-80, solución tampón de TFA). Las fracciones se recolectaron y liofilizaron para rendir 41,2 mg (50%) del producto como un sólido blanco.

^1H NMR (DMSO-d_6) δ (ppm): 10,81 (s, 1H), 9,85 (br. s., 1H), 8,61 (d, J = 2,3 Hz, 1H), 8,30 (d, J = 4,0 Hz, 1H), 8,01 (dd, J = 9,0, 2,4 Hz, 1H), 7,82 (d, J = 2,0 Hz, 1H), 7,04 (d, J = 2,0 Hz, 1H), 6,95 (d, J = 8,8 Hz, 1H), 4,42 - 4,64 (m, 3H), 4,24 (br. s., 2H), 3,92 - 4,01 (m, 1H), 3,42 (br. s., 2H), 2,94 - 3,26 (m, 4H), 2,75 - 2,86 (m, 1H), 2,58 - 2,73 (m, 1H), 2,03 - 2,12 (m, 1H), 1,87 (d, J = 12,4 Hz, 1H), 1,66 (d, J = 12,6 Hz, 1H), 1,31 - 1,61 (m, 3H), 0,62 - 0,73 (m, 2H), 0,46 - 0,57 (m, 2H). [M+H] calculado para C25H31N7O2, 462; encontrado, 462.

Compuesto 80: 7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Compuesto 80A: 6-((2-metoxi-2-oxoetil)(metil)amino)-5-nitronicotinato de Metilo: Se agregó 6-cloro-5-nitronicotinato de metilo (2,0 g, 9,23 mmol) a 2-(metilamino)acetato de metilo (1,9 g, 18,47 mmol) puro mientras se agita a temperatura ambiente. La reacción amarilla viscosa se calentó a 90°C por una hora y luego de vuelta se dejó enfriar a temperatura ambiente. La reacción se diluyó con diclorometano (20 mL) y se purificó utilizando columna cromatográfica evaporativa (SiO_2 220 g, acetato de etilo en hexanos gradiente 20-30%,) para rendir 2,60 g (rindiendo 99%) del compuesto del título como un aceite amarillo. [M+H] calculado para C11H13N3O6, 284; encontrado, 284.

Compuesto 80B: 4-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo: Se disolvió 6-((2-metoxi-2-oxoetil)(metil)amino)-5-nitronicotinato de metilo (2,7 g, 9,53 mmol) en diclorometano (10 mL). A la solución amarilla se agregó metavanadato de amonio (30,0 mg, 0,256 mmol), trifenil fosfito (aprox 30 ul, 0,097 mmol), y Pt/C (300 mg, 5% w/w). La mezcla de reacción se presurizó con gas hidrógeno (110 psi) y se agitó a temperatura ambiente por 16 horas. La reacción luego se despresurizó y se diluyó

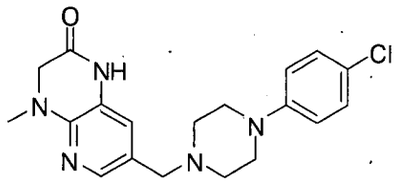
con diclorometano (100 mL) la cual fue calentada a reflujo por 30 minutos. La solución caliente se filtró a través de un lecho de celite y se lavó con diclorometano caliente (3 x 20 mL). El filtrado se concentró al vacío para rendir el compuesto del título (1,45 g, 68%) como un sólido blanco. [M+H] calculado para C10H11N3O3, 222; encontrado, 222.

Compuesto 80C: 7-(hidroximetil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se resuspendió el 4-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo (500 mg, 2,25 mmol) en tetrahidrofurano (25 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 136 mg, 3,40 mmol) y se agitó 30 minutos. La reacción luego se enfrió a -45°C y se agregó hidruro de aluminio y litio (2M en THF, 3,3 mL, 6,6 mmol). La reacción se agitó a una temperatura entre -20 y -10°C por 1 hora. La reacción luego de vuelta se enfrió a -60 °C y se agregó MeOH (1 mL) seguido por agua (1 mL). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (300 mL) y agua (200 mL). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (3 x 100 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron con sulfato de sodio y se concentraron para rendir el compuesto del título (415 mg, 95%) como un sólido blanco. [M+H] calculado para C9H11N3O2, 194; encontrado, 194.

Compuesto 80: 7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se suspendió el 7-(hidroximetil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona (85,0 mg, 0,44 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (103,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió

a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión se enfrió de nuevo a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (30,2 mg, 19%) como un sólido blanco. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,51 (s, 1H), 7,64 (s, 1H), 7,41 - 7,47 (m, 2H), 7,34 - 7,40 (m, 2H), 6,97 (d, J = 1,8 Hz, 1H), 6,18 (s, 1H), 3,93 (s, 2H), 3,41 (s, 2H), 3,01 (br. s., 2H), 2,91 (s, 3H), 2,60 (br. s., 2H), 2,39 - 2,47 (m, J = 7,3 Hz, 2H). [M+H] calculado para C20H21ClN4O, 369; encontrado, 369.

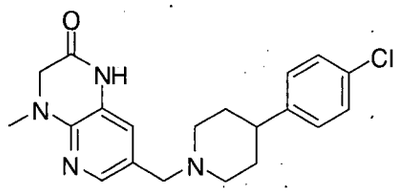
Compuesto 81: 7-((4-(4-clorofenil)piperazin-1-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Se suspendió el 7-(hidroximetil)-4-metil-3,4-dihidropirido [2,3-b]pirazin-2(1H)-ona (85,0 mg, 0,44 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-clorofenil) piperazina (104,8 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión luego de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (14,7 mg, 8%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,50 (s, 1H), 7,63 (d, J = 1,8 Hz, 1H), 7,21 (d, J = 9,1 Hz, 2H), 6,96 (d, J = 2,0 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 3,93 (s, 2H), 3,34 (s, 2H), 3,10 (br. s., 4H), 2,91 (s, 3H), 2,46 (br. s., 4H). [M+H] calculado para C19H22ClN5O, 372; encontrado, 372.

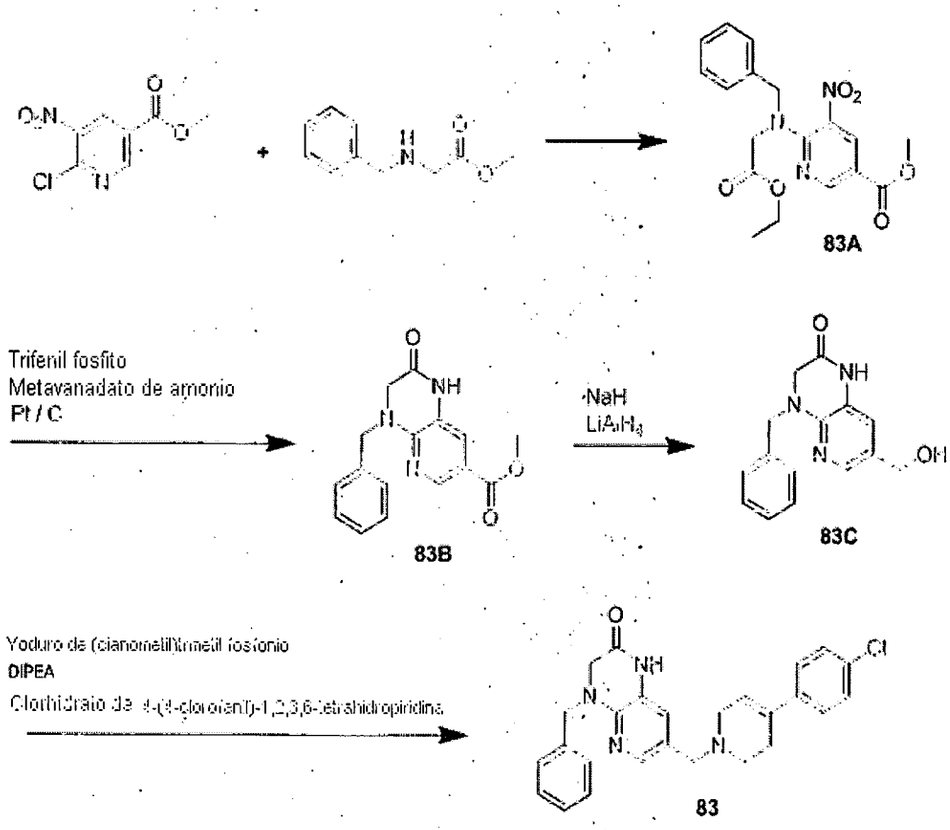
Compuesto 82: 7-((4-(4-clorofenil)piperidin-1-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Se suspendió el 7-(hidroximetil)-4-metil-3,4-dihidropirido [2,3-b]pirazín-2(1H)-ona (85,0 mg, 0,44 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)piperidina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (18,1 mg, 11%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,49 (s, 1H), 7,61 (d, J = 2,0 Hz, 1H), 7,30 - 7,36 (m, 2H), 7,23 - 7,29 (m, 2H), 6,95 (d, J = 2,0 Hz, 1H), 3,92 (s, 2H), 3,32 (s, 3H), 2,84 - 2,92 (m, 5H), 1,98 (t, J = 10,7 Hz, 2H), 1,66 - 1,75 (m, 2H), 1,50 - 1,64 (m, 2H). [M+H] calculado para C20H23ClN4O, 371; encontrado, 371.

Compuesto 83: 4-bencil-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Compuesto 83A: 6-(bencil(2-etoxi-2-oxoetil)amino)-5-nitronicotinato de metilo: El 6-cloro-5-nitronicotinato de metilo (2,0 g, 9,23 mmol) se agregó a 2-(bencilamino)acetato de metilo (6,0 g, 31,05 mmol) puro mientras se agita a temperatura ambiente. La reacción amarilla viscosa se calentó a 90°C por una hora y luego de vuelta se dejó enfriar a temperatura ambiente. La reacción se diluyó con diclorometano (20 mL) y se purificó mediante columna cromatográfica (SiO_2 220 g, acetato de etilo en hexanos gradiente 20-30%,) para rendir el compuesto del título (3,10 g, rindiendo 90%) como un aceite amarillo. [M+H] calculado para C18H19N3O6, 374; encontrado, 374.

Compuesto 83B: 4-bencil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo: Se disolvió el 6-(bencil(2-etoxi-2-oxoetil)amino)-5-nitronicotinato de metilo (445 mg g, 1,19 mmol) en diclorometano (5 mL). A la solución amarilla se agregó metavanadato de amonio (10,0 mg, 0,085 mmol), trifenil fosfito (aproximadamente 10 ul, 0,032 mmol), y Pt/C (50 mg, 5% w/w). La mezcla de reacción se presurizó con gas hidrógeno (75 psi) y se agitó a temperatura ambiente por 48 horas. La reacción luego se presurizó y se diluyó con

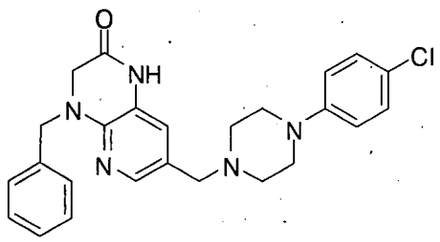
diclorometano (20 mL) la cual se calentó a reflujo por 30 minutos. La solución caliente se filtró a través de un lecho de celite y se lavó con diclorometano caliente (3 x 10 mL). El filtrado se concentró para rendir el compuesto del título (250 mg, 71%) como un sólido blanco. [M+H] calculado para C16H15N3O3, 298; encontrado, 298.

Compuesto 83C: 4-bencil-7-(hidroximetil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se resuspendió el 4-bencil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo (600 mg, 2,02 mmol) en tetrahidrofurano (25 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 121 mg, 3,03 mmol) y se agitó 30 minutos. La reacción luego se enfrió a -78°C y se agregó hidruro de aluminio y litio (3 mL, 2M en THF). La reacción se agitó a una temperatura entre -20 y -10°C por 2 horas. La reacción luego de vuelta se enfrió a -78°C y se agregó MeOH (1 mL) seguido por agua (1 mL). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (200 mL) y agua (100 mL). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (2 x 50 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron con sulfato de sodio y se concentraron para proporcionar el compuesto del título (540 mg, 99%) como un sólido blanco. [M+H] calculado para C15H15N3O2, 270; encontrado, 270.

Compuesto 83: 4-bencil-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: se suspendió el 4-bencil-7-(hidroximetil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona (100 mg, 0,37 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL)

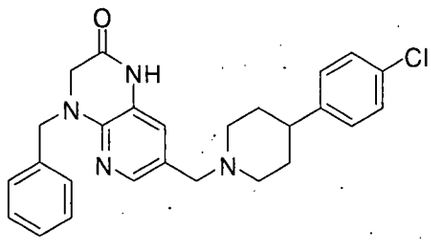
por 1 hora. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (45,3 mg, 27%) como un sólido blanco. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,57 (s, 1H), 7,66 (d, J = 2,0 Hz, 1H), 7,41 - 7,48 (m, 2H), 7,23 - 7,41 (m, 7H), 7,03 (d, J = 2,0 Hz, 1H), 6,19 (s, 1H), 4,72 (s, 2H), 3,86 (s, 2H), 3,43 (s, 2H), 3,03 (d, J = 2,8 Hz, 2H), 2,58 - 2,65 (m, 2H), 2,44 (br. s., 2H). [M+H] calculado para C26H25ClN4O, 445; encontrado, 445.

Compuesto 84: 4-bencil-7-((4-(4-clorofenil)piperazin-1-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Se suspendió el 4-bencil-7-(hidroximetil)-3,4-dihidropirido-[2,3-b]pirazin-2(1H)-ona (100 mg, 0,37 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-clorofenil)piperazina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión se enfrió de nuevo a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (66,6 mg, 40%) como un sólido blanco.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,57 (s, 1H), 7,64 (d, J = 1,8 Hz, 1H), 7,33 (d, J = 4,5 Hz, 4H), 7,25 - 7,30 (m, 1H), 7,19 - 7,24 (m, 2H), 7,01 (d, J = 1,8 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 4,72 (s, 2H), 3,86 (s, 2H), 3,36 (s, 2H), 3,07 - 3,15 (m, 4H), 2,44 - 2,49 (m, 4H). [M+H] calculado para C25H26ClN5O, 448; encontrado, 448.

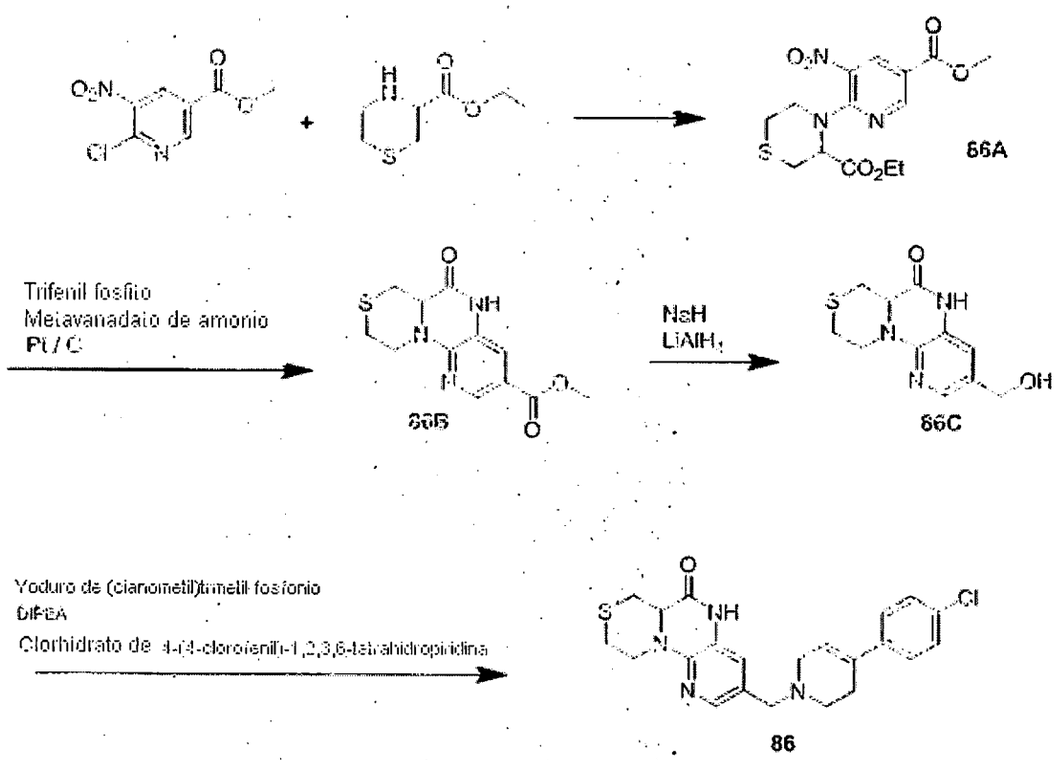
Compuesto 85: 4-bencil-7-((4-(4-clorofenil)piperidin-1-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona



Se suspendió el 4-bencil-7-(hidroximetil)-3,4-dihidropirido [2,3-b]pirazin-2(1H)-ona (100 mg, 0,37 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isoprópilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)piperidina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se filtró y se secó al vacío para proporcionar el compuesto del título (69,9 mg, 42%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,56 (s, 1H), 7,63 (d, J = 2,0 Hz, 1H), 7,30 - 7,37 (m, 6H), 7,23 - 7,30 (m, 3H), 7,00 (d, J = 2,0 Hz, 1H), 4,71 (s, 2H), 3,85 (s, 2H), 3,33 (s, 3H), 2,89 (d, J = 11,4 Hz, 2H), 1,99 (t, J = 10,6 Hz, 2H), 1,67 - 1,78 (m, 2H), 1,48 - 1,66 (m, 2H). [M+H] calculado para C11H15Cl2N, 447; encontrado, 447.

Compuesto 86: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona



Compuesto 86A: 4-(5-(metoxicarbonil)-3-nitropiridin-2-il)tiomorfolina-3-carboxilato de etilo: 6-cloro-5-nitronicotinato de metilo (1,1 g, 5,10 mmol) se agregó a tiomorfolina-3-carboxilato de etilo (2,0 g, 11,41 mmol) puro mientras se agita a temperatura ambiente. La reacción amarilla viscosa se calentó a 90°C por una hora y luego se dejó de vuelta enfriar a temperatura ambiente. La reacción se diluyó con diclorometano (20 mL) y se purificó mediante columna cromatográfica (SiO_2 220 g, acetato de etilo en hexanos, gradiente 20-30%) para rendir el compuesto del título (1,71 g, 95%) como un aceite amarillo. [M+H] calculado para C15H18N2O6S, 356; encontrado, 356.

Compuesto 86B: 6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de metilo: Se disolvió el 4-(5-(metoxicarbonil)-3-nitropiridin-2-il)tiomorfolina-3-carboxilato de etilo (600 mg g, 1,69 mmol) en diclorometano (5 mL). A la solución amarilla se agregó metavanadato de amonio (10,0 mg, 0,085 mmol), trifenil fosfito (aproximadamente 10 ul, 0,032 mmol), y Pt/C (50 mg, 5% w/w). La mezcla de reacción se presurizó con gas hidrógeno (110

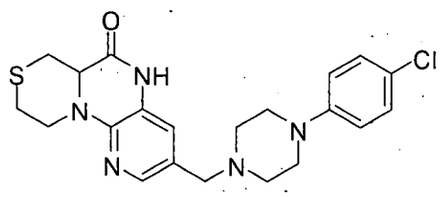
psi) y se agitó a temperatura ambiente por 16 horas. La reacción luego se despresurizó y se diluyó con diclorometano (20 mL) la cual se calentó a reflujo por 30 minutos. La solución caliente se filtró a través de un lecho de celite y se lavó con diclorometano caliente (3 x 10 mL). El filtrado se concentró para rendir el compuesto del título (452 mg, 96%) como un sólido blanco. [M+H] calculado para C12H13N3O3S, 280; encontrado, 280.

Compuesto 86C: 3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona: Se resuspendió el 6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de metilo (386 mg, 1,38 mmol) en tetrahidrofurano (25 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 121 mg, 3,03 mmol) y se agitó 30 minutos. La reacción se enfrió a -78°C y se agregó hidruro de aluminio y litio (3 mL, 2M en THF). La reacción se agitó a una temperatura entre -20 y -10°C por 3 horas. La reacción se enfrió de nuevo a -78°C y se agregó MeOH (1 mL) seguido por agua (1 mL). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (200 mL) y agua (100 mL). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (2 x 50 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (100 mL), se secaron con sulfato de sodio y se concentraron para proporcionar el compuesto del título (497 mg, 98%) como un sólido blanco. [M+H] calculado para C11H13N3O2S, 252; encontrado, 252.

Compuesto 86: 3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona: Se suspendió el 3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]-tiazino[4,3-a]pirazin-6(5H)-ona (100 mg, 0,36 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)-1,2,3,6-

tetrahidropiridina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. Los sólidos se recolectaron para proporcionar el compuesto del título (79,5 mg, 19%) como un sólido blanco.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,66 (s, 1H), 7,70 (d, J = 2,0 Hz, 1H), 7,41 - 7,47 (m, 2H), 7,33 - 7,40 (m, 2H), 7,02 (d, J = 2,0 Hz, 1H), 6,18 (br. s., 1H), 4,88 (dt, J = 13,6, 2,7 Hz, 1H), 4,27 (dd, J = 10,6, 3,0 Hz, 1H), 3,43 (d, J = 3,5 Hz, 2H), 2,98 - 3,07 (m, 3H), 2,66 - 2,83 (m, 3H), 2,58 - 2,65 (m, 2H), 2,39 - 2,48 (m, 3H). [M+H] calculado para C22H23ClN4OS, 427; encontrado, 427.

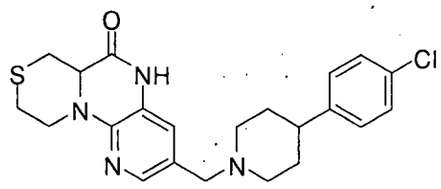
Compuesto 87: 3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona



se suspendió el 3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (Compuesto 86C; 100 mg, 0,36 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-clorofenil)piperazina (104,9 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión de vuelta se enfrió a temperatura ambiente y se filtró. Los sólidos se recolectaron para proporcionar el compuesto del título (86,1 mg, 56%) como un sólido blanco.
^{1}H NMR (DMSO-d_6) δ: 10,66 (s, 1H), 7,69 (d, J = 2,0 Hz, 1H), 7,16 - 7,26 (m, 2H), 7,00 (d, J = 2,0 Hz, 1H), 6,86 - 6,96 (m, 2H), 4,88 (dt, J = 13,6, 2,7 Hz, 1H), 4,26 (dd, J = 10,7, 2,9 Hz, 1H), 3,34 -

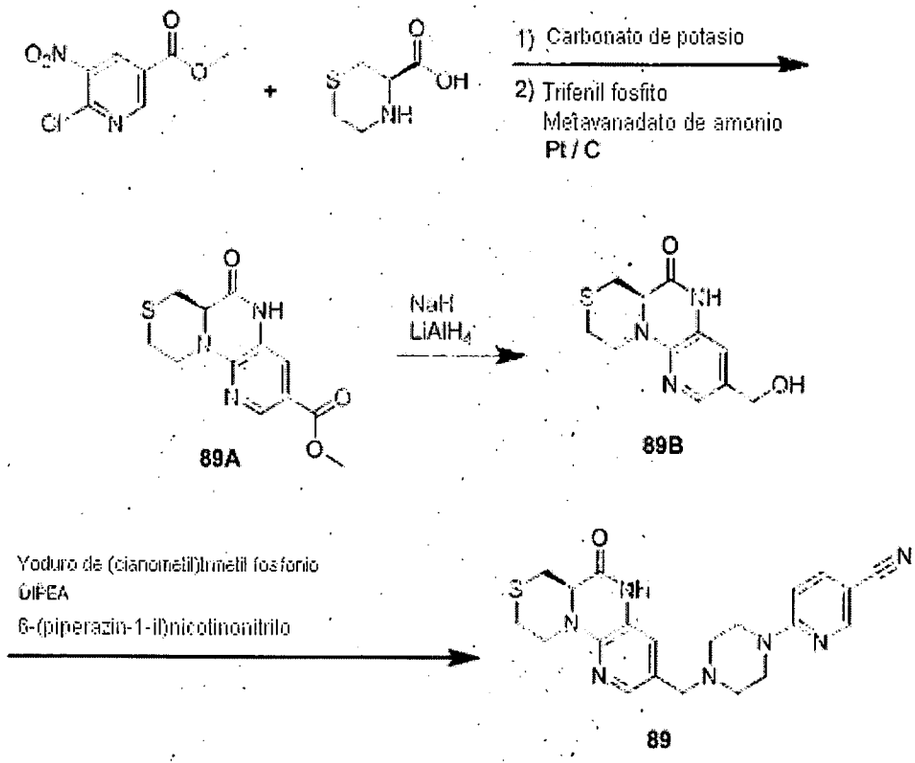
3,42 (m, 2H), 3,07 - 3,16 (m, 4H), 3,02 (td, J = 12,8, 2,3 Hz, 1H), 2,65 - 2,83 (m, 3H), 2,43 - 2,48 (m, 5H). [M+H] calculado para C21H24ClN5OS; 430; encontrado, 430.

Compuesto 88: 3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona



Se suspendió el 3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (Compuesto 86C; 100 mg, 0,36 mmol) en propionitrilo (1 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (123,0 mg, 0,51 mmol) seguido por N-etil-N-isopropilpropan-2-amina (180 ul, 1,03 mmol). A la mezcla agitada se agregó luego clorhidrato de 4-(4-clorofenil)piperidina (104,5 mg, 0,45 mmol). La reacción se calentó a 90°C con agitación por 2 horas. La reacción luego se enfrió a temperatura ambiente y se diluyó con agua (3 mL) y se filtró. Los sólidos se recolectaron y se calentaron a reflujo en etanol (5 mL) por 1 hora. La suspensión se enfrió de nuevo a temperatura ambiente y se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (86,1 mg, 56%) como un sólido blanco. ^{1}H NMR (DMSO-d_6) δ (ppm): 10,44 - 10,83 (m, 1H), 7,68 (d, J = 1,8 Hz, 1H), 7,30 - 7,38 (m, 2H), 7,23 - 7,29 (m, 2H), 6,99 (d, J = 2,0 Hz, 1H), 4,83 - 4,91 (m, 1H), 4,22 - 4,29 (m, 1H), 3,33 (s, 3H), 2,96 - 3,07 (m, 1H), 2,83 - 2,94 (m, 2H), 2,65 - 2,83 (m, 3H), 2,39 - 2,48 (m, 1H), 1,91 - 2,06 (m, 2H), 1,66 - 1,78 (m, 2H), 1,49 - 1,66 (m, 2H) [M+H] calculado para C22H25ClN4OS, 429; encontrado, 429.

Compuesto 89: (R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo



Compuesto 89A: 6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de (R)-metilo: A una suspensión de ácido (R)-tiomorfolina-3-carboxílico (1,009 g, 6,86 mmol) en THF se agregó 6-cloro-5-nitronicotinato de metilo (1,35 g, 6,23 mmol) y carbonato de potasio (2,58 g, 18,70 mmol). La suspensión se calentó a reflujo por 3 horas. La solución cruda color naranja se dejó enfriar a temperatura ambiente y se filtró a través de un lecho de celite la cual se lavó con DCM (50 mL), y se transfirió a una bomba hidrogenadora. A La solución se agregó trifenil fosfito (0,019 ml, 0,061 mmol), platino (0,238 g, 0,061 mmol), y metavanadato de amonio. El matraz se selló y presurizó a 140 psi con agitación por 24 horas a temperatura ambiente. El matraz se despresurizó y la mezcla se diluyó con DCM (100 mL) y se calentó a reflujo por 30 minutos. La mezcla caliente se filtró a través de celite y se concentró para rendir 887 mg (52%) del producto como un sólido blanco. [M+H] calculado para C12H13N3O3S, 280; encontrado, 280.

Compuesto 89B: (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona: Se suspendió el 6-oxo-

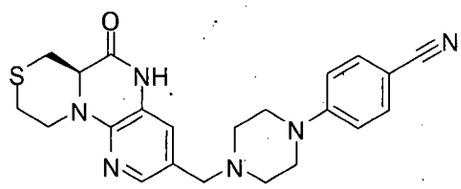
5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de (R)-metilo (887 mg, 3,18 mmol) en tetrahidrofurano (40 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 191 mg, 4,76 mmol,) y se agitó 30 minutos. La reacción luego se enfrió a -45°C y se agregó hidruro de aluminio y litio (4,76 mL, 2M en THF). La reacción se agitó a una temperatura entre -20 y -10°C por 1 hora. La reacción luego de vuelta se enfrió a -78°C y se agregó metanol (5 ml) seguido por agua (1 ml). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (400 ml) y agua (100 ml). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. El filtrado se recolectó. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (1 x 100 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (100 ml), y se concentraron para rendir 710,8 mg (89%) del compuesto del título como un sólido blanco. [M+H] calculado para C11H13N3O2S, 252; encontrado, 252.

Compuesto 89: (R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo: Se suspendió (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]- tiazino[4,3-a]pirazin-6(5H)-ona (80,0 mg, 0,318 mmol) en propionitrilo (0,8 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (93,0 mg, 0,382 mmol) seguido por N-etil-N-isopropilpropan-2-amina (167 ul, 0,955 mmol). A la mezcla agitada se agregó luego 6-(piperazin-1-il)nicotinonitrilo (59,9 mg, 0,318 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción se enfrió a temperatura ambiente y se dejó reposar por 48 horas. El precipitado se recogió por filtración, se lavó con etanol (5 mL) y se secó al vacío para proporcionar el compuesto del título (53,9 mg, 40,2%) como un sólido blanco.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,41 (d, J = 1,8 Hz, 1H), 7,78 (d, J = 1,8 Hz, 2H), 7,62 (dd, J = 8,8, 2,3 Hz, 1H), 6,95 (br. s., 1H), 6,60 (d, J = 8,8 Hz, 1H), 5,06 (dt, J = 13,6, 2,8 Hz, 1H), 4,43 (dd, J = 10,4, 3,3 Hz, 1H), 3,70 (br. s., 4H), 3,45 (br. s., 2H), 3,15 (td, J = 12,9, 2,3 Hz, 1H), 3,00 (td, J = 12,8, 2,8 Hz, 1H), 2,78 - 2,94 (m,

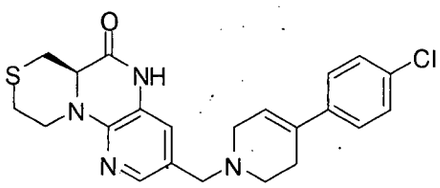
2H), 2,54 (br. s., 4H), 2,40 (dd, J = 13,6, 1,5 Hz, 1H). [M+H] calculado para C21H23N7OS, 422; encontrado, 422.

Compuesto 90: (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo



Se suspendió el (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (80,0 mg, 0,318 mmol) en propionitrilo (0,8 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (93,0 mg, 0,382 mmol) seguido por N-etil-N-isopropilpropan-2-amina (167 ul, 0,955 mmol). A la mezcla agitada se agregó luego 4-(piperazin-1-il)benzonitrilo (59,6 mg, 0,318 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción se enfrió a temperatura ambiente y se dejó reposar 48 horas. El precipitado se recogió por filtración, se lavó con etanol (5 mL) y se secó al vacío para proporcionar el compuesto del título (36,0 mg, 26,9%) como un sólido blanco. ^{1}H NMR (CLOROFORMO-d) δ (ppm): 8,26 (br. s., 1H), 7,79 (d, J = 1,8 Hz, 1H), 7,44 - 7,60 (m, 2H), 6,96 (br. s., 1H), 6,76 - 6,91 (m, 2H), 5,05 (dt, J = 13,6, 2,7 Hz, 1H), 4,43 (dd, J = 10,7, 3,2 Hz, 1H), 3,27 - 3,63 (m, 6H), 3,15 (td, J = 12,8, 2,3 Hz, 1H), 3,00 (td, J = 12,8, 2,7 Hz, 1H), 2,77 - 2,93 (m, 2H), 2,59 (br. s., 4H), 2,34 - 2,45 (m, 1H). [M+H] calculado para C22H24N6OS, 421; encontrado, 421.

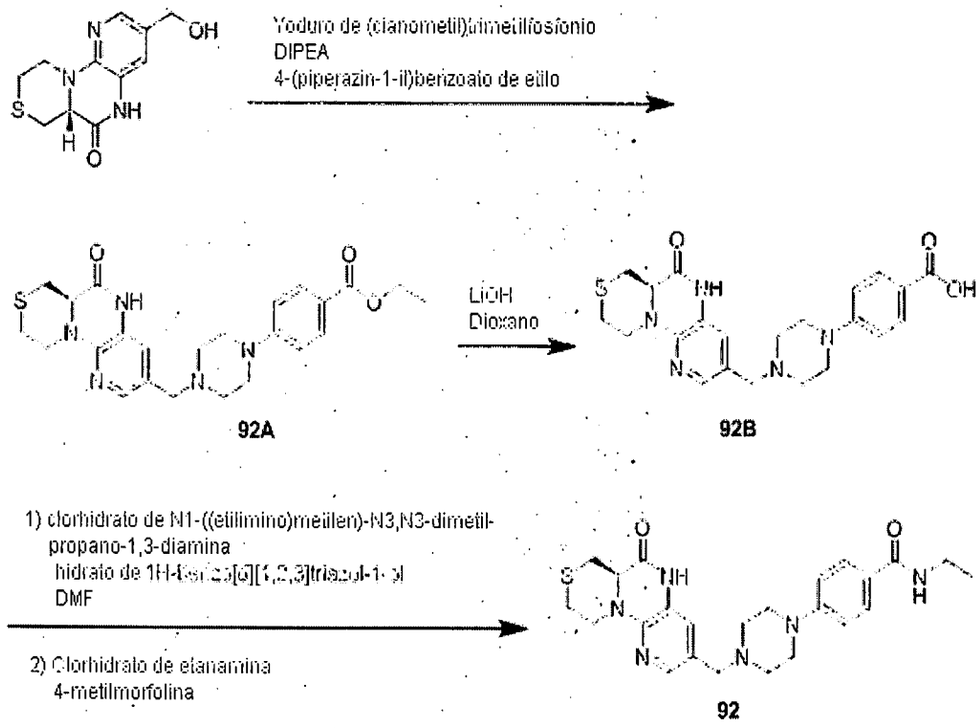
Compuesto 91: (R)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona



A una suspensión de (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (70 mg,

0,279 mmol) en propiononitrilo (Volumen: 696 µl) se agregó yoduro de (cianometil)trimetilfosfonio (81 mg, 0,334 mmol), DIEA (146 µl, 0,836 mmol) y finalmente clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (64,1 mg, 0,279 mmol). Se calentó el frasco a 90°C por 12 horas. Se enfrió a temperatura ambiente y se concentró a un resíduo café la que se trató con MeOH (5 mL). El precipitado se filtró, los sólidos se recolectaron, se suspendieron en EtOH (15mL) y se calentaron a reflujo por 2 horas. Se dejaron reposar a temperatura ambiente. Se filtraron, se secaron al vacío y se recuperaron 75,6 mg (63,6%) del compuesto del título como un sólido blanco. ^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,80 (d, J = 1,8 Hz, 1H), 7,66 (br. s., 1H), 7,30 (d, J = 3,8 Hz, 5H), 7,04 (br. s., 1H), 6,02 - 6,09 (m, 1H), 5,06 (ddd, J = 13,5, 2,8, 2,7 Hz, 1H), 4,42 (dd, J = 10,5, 3,2 Hz, 1H), 3,54 (br. s., 2H), 3,10 - 3,26 (m, 3H), 3,00 (td, J = 12,8, 2,7 Hz, 1H), 2,85 - 2,92 (m, 1H), 2,75 (br. s., 2H), 2,56 (br. s., 2H), 2,35 - 2,44 (m, 1H). [M+H] calculado para C22H23ClN4OS, 427; encontrado, 427.

Compuesto 92: (R)-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 92A: 4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (R)-etilo: A una suspensión de (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (333 mg, 1,325 mmol) en propiononitrilo (3313 µl) se agregó yoduro de (cianometil)trimetilfosfonio (386 mg, 1;590 mmol) y DIPEA (694 µl, 3,98 mmol) y finalmente 4-(piperazin-1-il)benzoato de etilo (310 mg, 1,325 mmol). Se calentó el frasco a 90°C por 12 horas. La reacción luego se enfrió a temperatura ambiente, se diluyó con EtOH (8 ml) y agua (1 mL), luego se filtró. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título 508 mg, 82%) como un sólido blanco. [M+H] calculado para C24H29N5O3S, 468; encontrado, 468.

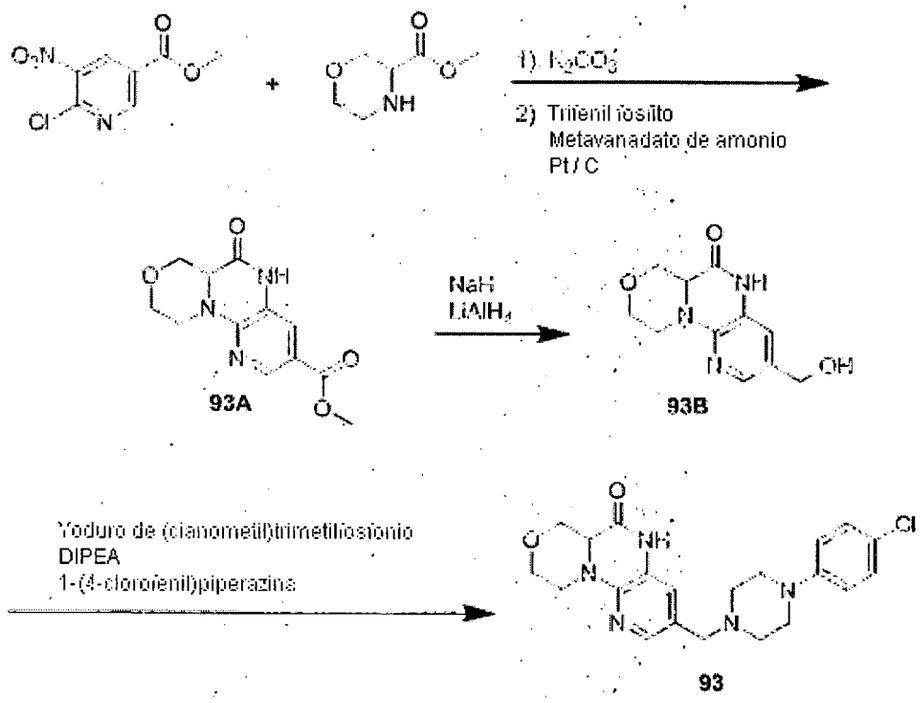
Compuesto 92B: ácido (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)-metil)piperazin-1-il)benzoico: Se resuspendió 4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (R)-etilo (180 mg, 0,385 mmol) en

dioxano (2081 µl) y se agregó LiOH (1N, 2310 µl, 2,310 mmol). La reacción se agitó 16 horas a temperatura ambiente. La reacción se concentró al vacío y el resíduo se suspendió en agua (5 mL) y se acidificó con (HCl 4,5N) a pH 4. Un precipitado color tostado se formó, el cual se filtró y los sólidos se recolectaron, se secaron y se determinó que el producto (166 mg, 98%) es como un sólido color tostado. [M+H] calculado para C22H25N5O3S, 440; encontrado, 440.

Compuesto 92: (R)-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida: El ácido (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoico (50 mg, 0,114 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropane-1,3-diamina (32,7 mg, 0,171 mmol), hidrato de 1H-benzo[d][1,2,3]triazol-1-ol (26,1 mg, 0,171 mmol), y DMF (Volumen: 0,5 mL) se agitaron conjuntamente para proporcionar una solución amarilla. Se agregó clorhidrato de etanamina (9,28 mg, 0,114 mmol) y 4-metilmorfolina (0,065 mL, 0,593 mmol). La reacción se agitó a temperatura ambiente por 4 horas. La reacción cruda se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (12,0 mg, 22,6%) como un sólido blanco.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,79 (s, 1H), 7,68 (d, J = 8,8 Hz, 2H), 7,53 (s, 1H), 6,85 - 7,00 (m, 3H), 5,96 (br. s., 1H), 5,06 (d, J = 13,4 Hz, 1H), 4,43 (dd, J = 10,5, 3,4 Hz, 1H), 3,39 - 3,54 (m, 4H), 3,30 (br. s., 4H), 3,15 (td, J = 12,9, 2,3 Hz, 1H), 3,00 (br. s., 1H), 2,87 (d, J = 10,4 Hz, 2H), 2,60 (br. s., 4H), 2,42 (d, J = 1,5 Hz, 1H), 1,25 (t, J = 7,2 Hz, 3H). [M+H] calculado para C24H30N6O2S, 467; encontrado, 467. MP: 288,9 °C

Compuesto 93: 3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona



Compuesto 93A: 6-oxo-5,6,6a,7,9,10-hexahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-3-carboxilato de metilo: A una suspensión de morfolina-3-carboxilato de metilo (2,0 g, 13,78 mmol) en THF se agregó 6-cloro-5-nitronicotinato de metilo (2,71 g, 12,53 mmol) y carbonato de potasio (5,19 g, 37,6 mmol). La suspensión se calentó a reflujo por 3 horas. La solución cruda de color naranja se dejó enfriar a temperatura ambiente y se filtró a través de un lecho de celite el cual se lavó con DCM (50 mL) y se transfirió a una bomba de hidrogenación. A la solución se agregó trifenil fosfito (0,039 ml, 0,125 mmol), platino (5%, 0,489 g, 0,125 mmol), y metavanadato de amonio (0,117 g, 1,0 mmol). El matraz se selló y presurizó a 140 psi con agitación por 24 horas a temperatura ambiente. El matraz se despresurizó y la mezcla se diluyó con DCM (100 mL) y se calentó a reflujo por 30 minutos. La mezcla caliente se filtró a través de celite y se concentró para rendir 1,98 g (60%) del producto como un sólido blanco. [M+H] calculado para C12H13N3O4, 264; encontrado, 264.

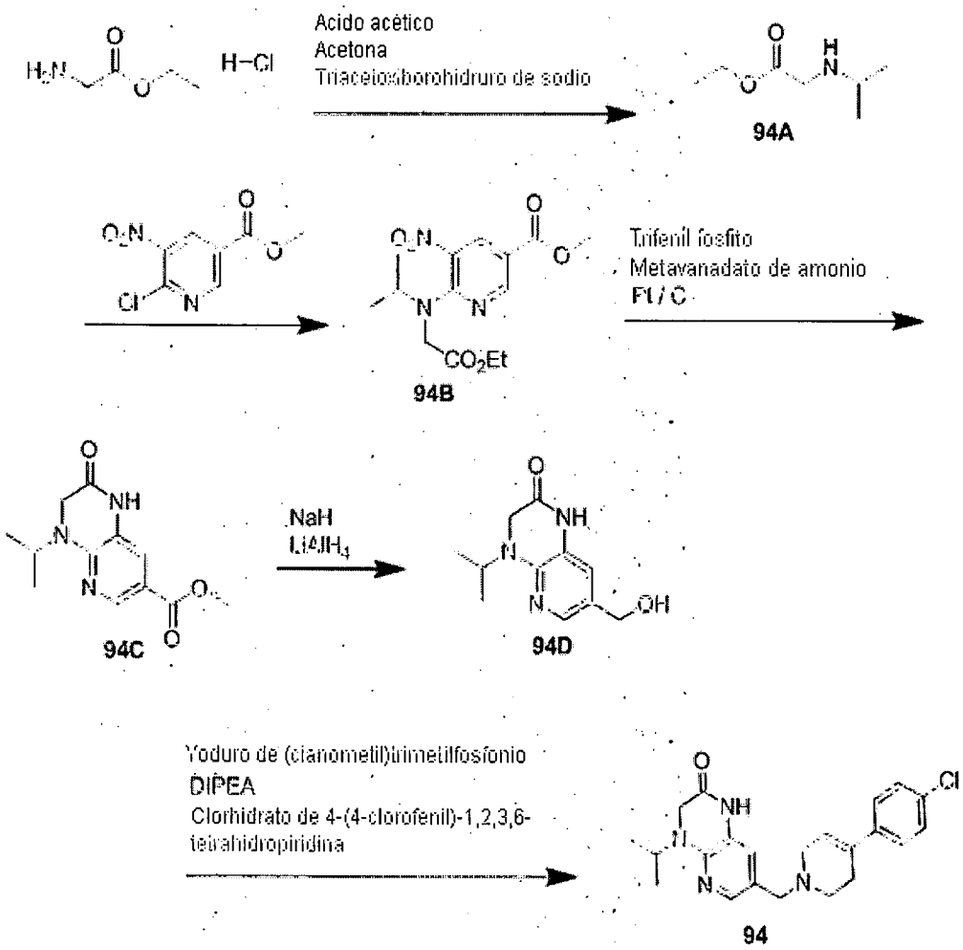
Compuesto 93B: 3-(hidroximetil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona: Se resuspendió el 6-oxo-5,6,6a,7,9,10-hexahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-3-carboxilato de metilo (1000 mg, 3,80 mmol) en tetrahidrofurano (47 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 228 mg, 5,70 mmol,) y se agitó 30 minutos. La reacción luego se enfrió a -45°C y se agregó hidruro de aluminio y litio (11,4 mL, 1M en THF). La reacción se agitó a una temperatura entre -20 y -10°C por 1 hora. La reacción luego se enfrió de nuevo a -78°C y se agregó metanol (3 ml) seguido por agua (1 ml). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (400 ml) y agua (100 ml). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. El filtrado se recolectó. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (1 x 100 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (100 ml), y se concentraron para rendir 657 mg (73,5%) del compuesto del título como un sólido blanco. [M+H] calculado para C11H13N3O3, 236; encontrado, 236.

Compuesto 93: 3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona: A una suspensión de 3-(hidroximetil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]-pirazin-6(5H)-ona (73,2 mg, 0,311 mmol) en propionitrilo (778 µl) se agregó yoduro de (cianometil)trimetilfosfonio (91 mg, 0,373 mmol) y DIPEA (163 µl, 0,934 mmol) y finalmente 1-(4-clorofenil)piperazina (61,2 mg, 0,311 mmol). La mezcla se calentó a 90°C por 4 horas. El producto crudo se enfrió a temperatura ambiente y se dejó reposar 16 horas, luego se trató con MeOH (5 mL). El precipitado se recolectó y se calentó a reflujo en EtOH (15mL) por 2 horas. La suspensión se enfrió a temperatura ambiente y se filtró para recuperar el compuesto del título (75,6 mg, 58,7%) como un sólido blanco.

^{1}H NMR (CLOROFORMO-d) δ (ppm): 7,82 (d, J = 1,8 Hz, 1H), 7,72 (br. s., 1H), 7,16 - 7,24 (m, 2H), 6,99 (br. s., 1H), 6,77 - 6,89 (m, 2H), 4,41 (dd, J = 11,5, 3,7 Hz, 1H), 4,26 (dd, J = 13,3, 1,6 Hz, 1H),

3,95 - 4,12 (m, 2H), 3,59 - 3,75 (m, 2H), 3,46 (br. s., 2H), 3,16 (br. s., 4H), 2,94 - 3,06 (m, 1H), 2,60 (br. s., 4H). [M+H] calculado para C21H24ClN5O2, 414; encontrado, 414.

Compuesto 94: 7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona.



Compuesto 94A: 2-(isopropilamino)acetato de etilo: A una suspensión de clorhidrato de 2-aminoacetato de etilo (20 g, 143,28 mmol) en THF (400 mL) se agregó ácido acético glacial (20 mL) seguido por acetona (11,59 mL, 151,62 mmol). La reacción se agitó 30 minutos a temperatura ambiente. Se agregó triacetoxiborohidruro de sodio (60,73 g, 286,56 mmol) durante el curso de una hora. La reacción se vertió lentamente en una mezcla bifásica agitada vigorosamente de agua (300 mL) y acetato de etilo (800 mL). La capa acuosa se ajustó a pH 13 utilizando una solución de 50% (en peso) de NaOH. La mezcla se agitó

30 minutos y se vertió en un embudo de decantación. La capa orgánica se recolectó y la capa acuosa se volvió a extraer con acetato de etilo (3 x 200 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (300 mL), se secaron con sulfato de sodio, y se concentraron para rendir el compuesto del título (17,6 g, 85%) como un aceite transparente el cual se utilizó en la siguiente etapa sin posterior purificación. [M+H] calculado para C7H15NO2, 146; encontrado, 146.

Compuesto 94B: 6-((2-etoxi-2-oxoetil)(isopropil)amino)-5-nitronicotinato de metilo: 6-cloro-5-nitronicotinato de metilo (2 g, 9,23 mmol) se agregó a 2-(isopropilamino) acetato de etilo (5,0 g, 34,5 mmol) puro mientras se agita a temperatura ambiente. La reacción amarilla viscosa se calentó a 90°C por una hora y luego se dejó enfriar de nuevo a temperatura ambiente. La reacción se diluyó con diclorometano (20 mL) y se purificó mediante columna cromatográfica (SiO_2 220 g, acetato de etilo en hexanos gradiente, 20-30%) para rendir el compuesto del título (2,39 g, 83%) como un aceite amarillo. [M+H] calculado para C14H19N3O6, 326; encontrado, 326.

Compuesto 94C: 4-isopropil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo: Se disolvió el 6-((2-etoxi-2-oxoetil)(isopropil)amino)-5-nitronicotinato de metilo (2,39 g, 7,35 mmol) en diclorometano (10 mL). A la solución amarilla se agregó metavanadato de amonio (15,0 mg, 1,13 mmol), trifenil fosfito (aprox 10 ul, 0,032 mmol), y Pt/C (240 mg, 5% w/w). La mezcla de reacción se presurizó con gas hidrógeno (110 psi) y se agitó a temperatura ambiente por 16 horas. La reacción luego se despresurizó y se diluyó con diclorometano (80 mL) la cual se calentó a reflujo por 30 minutos. La solución caliente se filtró a través de un lecho de celite y se lavó con diclorometano caliente (3 x 20 mL). El filtrado se concentró para rendir el compuesto del título (1,70 g, 93%) como un sólido blanco. [M+H] calculado para C12H15N3O3, 250; encontrado, 250.

Compuesto 94D: 7-(hidroximetil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se suspendió el 4-isopropil-2-oxo-1,2,3,4-

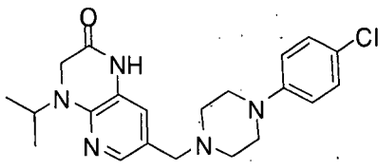
tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo (1,3 g, 5,45 mmol) en tetrahidrofurano (68 mL). La suspensión blanca se enfrió a 0°C y NaH se agregó (dispersión en aceite mineral al 60%, 0,327 g, 8,17 mmol). La reacción se retiró del baño de hielo y se dejó agitar a temperatura ambiente por 0,5 hora. La solución luego se enfrió a -78°C y se agregó $LiAlH_4$ durante 2 minutos. Se mantuvo a una temperatura entre -30 y -20°C. La reacción se enfrió a -78°C y se agregó MeOH (2 mL). La reacción se agitó a temperatura ambiente por 30 minutos. La reacción se vertió en acetato de etilo (400 mL) y agua (100 mL), y se agitó por 1 hora. La mezcla se filtró a través de un medio de frita para retirar los sólidos tostados. La capa acuosa se extrajo con acetato de etilo (1X100mL). Las fracciones orgánicas se combinaron, se lavaron una vez con salmuera (100 mL), se secaron con sulfato de sodio y se concentraron para dar el compuesto del título (1,10 g, 91%) como un sólido blanco. [M+H] calculado para C11H15N3O2, 222; encontrado, 222.

Compuesto 94:-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona: Se suspendió nuevamente como una suspensión el 7-(hidroximetil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona (100 mg, 0,452 mmol) en propiononitrilo (1 mL). A continuación se agregó yoduro de (cianometil)trimetil- fosfonio (132 mg, 0,542 mmol) seguido por DIPEA (0,237 mL, 1,356 mmol). A la suspensión blanca agitada se agregó luego el clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina (114 mg, 0,50 mmol). La reacción se calentó a 90°C y se agitó durante la noche. La reacción cruda se enfrió a temperatura ambiente y se concentró a un residuo, luego se resuspendió en 3 mL DMSO y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (46,9 mg, 26%) como un sólido blanco.

^1H NMR (DMSO-d_6) δ (ppm): 10,50 (s, 1H), 7,65 (d, J = 1,8 Hz, 1H), 7,40 - 7,46 (m, 2H), 7,34 - 7,39 (m, 2H), 6,98 (d, J = 2,0 Hz, 1H), 6,18 (br. s., 1H), 4,76 - 4,87 (m, 1H), 3,81 (s, 2H), 3,40 (s, 2H),

3,01 (d, J = 2,8 Hz, 2H), 2,60 (t, J = 5,6 Hz, 2H), 2,43 (br. s., 2H), 1,12 (d, J = 6,8 Hz, 6H). [M+H] calculado para C22H25ClN4O, 397; encontrado, 397.

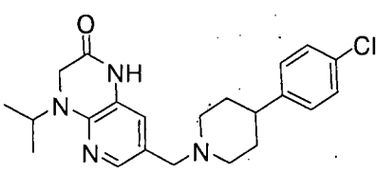
Compuesto 95: 7-((4-(4-clorofenil)piperazin-1-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona.



El 7-(hidroximetil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona (100 mg, 0,452 mmol) se pesó en un frasco y se resuspendió como una suspensión en propiononitrilo (1 mL). A continuación se agregó yoduro de (cianometil)trimetilfosfonio (132 mg, 0,542 mmol) seguido por DIEA (0,237 mL, 1,356 mmol). A la suspensión blanca agitada se agregó luego el clorhidrato de 1-(4-clorofenil)piperazina (116 mg, 0,50 mmol). La reacción se agitó durante la noche a 90°C. La reacción cruda se enfrió a temperatura ambiente y se concentró a un resíduo, luego se suspendió en DMSO (3 mL) y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (46,6 mg, 26%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,49 (s, 1H), 7,63 (d, J = 2,0 Hz, 1H), 7,21 (d, J = 9,1 Hz, 2H), 6,97 (d, J = 1,8 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 4,74 - 4,87 (m, 1H), 3,81 (s, 2H), 3,33 (d, J = 2,0 Hz, 2H), 3,01 - 3,15 (m, 4H), 2,41 - 2,48 (m, 4H), 1,12 (d, J = 6,8 Hz, 6H). [M+H] calculado para C21H26ClN5O, 400; encontrado, 400.

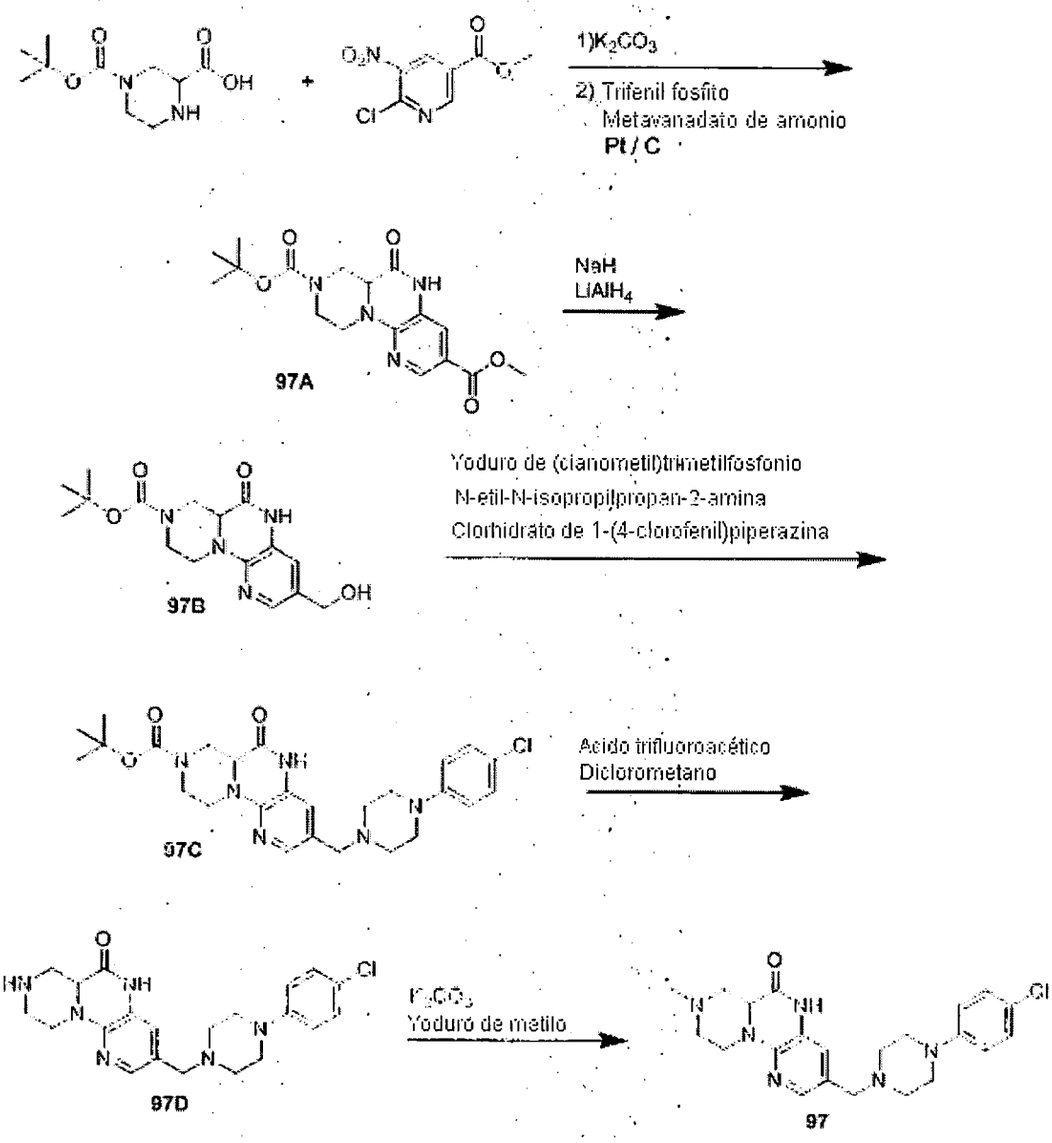
Compuesto 96: 7-((4-(4-clorofenil)piperidin-1-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona.



Se suspendió el 7-(hidroximetil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona (100 mg, 0,452 mmol) en propionitrilo (1 mL). A esto se agregó yoduro de (cianometil)trimetilfosfonio (132 mg, 0,542 mmol) seguido por DIEA (0,237 mL, 1,356 mmol) y clorhidrato de 4-(4-clorofenil)piperidina (115 mg, 0,50 mmol). La reacción se agitó a 90°C durante la noche. La reacción cruda se enfrió a temperatura ambiente y se concentró a un resíduo, luego se suspendió en DMSO (3 mL) y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se filtró y se secó al vacío para proporcionar el compuesto del título (28,3 mg, 16%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,49 (s, 1H), 7,62 (d, J = 2,0 Hz, 1H), 7,29 - 7,37 (m, 2H), 7,18 - 7,29 (m, 2H), 6,96 (d, J = 2,0 Hz, 1H), 4,75 - 4,87 (m, 1H), 3,81 (s, 2H), 3,32 (d, J = 12,9 Hz, 3H), 2,88 (d, J = 11,1 Hz, 2H), 1,87 - 2,07 (m, 2H), 1,65 - 1,77 (m, 2H), 1,57 (dd, J = 12,4, 3,3 Hz, 2H), 1,10 (d, 6H). [M+H] calculado para C22H27ClN4O, 399; encontrado, 399.

Compuesto 97: 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-2-metil-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona



Compuesto 97A: 10-Oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2,7-dicarboxilic acid 2-ter-butil éster 7-metil éster: A una suspensión de ácido 4-(ter-butoxicarbonil)piperazina-2-carboxílico (1169 mg, 5,08 mmol) en THF (46 mL) se agregó 6-cloro-5-nitronicotinato de metilo (1000 mg, 4,62 mmol) y K_2CO_3 (638 mg, 4,62 mmol). La suspensión se calentó a reflujo por 2 horas, se enfrió a temperatura ambiente, y se filtró a través de un lecho de celite. El celite se lavó con DCM (50 mL) y las porciones orgánicas se combinaron. La solución se cargó en una bomba de hidrogenación, luego se trató con trifenil fosfito (0,015 ml, 0,048 mmol), vanadato de amonio (44 mg, 0,380 mmol), y platino (1,853 g, 0,475 mmol). La

reacción se selló y se presurizó con gas hidrógeno (150 psi) durante la noche. La reacción luego se diluyó con DCM (100 mL) y se calentó a reflujo por 1 hora. La mezcla caliente se filtró a través de celite, se lavó con DCM (50 mL), y se concentró a 1,65 g (96%) del compuesto del título como un sólido blanquecino. [M+H] calculado para C17H22N4O5, 363; encontrado, 363.

Compuesto 97B: ter-butil éster del ácido 7-Hidroximetil-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico: Se resuspendió 2-ter-butil éster 7-metil éster del ácido 10-Oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2,7-dicarboxílico (545 mg, 1,504 mmol) en tetrahidrofurano (18 mL) en un ambiente inerte. A la suspensión agitada a temperatura ambiente se agregó NaH (dispersión en aceite mineral al 60%, 90 mg, 2,26 mmol,) y se agitó por 30 minutos. La reacción luego se enfrió a -45°C y se agregó hidruro de aluminio y litio (2,26 ml, 2M en THF). La reacción se agitó a una temperatura entre -20 y -10°C por 1 hora. La reacción luego se enfrió de nuevo a -60°C y se agregó MeOH (5 ml) seguido por agua (1 ml). La reacción se dejó agitar a temperatura ambiente por 2 horas y luego se vertió en acetato de etilo (400 ml) y agua (100 ml). La mezcla bifásica se agitó vigorosamente y luego se filtró a través de un medio de frita. El filtrado se recolectó. Las capas se separaron y la fase acuosa se extrajo con acetato de etilo (1 x 100 ml). Las capas orgánicas se combinaron, se lavaron con salmuera (100 ml), y se concentraron a 429,4 mg (96%) del compuesto del título como un sólido blanquecino. [M+H] calculado para C16H22N4O4, 335; encontrado, 335

Compuesto 97C: ácido ter-butil éster 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico: Se suspendió el ter-butil éster del ácido 7-Hidroximetil-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico (22,0 mg, 0,598 mmol) en propionitrilo (1,5 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (174,0 mg, 0,718 mmol) seguido por N-etil-N-isopropilpropan-2-amina (313 ul, 1,794 mmol). A la mezcla agitada se agregó luego clorhidrato de 1-(4-

clorofenil)piperazina (139 mg, 0,598 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción cruda se enfrió a temperatura ambiente y se purificó sobre columna de sílica (24 g, 25% THF en acetato de etilo). Las fracciones se combinaron y se concentraron para proporcionar 250,9 mg (82%) del compuesto del título como un sólido café de pureza del 80%. [M+H] calculado para C26H33ClN6O3, 513; encontrado, 513.

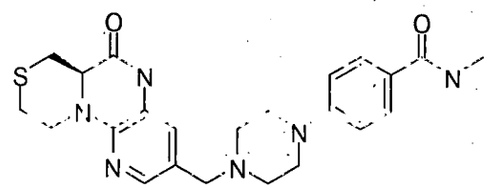
Compuesto 97D: 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona: Se disolvió el ter-butil éster del ácido 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico (250 mg, 0,487 mmol) en diclorometano (5 mL) y se agregó ácido trifluoroacético (3 mL) mientras, se agitó a temperatura ambiente. La reacción se agitó por 16 horas y se concentró a un resíduo. El resíduo se disolvió en DMF y se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (17,8 mg, 8,8%) como un sólido blanco.
^{1}H NMR (DMSO-d_6) δ (ppm): 10,68 (s, 1H); 7,70 (d, J = 2,0 Hz, 1H), 7,14 - 7,30 (m, 2H), 7,03 (d, J = 2,0 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 4,33 (d, J = 11,4 Hz, 1H), 3,97 (dd, J = 11,0, 3,4 Hz, 1H), 3,45 (dd, J = 12,5, 2,9 Hz, 4H), 3,32 - 3,36 (m, 4H), 3,16 (d, J = 9,6 Hz, 1H), 3,06 - 3,13 (m, 4H), 2,72 - 2,87 (m, 3H). [M+H] calculado para C26H33ClN6O3, 413; encontrado, 413.

Compuesto 97: 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-2-metil-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona: A una solución de 7-[4-(4-Cloro-fenil)-piperazin-1-ilmetil]-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona (139 mg, 0,337 mmol) en DMF (3,4 mL) se enfrió a 0°C se agregó carbonato de potasio (233 mg, 1,683 mmol) y yoduro de metilo (2 M en THF, 0,168 mL). La reacción se agitó 1 hora a 0°C y se filtró a través de celite. El filtrado se purificó mediante HPLC (acetonitrilo en agua 55-90%,

solución tampón de bicarbonato de amonio). Las fracciones se combinaron y se concentraron hasta un precipitado sólido blanco. El precipitado se recogió por filtración y se secó al vacío para proporcionar el compuesto del título (4,6 mg, 3,2%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ (ppm): 10,59 (s, 1H), 7,68 (d, J = 1,8 Hz, 1H), 7,15 - 7,28 (m, 2H), 7,01 (d, J = 2,0 Hz, 1H), 6,85 - 6,97 (m, 2H), 4,17 - 4,30 (m, 1H), 3,88 (dd, J = 10,6, 3,3 Hz, 1H), 3,37 (s, 2H), 3,14 - 3,20 (m, 1H), 3,06 - 3,14 (m, 4H), 2,84 (d, J = 11,6 Hz, 1H), 2,74 (td, J = 12,4, 3,0 Hz, 1H), 2,44 - 2,48 (m, 4H), 2,26 (s, 3H), 1,91 - 2,02 (m, 2H). [M+H] calculado para C22H27ClN6O, 427; encontrado, 427.

Compuesto 98: (R)-N-metil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida

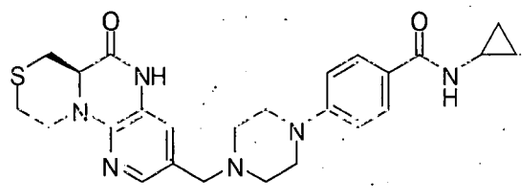


En un frasco equipado con un agitador de barra se cargó el ácido (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoico (50 mg, 0,114 mmol) suspendido en DMF (1,14 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (59 µl, 0,34 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (64,9 mg, 0,171 mmol), y clorhidrato de metanamina (8,45 mg, 0,125 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se recolectaron y liofilizaron para rendir 25,1 mg (49%) del producto como un sólido blanco.

^{1}H NMR (CLOROFORMO-d) δ: 8,37 (br. s., 1H), 7,58 - 7,89 (m, 3H), 7,15 (br. s., 1H), 6,87 (d, J = 8,8 Hz, 2H), 6,07 (d, J = 4,5 Hz, 1H), 5,06 (dt, J = 13,6, 2,5 Hz, 1H), 4,42 (dd, J = 10,1, 3,8 Hz, 1H), 3,55 (br. s., 2H), 3,36 (br. s., 4H), 3,08 - 3,24 (m, 1H), 2,56 -

3,08 (m, 8H), 2,40 (dd, J = 13,5, 1,1 Hz, 1H), 1,74 (br. s., 2H). [M+H] calculado para C23H28N6O2S, 453; encontrado, 453.

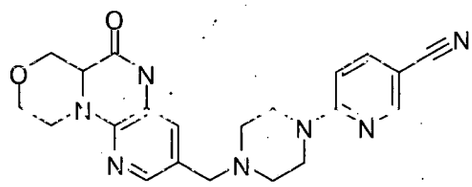
Compuesto 99: (R)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida



En un frasco equipado con un agitador de barra se cargó el ácido (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoico (50 mg, 0,114 mmol) se resuspendió en DMF (1,14 mL). A la mezcla se agregó N-etil-N-isopropilpropan-2-amina (59 µl, 0,34 mmol), hexafluorofosfato de O-(7-Azabenzotriazol-1-il)-N,N,N'N'-tetrametiluronio (64,9 mg, 0,171 mmol), y ciclopropanamina (9,16uL, 0,125 mmol). La reacción se agitó a temperatura ambiente durante la noche. La reacción se purificó mediante HPLC (acetonitrilo en agua 55-90%, solución tampón de bicarbonato de amonio). Las fracciones se recolectaron y liofilizaron para rendir 25,1 mg (49%) del producto como un sólido blanco

^{1}H NMR (CLOROFORMO-d) δ: 8,42 (br. s., 1H), 7,78 (d, J = 1,5 Hz, 1H), 7,65 (d, J = 8,8 Hz, 2H), 7,13 (br. s., 1H), 6,85 (d, J = 9,1 Hz, 2H), 6,17 (d, J = 2,3 Hz, 1H), 5,05 (ddd, J = 13,5, 2,7, 2,5 Hz, 1H), 4,42 (dd, J = 10,4, 3,5 Hz, 1H), 3,53 (br. s., 2H), 3,34 (br. s., 4H), 3,14 (td, J = 12,9, 2,3 Hz, 1H), 2,99 (td, J = 12,8, 2,7 Hz, 1H), 2,78 - 2,93 (m, 3H), 2,68 (br. s., 4H), 2,39 (dd, J = 13,6, 1,3 Hz, 1H), 0,80 - 0,90 (m, 2H), 0,54 - 0,67 (m, 2H). [M+H] calculado para C23H28N6O2S, 479; encontrado, 479.

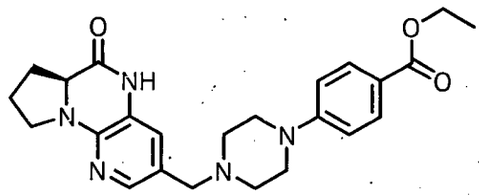
Compuesto 100: 6-(4-((6-oxo-5,6,6a,7,9,10-hexahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-3-il)metil)- piperazin-1-il)nicotinonitrilo



Se suspendió el 3-(hidroximetil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona (70,0 mg, 0,298 mmol) en propionitrilo (0,74 mL) y se agregó yoduro de (cianometil)trimetilfosfonio (87,0 mg, 0,357 mmol) seguido por N-etil-N-isopropilpropan-2-amina (115 ul, 0,893 mmol). A la mezcla agitada se agregó luego 6-(piperazin-1-il)nicotinonitrilo (56,0 mg, 0,298 mmol). La reacción se calentó a 90°C con agitación por 16 horas. La reacción se enfrió a temperatura ambiente y se dejó reposar 48 horas. El precipitado se recogió por filtración, se lavó con metanol (5 mL) y se secó al vacío para proporcionar el compuesto del título (72,5 mg, 60,1%) como un sólido blanco.

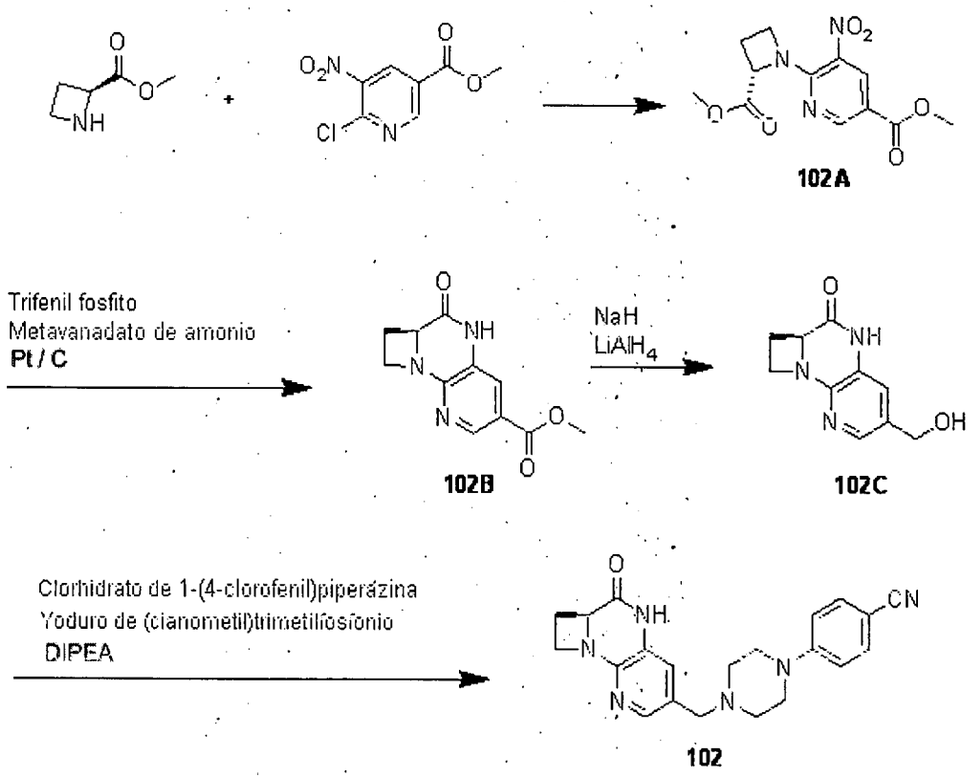
^{1}H NMR (CLOROFORMO-d) δ: 8,41 (d, J = 1,8 Hz, 1H), 8,20 (br. s., 1H), 7,80 (d, J = 2,0 Hz, 1H), 7,61 (dd, J = 9,0, 2,4 Hz, 1H), 6,99 (br. s., 1H), 6,59 (d, J = 9,1 Hz, 1H), 4,42 (dd, J = 11,5, 3,7 Hz, 1H), 4,26 (dd, J = 13,3, 1,6 Hz, 1H), 3,95 - 4,12 (m, 2H), 3,58 - 3,80 (m, 6H), 3,45 (s, 2H), 2,92 - 3,08 (m, 1H), 2,53 (br. s., 4H). [M+H] calculado para C21H23N7O2, 406; encontrado, 406.

Compuesto 101: 4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo



Se preparó el compuesto 101 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 23. [M+H] calculado para $C_{24}H_{29}N_5O_3$ 436; encontrado, 436,1.

Compuesto 102: (S)-4-(4-((6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo



Compuesto 102A: 6-(2-(metoxicarbonil)azetidin-1-il)-5-nitronicotinato de (S)-metilo: El clorhidrato de azetidin-2-carboxilato de (S)-metilo (1 g, 6,60 mmol) se diluyó con Tetrahidrofurano (Volumen: 20 ml) y se trató con TRIETILAMINA (0,919 ml, 6,60 mmol). La mezcla de reacción se agitó vigorosamente y se sonicó a intervalos regulares, hasta que resultó una suspensión fina. Esto se agitó por 1 hora y se filtró a través de un pequeño tapón de celite. El tapón se lavó bien con THF (20 mL) y el filtrado combinado y lavado se trató con 6-cloro-5-nitronicotinato de metilo (0,714 g, 3,30 mmol). La mezcla de reacción se concentró al vacío y se calentó brevemente (5 minutos) a 80°C. El LCMS mostró completa conversión. La mezcla de reacción se diluyó con DCM (10 mL) y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (SiO_2 80 g, acetato de etilo en hexanos 20-30%) para proporcionar el compuesto del título 6-(2-(metoxicarbonil)azetidin-1-il)-5-nitronicotinato de (S)-metilo (0,90 g, 3,05 mmol, rindiendo 92%) como un aceite amarillo. [M+H] calculado para $C_{12}H_{13}N_3O_6$, 295; encontrado, 295.

Compuesto 102B: 6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de (S)-metilo: se disolvió el 6-(2-(metoxicarbonil)azetidin-1-il)-5-nitronicotinato de (S)-metilo (0,90 g, 3,05 mmol) en diclorometano (Volumen: 15,24 ml) y a ésta solución se agregó trifenil fosfito (9,46 mg, 0,030 mmol), metavanadato de amonio (0,021 g, 0,183 mmol) y Pt/C (5% en peso) (0,119 g, 0,030 mmol). La mezcla de reacción se hidrogenó a 100 psi a 25°C por 2 horas. El LCMS mostró completa conversión de los materiales de partida a la correspondiente amina, pero no se observó ciclación del producto. La mezcla de reacción se filtró a través de un tapón corto de celite y el tapón y el precipitado se lavaron bien con diclorometano (30 mL) y metanol (20 mL). Los filtrados combinados se concentraron al vacío (LC: CR1) y se disolvieron en AcOH (5 mL) (LC: AA-temperatura ambiente). Esta solución se calentó a 80°C por 5 minutos (LCMS-AA-90C-5 minutos-completa conversión al producto deseado) y se concentró al vacío. El residuo se cristalizó con etil éter (20 mL) y se sonicó hasta una suspensión fina, se obtuvo el precipitado, se recogió por filtración y se secó al vacío para proporcionar 6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de (S)-metilo (0,5840, 2,504 mmol, rindiendo 82%) como un sólido rosado claro. [M+H] calculado para $C_{11}H_{11}N_3O_3$, 234; encontrado, 234.

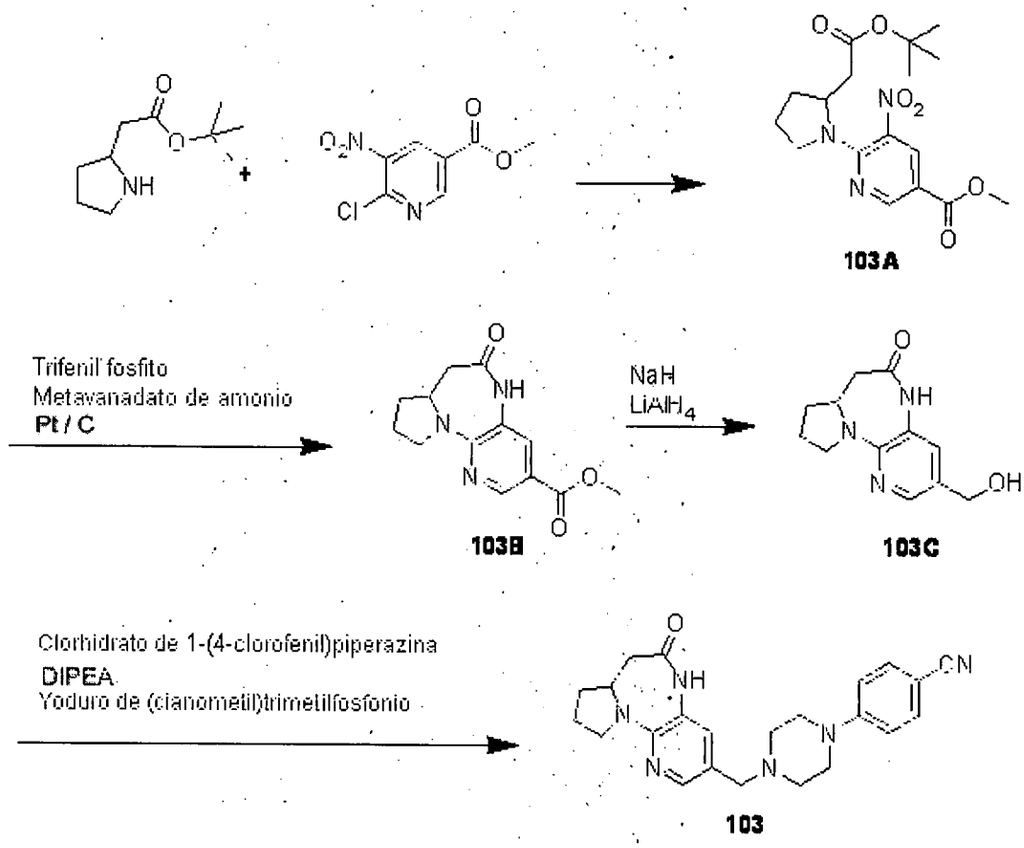
Compuesto 102C: (S)-3-(hidroximetil)-7,8-dihidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-6(6aH)-ona: Se suspendió el 6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de (S)-metilo (0,570 g, 2,444 mmol) en Tetrahidrofurano (Volumen: 8,15 ml) bajo atmósfera de nitrógeno y se agregó NaH (196 mg, 4,9 mmol) en varias porciones durante dos minutos. La mezcla de reacción se agitó a temperatura ambiente por 10 minutos y se enfrió por debajo de -50°C. El hidruro de aluminio y litio (2,200 ml, 4,40 mmol) se agregó durante un periodo de 5 minutos y la reacción se mantuvo a una temperatura entre -30 y -20°C por 1 hora (LCMS: >95% conversión). La mezcla se enfrió por debajo de -50°C y se agregó MeOH (4 mL). Se agregó agua (1 mL) y la mezcla de reacción se agitó a temperatura ambiente por 10 minutos. Se agregaron sales de Rochelle (solución del

20%) (10 mL) y la mezcla se extrajo con EtOAc (3x30 mL) y THF (3X100 mL). Los extractos orgánicos combinados se secaron con (Na_2SO_4 y $MgSO_4$), se filtraron y se concentraron al vacío. El resíduo se suspendió en THF/etil éter (1:1, 20 mL), se recogió por filtración y se secó al vacío para proporcionar (S)-3-(hidroximetil)-7,8-dihidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-6(6aH)-ona (0,332 g, 1,618 mmol, rindiendo 66,2%) como un sólido tostado claro. [M+H] calculado para $C_{10}H_{11}N_3O_2$, 205; encontrado, 205.

Compuesto 102: (S)-4-(4-((6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo: Se suspendieron (S)-3-(hidroximetil)-7,8-dihidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-6(6aH)-ona (103 mg, 0,5 mmol), 4-(piperazin-1-il)benzonitrilo (108 mg, 0,575 mmol), yoduro de (cianometil)trimetilfosfonio (207 mg, 0,850 mmol) y N,N-diisopropiletilamina (0,437 ml, 2,500 mmol) en propiononitrilo (Volumen: 1,502 ml) y se calentó en un frasco cerrado a 90°C por 23 horas. La mezcla de reacción se enfrió, se diluyó con MeOH (2 mL) y se purificó utilizando HPLC preparativa (fase básica). Las fracciones que contienen producto se concentraron al vacío y cristalizaron de agua-metanol (3 mL, ~5:1) El precipitado se filtró y se secó al vacío para proporcionar (S)-4-(4-((6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo (11,7 mg, 0,031 mmol, rindiendo 6,25%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 2,37 - 2,47 (m, 4 H) 2,68 - 2,80 (m, 1 H) 2,94 (tt, *J*=10,67, 7,26 Hz, 1 H) 3,30 (d, *J*=4,80 Hz, 4 H) 3,36 (s, 2 H) 3,87 - 4,00 (m, 1 H) 4,21 (q, *J*=7,66 Hz, 1 H) 4,93 (t, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,00 (d, *J*=9,09 Hz, 2 H) 7,57 (d, *J*=9,09 Hz, 2 H) 7,65 (d, *J*=1,77 Hz, 1 H) 10,34 (s, 1 H). [M+H] calculado para $C_{21}H_{22}N_6O$, 374; encontrado, 374.

Compuesto 103: 4-(4-((6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-il)metil)piperazin-1-il)benzonitrilo



Compuesto 103A: 6-(2-(2-ter-butoxi-2-oxoetil)pirrolidin-1-il)-5-nitronicotinato de metilo: El 2-(pirrolidin-2-il)acetato de ter-butilo (1,00 g, 5,40 mmol) se agregó a una solución de 6-cloro-5-nitronicotinato de metilo (1,169 g, 5,40 mmol) en THF (Volumen: 10 ml). La mezcla de reacción se agitó a temperatura ambiente por 1 hora y se agregó K_2CO_3 (0,760 g, 5,50 mmol). La mezcla de reacción se agitó por 2 horas y se agregó trietilamina (0,379 ml, 2,70 mmol). La mezcla se agitó por 1 hora, se filtró y se concentró al vacio. La columna cromatográfica evaporativa sobre sílica gel (SiO_2 120 g, hexanos:acetato de etilo 9:1) proporcionó 6-(2-(2-ter-butoxi-2-oxoetil)pirrolidin-1-il)-5-nitronicotinato de metilo (1,79 g, 4,90 mmol, rindiendo 91%) como un aceite amarillo. [M+H] calculado para $C_{17}H_{23}N_3O_6$, 365; encontrado, 365.

Compuesto 103B: 6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-carboxilato de metilo: El 6-(2-(2-

ter-butoxi-2-oxoetil)pirrolidin-1-il)-5-nitronicotinato de metilo (1,79 g, 4,90 mmol) se disolvió en diclorometano (Volumen: 24,49 ml) y a ésta solución se agregó trifenil fosfito (0,015 g, 0,049 mmol), metavanadato de amonio (0,034 g, 0,294 mmol) y Pt/C (5% en peso) (0,191 g, 0,049 mmol). La mezcla de reacción se hidrogenó a 100 psi a 25°C por 3 horas. La mezcla de reacción se filtró a través un tapón corto de celite y el tapón y el precipitado se lavaron bien con diclorometano (30 mL). Los filtrados combinados se concentraron al vacío y se disolvieron en AcOH (7 mL). Ésta solución se calentó a 90°C por 10 minutos y se concentró al vacío. El resíduo se cristalizó con etil éter (20 mL) y se sonicó hasta una suspensión fina y se obtuvo el precipitado, se recogió por filtración y se secó al vacío para proporcionar 6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-carboxilato de metilo (0,927 g, 3,55 mmol, rindiendo 72,4%) como un sólido rosado claro.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,55 - 1,71 (m, 1 H) 1,74 - 1,89 (m, 1 H) 1,89 - 1,99 (m, 1 H) 2,19 (d, *J*=5,81 Hz, 1 H) 2,59 (dd, *J*=14,78, 1,64 Hz, 1 H) 2,77 (dd, *J*=14,78, 9,98 Hz, 1 H) 3,56 - 3,67 (m, 1 H) 3,67 - 3,76 (m, 1 H) 3,78 (s, 3 H) 3,99 (td, *J*=9,85, 5,56 Hz, 1 H) 7,64 (d, *J*=2,02 Hz, 1 H) 8,40 (d, *J*=2,02 Hz, 1 H) 9,73 (d, 1 H) [M+H] calculado para $C_{13}H_{15}N_3O_3$, 261; encontrado, 261.

Compuesto 103C: 3-(Hidroximetil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-6(7H)-ona: Se suspendió el 6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-carboxilato de metilo (0,900 g, 3,44 mmol) en THF (Volumen: 11,48 ml) bajo atmósfera de nitrógeno y se agregó en varias porciones NaH (276 mg, 6,9 mmol) durante dos minutos. La mezcla de reacción se agitó a temperatura ambiente por 10 minutos y se enfrió por debajo de -50°C. Se agregó hidruro de aluminio(III) litio (3,10 ml, 6,20 mmol) durante el período de 5 minutos y la reacción se mantuvo a una temperatura entre -30 y -20°C por 1 hora (LCMS: >95% conversión). La mezcla se enfrió por debajo de -50°C y se agregó MeOH (4 mL). Se agregó agua (1 mL) y la mezcla de reacción se agitó a temperatura ambiente por 10 minutos. Se agregó sal de Rochelle (solución al 20%) (10 mL) y la mezcla se extrajo con THF (4X10 mL). Los extractos

orgánicos combinados se secaron con (Na_2SO_4 y $MgSO_4$), se filtraron y se concentraron al vacío. El residuo se recristalizó de THF/Etil éter (1:1, 20 mL). El sólido se recogió por filtración y se secó al vacío para proporcionar 3-(hidroximetil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-6(7H)-ona (0,654 g, 2,80 mmol, rindiendo 81%) como un sólido blanco.

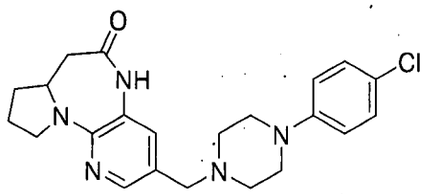
^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,58 (m, *J*=11,62, 11,62, 9,73, 6,69 Hz, 1 H) 1,74 - 1,85 (m, 1 H) 1,86 - 1,96 (m, 1 H) 2,14 (m, *J*=11,91, 5,98, 5,98, 1,89 Hz, 1 H) 2,52 - 2,58 (m, 1 H) 2,58 - 2,67 (m, 1 H) 3,49 (ddd, *J*=10,93, 8,15, 2,15 Hz, 1 H) 3,66 (td, *J*=10,61, 6,82 Hz, 1 H) 3,81 - 3,93 (m, 1 H) 4,31 (d, *J*=5,31 Hz, 2 H) 5,01 (t, *J*=5,43 Hz, 1 H) 7,14 (d, *J*=2,02 Hz, 1 H) 7,77 (d, *J*=2,02 Hz, 1 H) 9,60 (d, 1 H). [M+H] calculado para $C_{12}H_{15}N_3O_2$, 233; encontrado, 233.

Compuesto 103: 4-(4-((6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-il)metil)-piperazin-1-il)benzonitrilo: Se suspendieron 4-(4-((6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo-[1,2-d]-[1,4]diazepin-3-il)metil)piperazin-1-il)-benzonitrilo: . 3-(hidroximetil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b] pirrolo[1,2-d][1,4]diazepin-6(7H)-ona (100 mg, 0,429 mmol), 4-(piperazin-1-il)benzonitrilo (96 mg, 0,514 mmol), yoduro de (cianometil)trimetilfosfonio (167 mg, 0,685 mmol) y N,N-diisopropiletilamina (0,374 mL, 2,141 mmol) en propionitrilo (Volumen: 2 mL) y se calentaron en un frasco cerrado a 90°C por 5 horas. La mezcla de reacción se enfrió, se diluyó con DMSO (2 mL) y se purificó utilizando HPLC preparativa (fase básica, ACN 25-95%). Las fracciones que contienen producto se concentraron al vacío y se cristalizaron de agua (5 mL). El precipitado se filtró y se secó al vacío para proporcionar 4-(4-((6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-il)metil)piperazin-1-il)benzonitrilo (124,2 mg, 0,309 mmol, rindiendo 72,1%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,51 - 1,65 (m, 1 H) 1,72 - 1,86 (m, 1 H) 1,87 - 1,97 (m, 1 H) 2,14 (qd, *J*=5,81, 4,04 Hz, 1 H) 2,40 - 2,48 (m, 4 H) 2,52 - 2,59 (m, 1 H) 2,66 (dd, 1 H) 3,30 (br. s., 4 H) 3,33

- 3,40 (m, 2 H) 3,45 - 3,54 (m, 1 H) 3,66 (td, *J*=10,61, 6,82 Hz, 1 H) 3,88 (td, *J*=9,47, 6,06 Hz, 1 H) 7,00 (d, *J*=9,35 Hz, 2 H) 7,14 (d, *J*=2,02 Hz, 1 H) 7,57 (d, *J*=9,09 Hz, 2 H) 7,75 (d, *J*=2,02 Hz, 1 H) 9,56 (d, 1 H). [M+H] calculado para $C_{23}H_{26}N_6O$, 402; encontrado, 402.

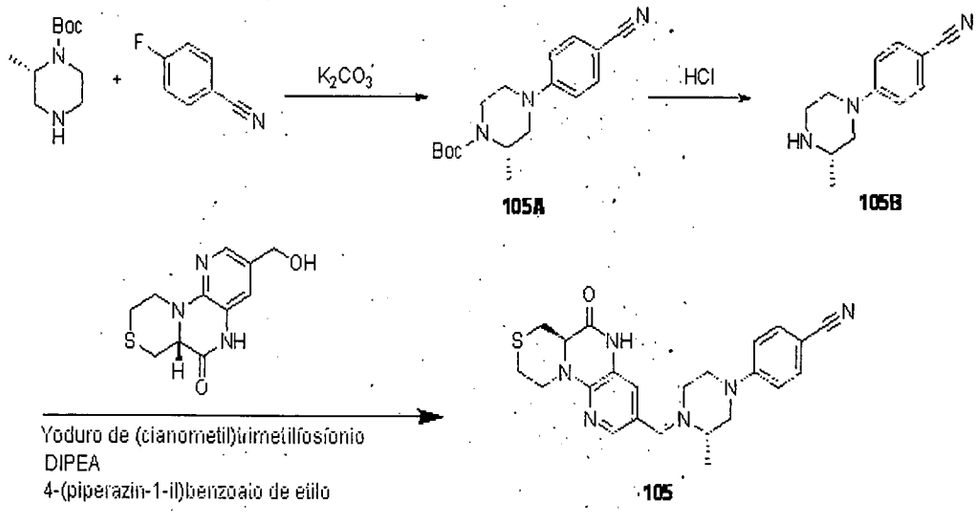
Compuesto 104: 3-((4-(4-clorofenil)piperazin-1-il)metil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-6(7H)-ona



Se preparó El compuesto 104 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 103, excepto que se utilizó el clorhidrato 1-(4-clorofenil)piperazina en lugar del clorhidrato de 1-(4-cianofenil)piperazina.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,51 - 1,65 (m, 1 H) 1,70 - 1,87 (m, 1 H) 1,87 - 1,98 (m, 1 H) 2,09 - 2,21 (m, 1 H) 2,40 - 2,48 (m, 4 H) 2,55 (d, 1 H) 2,66 (dd, 1 H) 3,04 - 3,15 (m, 4 H) 3,34 (dd, 2 H) 3,46 - 3,55 (m, 1 H) 3,66 (td, *J*=10,55, 6,69 Hz, 1 H) 3,88 (td, *J*=9,35, 6,06 Hz, 1 H) 6,92 (d, *J*=9,09 Hz, 2 H) 7,14 (d, *J*=1,77 Hz, 1 H) 7,21 (d, *J*=9,09 Hz, 2 H) 7,76 (d, *J*=1,77 Hz, 1 H) 9,55 (br. s., 1 H). [M+H] calculado para $C_{23}H_{26}ClN_5O$, 411; encontrado, 411.

Compuesto 105: 4-((S)-3-metil-4-((R)-6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo



Compuesto 105A: 4-(4-cianofenil)-2-metilpiperazina-1-carboxilato de (S)-ter-butilo: El 2-metilpiperazina-1-carboxilato de (S)-ter-butilo (1g, 4,99 mmol), 4-fluorobenzonitrilo (0,605 g, 4,99 mmol), y K_2CO_3 (0,897 g, 6,49 mmol) se combinaron en un frasco equipado con un agitador de barra bar. La reacción se calentó a 110°C por 48 horas. Se enfrió a temperatura ambiente, se diluyó con EA y se filtró. Se concentró a un aceite transparente y se purificó sobre sílica gel (80 g, EA en Hexano 10-20%) para proporcionar un aceite transparente (450 mg, rindiendo 30%) el cual se volvió bajo reposo, un sólido cristalino. [M+H] calculado para $C_{17}H_{23}N_3O_2$, 301; encontrado, 301.

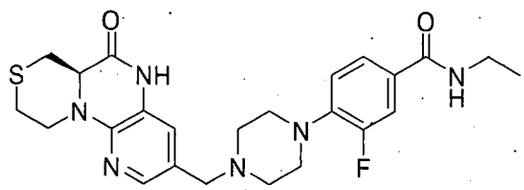
Compuesto 105B: clorhidrato de (S)-4-(3-metilpiperazin-1-il)benzonitrilo: El 4-(4-cianofenil)-2-metilpiperazina-1-carboxilato de (S)-ter-butilo (0,404 g, 1,340 mmol) se diluyó con HCl 4,0M en dioxano (3 mL) y se agitó por 30 minutos. El precipitado blanco grueso que se formó se diluyó con etil éter (10 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró bajo nitrógeno y se secó al vacío para proporcionar un sólido blanco (300 mg, 94%). [M+H] calculado para $C_{12}H_{15}N_3$, 201; encontrado, 201.

Compuesto 105: 4-((S)-3-metil-4-(((R)-6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo: A una suspensión de (R)-3-

(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e]-[1,4] tiazino[4,3-a]pirazin-6(5H)-ona (100 mg, 0,617 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (180 mg, 0,74 mmol) y DIEA (0,323 ml, 1,80 mmol) y finalmente clorhidrato de (S)-4-(3-metilpiperazin-1-il)benzonitrilo (0,147 g, 0,617 mmol). Se calentó el frasco a 90°C durante 16 horas. El rxn crudo se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico) para proporcionar el producto como un sólido color tostado (58 mg, rindiendo 22%).

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 10,62 (s, 1H), 7,69 (d, J = 2,0 Hz, 1H), 7,56 (d, J = 9,1 Hz, 2H), 6,92 - 7,11 (m, 3H), 4,87 (dt, J = 13,6, 2,7 Hz, 1H), 4,25 (dd, J = 10,9, 3,0 Hz, 1H), 3,84 (d, J = 13,4 Hz, 1H), 3,66 (d, J = 10,6 Hz, 1H), 3,58 (d, J = 12,6 Hz, 1H), 2,87 - 3,12 (m, 3H), 2,64 - 2,83 (m, 5H), 2,39 - 2,48 (m, 2H), 2,06 - 2,19 (m, 1H), 1,14 (d, J = 6,1 Hz, 3H). [M+H] calculado para $C_{23}H_{26}N_6OS$, 434; encontrado, 434.

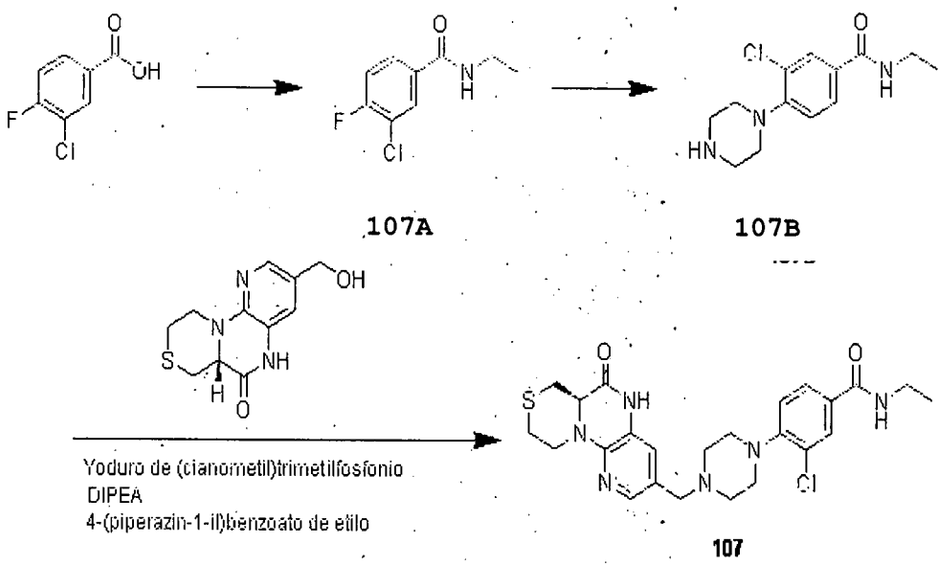
Compuesto 106: (R)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida



A una suspensión de (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (146 mg, 0,581 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (169 mg, 0,697 mmol) y clorhidrato de N-etil-3-fluoro-4-(piperazin-1-il)benzamida (167 mg, 0,581 mmol) y DIEA (304 µl, 1,743 mmol)). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado fue visible y se filtró. Se lavaron los sólidos con agua y se recolectaron para recuperar el producto como un sólido blanco (97 mg, rindiendo 34%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10,66 (s, 1H), 8,35 (t, J = 5,6 Hz, 1H), 7,69 (d, J = 1,8 Hz, 1H), 7,55 - 7,65 (m, 2H), 6,97 - 7,08 (m, 2H), 4,88 (dt, J = 13,6, 2,7 Hz, 1H), 4,27 (dd, J = 10,9, 3,0 Hz, 1H), 3,38 (d, J = 2,0 Hz, 2H), 3,20 - 3,30 (m, 2H), 2,95 - 3,15 (m, 5H), 2,65 - 2,87 (m, 3H), 2,51 (br. s., 4H), 2,45 (dd, J = 13,4, 1,8 Hz, 1H), 1,09 (t, J = 7,2 Hz, 3H). [M+H] calculado para $C_{24}H_{29}FN_6O_2S$, 484; encontrado, 484.

Compuesto 107: (R)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 107A: 3-cloro-4-fluoro-N-etilbenzamida: Utilizando clorhidrato de etanamina y ácido 3-cloro-4-fluorobenzoico en el procedimiento general para el acoplamiento de aminas a ácidos carboxílico, el compuesto del título se obtuvo (rindiendo 77%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,12 (t, *J*=7,20 Hz, 3 H) 3,28 (qd, *J*=7,16, 5,56 Hz, 2 H) 7,53 (t, *J*=8,84 Hz, 1 H) 7,87 (ddd, *J*=8,72, 4,80, 2,15 Hz, 1 H) 8,06 (dd, *J*=7,33, 2,27 Hz, 1 H) 8,61 (t, *J*=4,67 Hz, 1 H). ESI-MS: m/z 202,0 $(M+H)^+$. mp = 101,7-101,8°C.

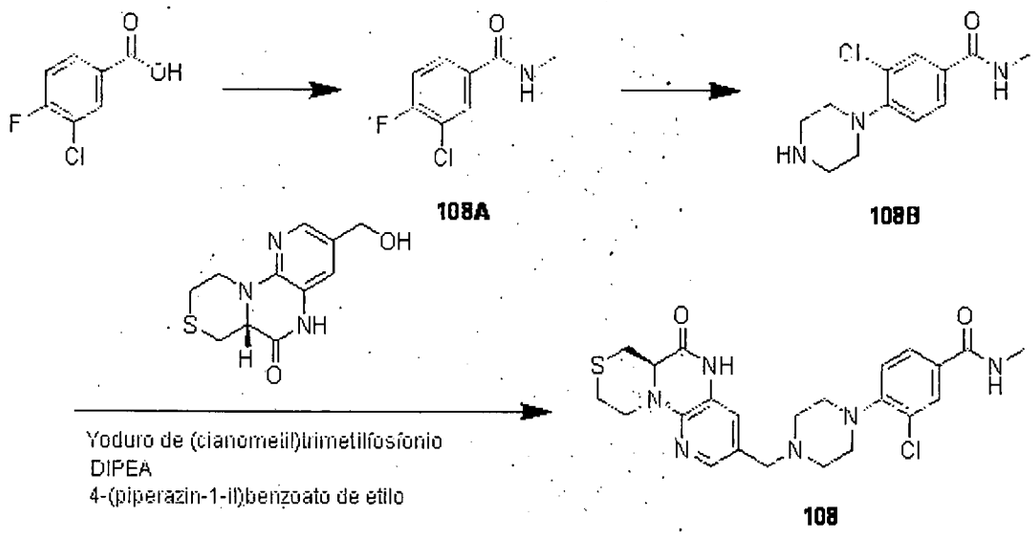
Compuesto 107B: 3-cloro-N-etil-4-(piperazin-1-il)benzamida: Utilizando 3-cloro-4-fluoro-N-etilbenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, el compuesto del título se obtuvo (rindiendo 74%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,10 (t, J=7,20 Hz, 3 H) 2,24 (br. s., 1 H) 2,81 - 2,87 (m, 4 H) 2,90 - 2,98 (m, 4 H) 3,26 (qd, J=7,24, 5,56 Hz, 2 H) 7,15 (d, J=8,59 Hz, 1 H) 7,77 (dd, J=8,34, 2,02 Hz, 1 H) 7,87 (d, J=2,27 Hz, 1 H) 8,43 (t, J=5,56 Hz, 1 H). ESI-MS: m/z 268,2 $(M+H)^+$. mp = 117,3-118,7°C.

Compuesto 107: (R)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida: A una suspensión de (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (154 mg, 0,613 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (179 mg, 0,735 mmol) y clorhidrato de 3-cloro-N-etil-4-(piperazin-1-il)benzamida (186 mg, 0,613 mmol) y DIEA (321 µl, 1,838 mmol). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta un precipitado que fue visible y se filtró. Se lavaron los sólidos con agua y se recolectaron para recuperar el producto como un sólido blanco (80 mg, rindiendo 26%).

^{1}H NMR (400 MHz, DMSO-$d6$) δ ppm 10,67 (s, 1H), 8,43 (t, J = 5,6 Hz, 1H), 7,87 (d, J = 2,0 Hz, 1H), 7,76 (dd, J = 8,6, 2,0 Hz, 1H), 7,70 (d, J = 2,0 Hz, 1H), 7,17 (d, J = 8,3 Hz, 1H), 7,01 (d, J = 2,0 Hz, 1H), 4,88 (dt, J = 13,6, 2,7 Hz, 1H), 4,27 (dd, J = 10,7, 3,2 Hz, 1H), 3,40 (s, 2H), 3,18 - 3,30 (m, 2H), 2,90 - 3,16 (m, 5H), 2,67 - 2,85 (m, 3H), 2,52 (br. s., 4H), 2,45 (dd, J = 13,5, 1,6 Hz, 1H), 1,10 (t, J = 7,2 Hz, 3H). [M+H] calculado para $C_{24}H_{29}ClN_6O_2S$, 501; encontrado, 501.

Compuesto 108: (R)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida



108A

108B

108

Compuesto 108A: 3-cloro-4-fluoro-N-metilbenzamida: A una suspensión de ácido 3-cloro-4-fluorobenzoico (25,0 g, 143 mmol), clorhidrato de Metilamina (11,60 g, 172 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (41,2 g, 215 mmol), 1H-benzo[d][1,2,3]triazol-1-ol hidrato (32,9 g, 215 mmol) en DMF (Volumen: 150 mL) se agregó 4-metilmorfolina (79 mL, 716 mmol) a 23°C. La reacción se agitó a 23°C por 3 horas. La mezcla de reacción se diluyó con agua (500 mL) para proporcionar una solución amarillo-naranja. La solución se agitó durante la noche a 23°C proporcionando una suspensión. La suspensión se filtró, se lavó con H_2O (3 x 100 mL), y el sólido resultante se secó *al vacío* a 30°C para proporcionar 3-cloro-4-fluoro-N-metilbenzamida (14,24g, 76 mmol, rindiendo 53,0%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,78 (d, *J*=4,55 Hz, 3 H) 7,53 (t, *J*=8,97 Hz, 1 H) 7,86 (ddd, *J*=8,59, 4,80, 2,27 Hz, 1 H) 8,04 (dd, *J*=7,20, 2,15 Hz, 1 H) 8,51 - 8,65 (m, 1 H). ESI-MS: m/z 188,0 $(M+H)^+$. Mp = 108,3-110,0°C.

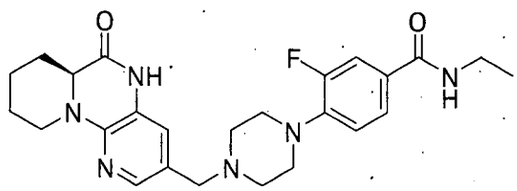
Compuesto 108B: 3-cloro-N-metil-4-(piperazin-1-il)benzamida: Utilizando 3-cloro-4-fluoro-N-metilbenzamida en el procedimiento

general para reacciones de sustitución nucleofílica aromática, se obtuvo el compuesto del título (rindiendo 29%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,59 - 2,70 (m, 2 H) 2,73 - 2,79 (m, 3 H) 2,87 - 2,93 (m, 2 H) 2,95 - 3,01 (m, 2 H) 3,03 - 3,11 (m, 2 H) 3,23 - 4,03 (m, 1 H) 7,14 - 7,23 (m, 1 H) 7,77 (dd, *J*=8,46, 2,15 Hz, 1 H) 7,85 - 7,90 (m, 1 H) 8,38 - 8,48 (m, 1 H). ESI-MS: m/z 254,2 $(M+H)^+$. mp=176,4-189,1°C.

Compuesto 108: (R)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida: A una suspensión de (R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona (97 mg, 0,386 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (113 mg, 0,463 mmol) y clorhidrato de 3-cloro-N-metil-4-(piperazin-1-il)benzamida (112 mg, 0,386 mmol) y DIEA (202 µl, 1,158 mmol). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado fue visible y se filtró. Se lavaron los sólidos con agua y recolectaron para recuperar el producto como un sólido blanco (21 mg, rindiendo 11%).

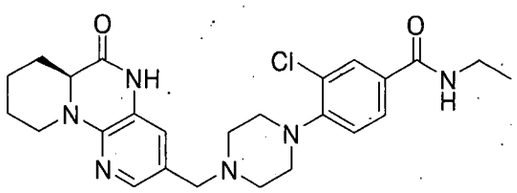
^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10,67 (s, 1H), 8,41 (d, J = 4,5 Hz, 1H), 7,86 (d, J = 2,0 Hz, 1H), 7,75 (dd, J = 8,6, 2,0 Hz, 1H), 7,70 (d, J = 1,8 Hz, 1H), 7,17 (d, J = 8,6 Hz, 1H), 7,00 (d, J = 2,0 Hz, 1H), 4,88 (ddd, J = 13,5, 2,7, 2,5 Hz, 1H), 4,27 (dd, J = 10,6, 3,0 Hz, 1H), 3,40 (s, 2H), 2,92 - 3,14 (m, 5H), 2,64 - 2,85 (m, 6H), 2,51 - 2,64 (m, 3H), 2,45 (dd, J = 13,4, 1,5 Hz, 2H). [M+H] calculado para $C_{23}H_{27}ClN_6O_2S$, 487; encontrado, 487.

Compuesto 109: (S)-N-etil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



A una suspensión de (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (83 mg, 0,355 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (104 mg, 0,426 mmol) y DIEA (0,186 ml, 1,066 mmol) y finalmente N-etil-3-fluoro-4-(piperazin-1-il)benzamida (102 mg, 0,355 mmol). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado fue visible y se filtró. Se lavaron los sólidos con agua y recolectaron para recuperar el producto como un sólido blanco (50 mg, rindiendo 30%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10,48 (s, 1H), 8,35 (t, J = 5,4 Hz, 1H), 7,49 - 7,72 (m, 3H), 6,87 - 7,15 (m, 2H), 4,50 (d, J = 12,9 Hz, 1H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,40 (d, J = 2,8 Hz, 2H), 3,18 - 3,30 (m, 2H), 3,08 (br. s., 4H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,49 (br. s., 4H), 2,03 (d, J = 12,9 Hz, 1H), 1,77 - 1,91 (m, 1H), 1,64 (d, J = 12,9 Hz, 1H), 1,32 - 1,57 (m, 3H), 1,09 (t, J = 7,2 Hz, 3H). [M+H]$^+$ calculado para $C_{25}H_{31}FN_6O_2$, 467; encontrado, 467.

Compuesto 110: (S)-3-cloro-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida

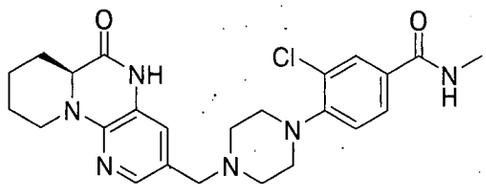


A una suspensión de (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (81 mg, 0,347

mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (101 mg, 0,417 mmol) y DIEA (182 µl, 1,042 mmol) y finalmente clorhidrato de 3-cloro-N-etil-4-(piperazin-1-il)benzamida (106 mg, 0,347 mmol). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado fue visible y se filtró. Se lavaron los sólidos con agua y se recolectaron para recuperar el producto como un sólido blanco (70 mg, rindiendo 20%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10,48 (s, 1H), 8,43 (t, J = 5,4 Hz, 1H), 7,87 (d, J = 2,3 Hz, 1H), 7,76 (dd, J = 8,3, 2,0 Hz, 1H), 7,66 (d, J = 1,8 Hz, 1H), 7,17 (d, J = 8,6 Hz, 1H), 6,97 (d, J = 2,0 Hz, 1H), 4,50 (d, J = 12,9 Hz, 1H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,38 (s, 2H), 3,18 - 3,31 (m, 2H), 3,03 (br. s., 4H), 2,60 (td, J = 12,7, 2,7 Hz, 1H), 2,51 (br. s., 4H), 2,04 (d, J = 12,9 Hz, 1H), 1,85 (d, J = 12,1 Hz, 1H), 1,64 (d, J = 12,6 Hz, 1H), 1,32 - 1,58 (m, 3H), 1,10 (t, J = 7,1 Hz, 3H). [M+H] calculado para $C_{25}H_{31}ClN_6O_2$, 483; encontrado, 483.

Compuesto 111: (S)-3-cloro-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida

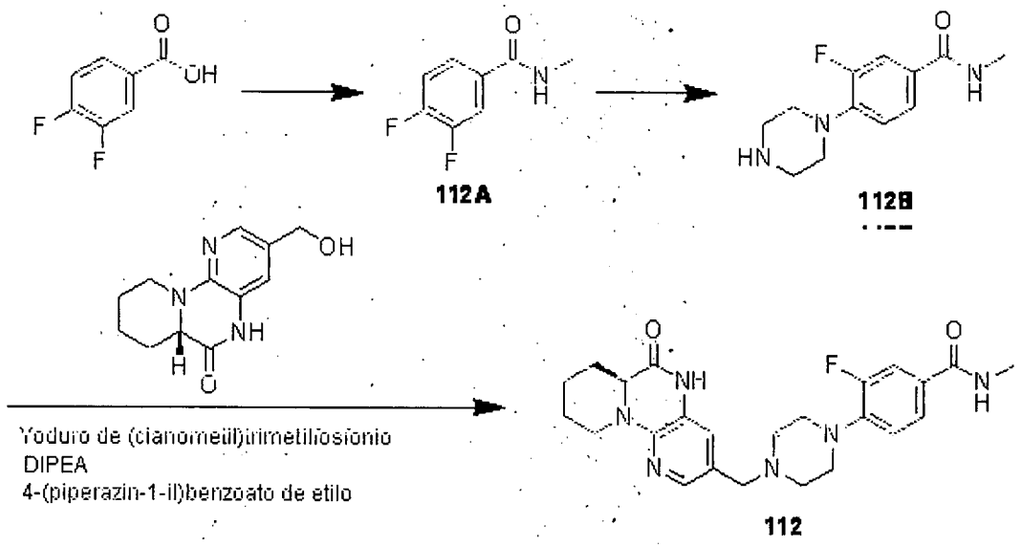


A una suspensión de (S)-3-((S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (111 mg, 0,476 mmol) en propiononitrilo (1,2 mL) se agregó yoduro de (cianometil)trimetilfosfonio (139 mg, 0,571 mmol) y DIEA (249 µl, 1,428 mmol) y finalmente clorhidrato de 3-cloro-N-metil-4-(piperazin-1-il)benzamida (138 mg, 0,476 mmol). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado

fue visible y se filtró. Se lavaron los sólidos con agua y se recolectaron para recuperar el producto como un sólido blanco (64 mg, rindiendo 29%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 10,52 (br. s., 1H), 8,43 (d, J = 4,3 Hz, 1H), 7,87 (s, 1H), 7,76 (dd, J = 8,3, 1,5 Hz, 1H), 7,66 (d, J = 2,0 Hz, 1H), 7,54 - 7,74 (m, 1H), 7,19 (d, J = 8,1 Hz, 1H), 6,99 (br. s., 1H), 4,52 (d, J = 12,6 Hz, 1H), 3,85 (br. s., 1H), 3,44 (br. s., 2H), 2,92 (d, J = 4,5 Hz, 4H), 2,75 (d, J = 4,5 Hz, 4H), 2,52 - 2,69 (m, 3H), 1,99 - 2,09 (m, 1H), 1,85 (d, J = 12,4 Hz, 1H), 1,64 (d, J = 12,4 Hz, 1H), 1,32 - 1,58 (m, 3H). [M+H] calculado para $C_{24}H_{29}ClN_6O_2$, 469; encontrado, 469.

Compuesto 112: (S)-3-fluoro-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 112A: 3,4-difluoro-N-metilbenzamida: Utilizando clorhidrato de metanamina y ácido 3,4-difluorobenzoico en el procedimiento general para acoplamiento de aminas a ácidos carboxílico, el compuesto del título se obtuvo (rindiendo 75%) como un sólido blanquecino.

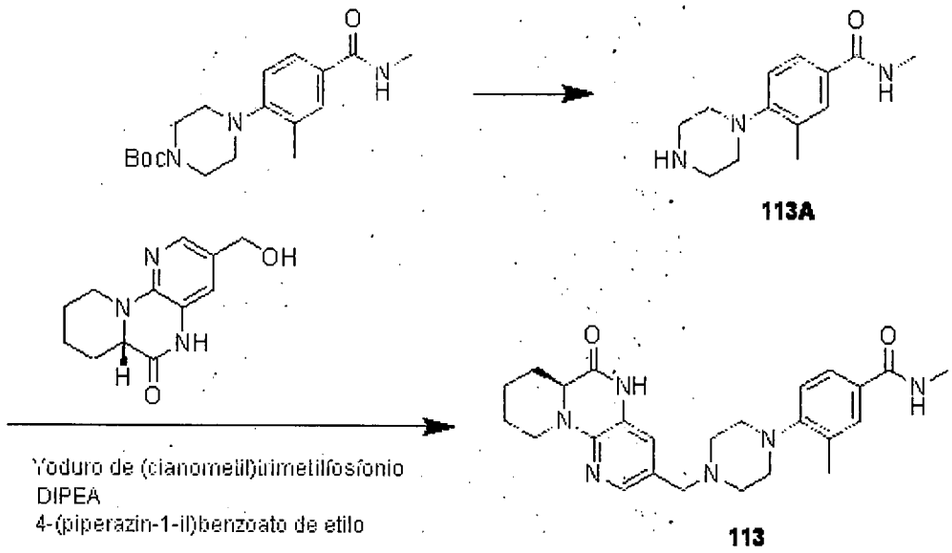
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,78 (d, *J*=4,55 Hz, 3 H) 7,55 (dt, *J*=10,61, 8,34 Hz, 1 H) 7,72 (dddd, *J*=8,59, 4,55, 2,15, 1,39 Hz, 1 H)

7,86 (ddd, *J*=11,68, 7,89, 2,15 Hz, 1 H) 8,48 - 8,59 (m, 1 H). ESI-MS: m/z 172,1 $(M+H)^+$. mp=142,7-145,0°C.

Compuesto 112B: 3-fluoro-N-metil-4-(piperazin-1-il)benzamida: Utilizando 3,4-difluoro-N-metilbenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, el compuesto del título se obtuvo (rindiendo 43%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,34 (br. s., 1 H) 2,57 - 2,66 (m, 1 H) 2,72 - 2,79 (m, 3 H) 2,80 - 2,88 (m, 3 H) 2,95 - 3,04 (m, 3 H) 3,07 - 3,16 (m, 1 H) 6,99 - 7,11 (m, 1 H) 7,52 - 7,65 (m, 2 H) 8,29 - 8,38 (m, 1 H). ESI-MS: m/z 238,2 $(M+H)^+$. mp = 174,1-192,9°C.

Compuesto 112: (S)-3-fluoro-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: A una suspensión de (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (129 mg, 0,553 mmol) en propiononitrilo (1,2 mL) se agregó (yoduro de (cianometil)trimetilfosfonio (161 mg, 0,664 mmol)) y clorhidrato de 3-fluoro-N-metil-4-(piperazin-1-il)benzamida (151 mg, 0,553 mmol) y DIEA (290 µl, 1,659 mmol)). Se calentó el frasco a 90°C durante 16 horas. El crudo rxn se enfrió a temperatura ambiente, se agregó DMSO (1 ml), y se purificó mediante HPLC (55-90, básico). Las fracciones se recolectaron, se concentraron hasta que un precipitado fue visible y se filtró. Se lavaron los sólidos con agua y se recolectaron para recuperar el producto como un sólido blanco (83 mg, rindiendo 33%). ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 10,48 (s, 1H), 8,33 (d, J = 4,5 Hz, 1H), 7,45 - 7,70 (m, 3H), 6,88 - 7,10 (m, 2H), 4,50 (d, J = 12,9 Hz, 1H), 3,83 (dd, J = 11,1, 2,5 Hz, 1H), 3,36 (s, 2H), 3,08 (br. s., 4H), 2,75 (d, J = 4,5 Hz, 3H), 2,56 - 2,64 (m, 1H), 2,50 (br. s., 4H), 1,97 - 2,12 (m, 1H), 1,85 (d, J = 11,1 Hz, 1H), 1,63 (d, J = 11,9 Hz, 1H), 1,29 - 1,57 (m, 3H). [M+H] calculado para $C_{24}H_{29}FN_6O_2$, 453; encontrado, 453.

Compuesto 113: (S)-N,3-dimetil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 113A: N,3-dimetil-4-(piperazin-1-il)benzamida: A 4-(2-metil-4-(metilcarbamoil)fenil)piperazina-1-carboxilato de ter-butilo (1,90 g, 5,70 mmol) se agregó solución de ácido clorhídrico (17,10 ml, 68,4 mmol) en dioxano a 23°C. La reacción se agitó a 23°C por 30 minutos. La suspensión resultante se diluyó con Et_2O (20 mL), se filtró, se lavó con Et_2O (3 x 10 mL), y el sólido resultante se secó *al vacío* para proporcionar diclorhidrato de N,3-dimetil-4-(piperazin-1-il)benzamida (1,70 g, 5,55 mmol, rindiendo 97%) como un sólido blanquecino, higroscópico.

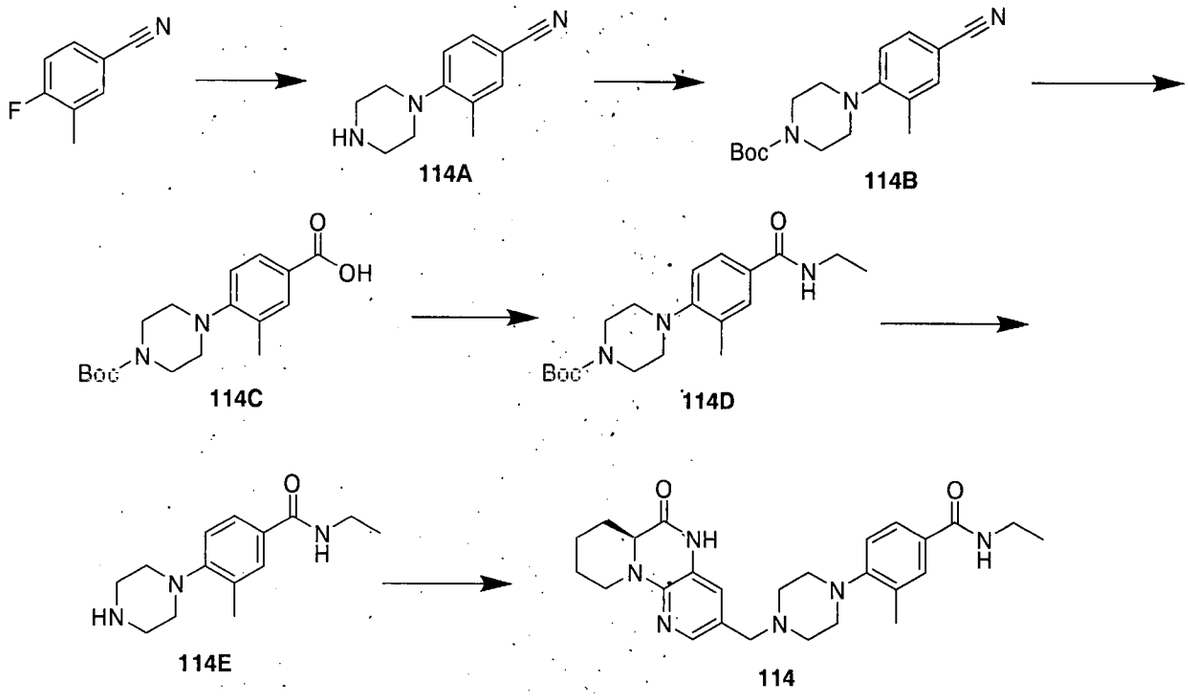
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,28 (s, 3 H) 2,72 - 2,79 (m, 3 H) 3,05 - 3,14 (m, 4 H) 3,17 - 3,28 (m, 4 H) 7,06 (d, *J*=8,34 Hz, 1 H) 7,64 - 7,68 (m, 1 H) 7,68 - 7,70 (m, 1 H) 8,29 - 8,39 (m, 1 H) 9,36 (br. s., 2 H). ESI-MS: m/z 234,2 $(M+H)^+$.

Compuesto 113: (S)-N,3-dimetil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol), diclorhidrato de N,3-dimetil-4-(piperazin-1-il)benzamida (131 mg, 0,429 mmol), yoduro de (cianometil)trimetilfosfonio (167 mg, 0,686 mmol) y N,N-diisopropiletilamina (374 µl, 2,143 mmol) en propiononitrilo (Volumen: 1.287 µl) y se calentaron en un frasco cerrado a 90°C por 4 horas. La mezcla de reacción se volvió una

solución café oscura. Se enfrió a temperatura ambiente y se purificó utilizando HPLC (ACN en agua 20-70%, solución tampón de NH_4HCO_3). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de MeCN (5 mL), se recogió por filtración, se lavó con agua (2 mL) y se secó al vacío para proporcionar (S)-N,3-dimetil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida (27,4 mg, 0,061 mmol, rindiendo 14,25%) como un sólido beige claro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,31 - 1,57 (m, 3 H) 1,64 (d, *J*=11,87 Hz, 1 H) 1,85 (d, *J*=11,37 Hz, 1 H) 2,04 (d, *J*=11,87 Hz, 1 H) 2,25 (s, 3 H) 2,51 - 2,70 (m, 5 H) 2,56 - 2,70 (m, 2 H) 2,74 (d, *J*=4,29 Hz, 3 H) 2,87 (br. s., 4 H) 3,37 - 3,45 (m, 2 H) 3,84 (dd, *J*=11,24, 2,40 Hz, 1 H) 4,50 (d, *J*=13,14 Hz, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,01 (d, *J*=8,34 Hz, 1 H) 7,61 (dd, *J*=8,46, 1,64 Hz, 1 H) 7,65 (dd, *J*=12,25, 1,64 Hz, 2 H) 8,23 (q, *J*=4,13 Hz, 1 H) 10,48 (s, 1 H); [M+H] calculado para $C_{25}H_{32}N_6O_2$, 449; encontrado, 449.

Compuesto 114: (S)-N-etil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 114A: 3-metil-4-(piperazin-1-il)benzonitrilo: A una solución de 4-fluoro-3-metilbenzonitrilo (2,5 g, 18,50 mmol) en DMSO (Volumen: 10,0 mL) se agregó piperàzina (7,97 g, 92 mmol) a 23°C. La reacción se agitó a 140°C por 16 horas. La mezcla de reacción se vertió en H_2O (100 mL) y el matraz de reacción se lavó con H_2O (~50 mL). La suspensión resultante se filtró, se lavó con H_2O (3 x 10 mL) y el sólido resultante se secó *al vacío* para proporcionar 3-metil-4-(piperazin-1-il)benzonitrilo (2,593g, 12,88 mmol, rindiendo 69,6%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2,21 - 2,30 (m, 3 H) 2,57 - 2,70 (m, 1 H) 2,83 (s, 8 H) 7,03 - 7,09 (m, 1 H) 7,55 - 7,62 (m, 2 H). ESI-MS: m/z 202,1 $(M+H)^+$.

Compuesto 114B: 4-(4-ciano-2-metilfenil)piperazina-1-carboxilato de ter-butilo: A una solución de 3-metil-4-(piperazin-1-il)benzonitrilo (2,533 g, 12,59 mmol) en THF (Razón: 1,000, Volumen: 25 mL) and MeOH (Razón: 1,000, Volumen: 25 mL) se agregó dicarbonato de di-ter-butilo (3,09 mL, 13,47 mmol) a 10°C. La reacción se agitó a 10°C por 15 minutos se calentó a 23°C y se agitó por 18 horas.
La suspensión resultante se filtró, se lavó con THF (3 x 5 mL) y el filtrado se concentró *al vacío*.
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,42 (s, 9 H) 2,28 (s, 3 H) 2,83 - 2,92 (m, 4 H) 3,42 - 3,52 (m, 4 H) 7,08 - 7,13 (m, 1 H) 7,57 - 7,65 (m, 2 H). ESI-MS: m/z 302,1 $(M+H)^+$.

Compuesto 114C: ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-metilbenzoico: A una suspensión de 4-(4-ciano-2-metilfenil)piperazina-1-carboxilato de ter-butilo (3,685 g, 12,23 mmol) en EtOH (Razón: 1,000, Volumen: 50 mL) y Agua (Razón: 1,000, Volumen: 10 mL) se agregó solución de hidróxido de sodio (8,48 mL, 162 mmol) a 23°C. Se enjuagó con hidróxido de sodio y sse continuó con agua (Razón: 1,000, Volumen: 2,5 mL) La reacción se agitó a 90°C por 10 horas. La mezcla de reacción se enfrió a 23°C, se neutralizó con HCl 3N (52 mL), se filtró, se lavó con H_2O (3 x 10 mL), y el sólido resultante se secó al vacío para proporcionar el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-metilbenzoico (3,588 g, 11,20 mmol, rindiendo 92%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,42 (s, 9 H) 2,29 (s, 3 H) 2,81 - 2,90 (m, 4 H) 3,42 - 3,53 (m, 4 H) 7,05 (d, *J*=8,08 Hz, 1 H) 7,70 - 7,77 (m, 2 H) 12,61 (br. s., 1 H). ESI-MS: m/z 321,2 $(M+H)^+$.

Compuesto 114D: 4-(4-(etilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo: Se suspendieron el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-metilbenzoico (0,866 g, 2,70 mmol), clorhidrato de etanamina (0,264 g, 3,24 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (0,777 g, 4,05 mmol) y 1H-benzo[d][1,2,3]triazol-1-ol hidrato (0,621 g, 4,05 mmol) en DMF (Volumen: 3,68 ml) y se agregó 4-metilmorfolina (1,486 ml, 13,52 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 horas. Se diluyó con agua (50 mL) y se extrajo con acetato de etilo (3X75 mL). Los extractos orgánicos combinados se lavaron con HCl 1N (acuoso, 25 mL), $NaHCO_3$ (saturado, acuoso, 25 mL), agua (25 mL), salmuera (25 mL), se secaron con ($MgSO_4$), se concentraron al vacío y se secaron bajo vacío para proporcionar 4-(4-(etilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo (0,9327 g, 2,68 mmol, rindiendo 99%) como un sólido blanco.

^{1}H NMR (DMSO-d_6, 400MHz): δ = 8,24 (t, *J*=5,4 Hz, 1 H), 7,66 (d, *J*=1,8 Hz, 2 H), 7,03 (d, *J*=8,3 Hz, 1 H), 3,42 - 3,52 (m, 4 H), 3,20 - 3,27 (m, 2 H), 2,78 - 2,87 (m, 4 H), 2,28 (s, 3 H), 1,43 (s, 9 H), 1,10 ppm (t, *J*=7,2 Hz, 3 H). ESI-MS: m/z 348;4 $(M+H)^+$.

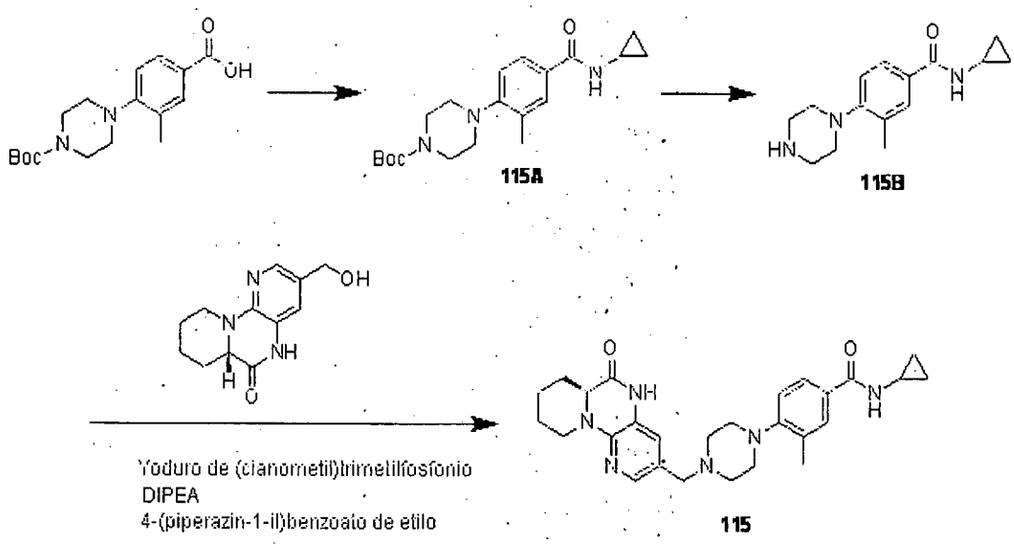
Compuesto 114E: N-etil-3-metil-4-(piperazin-1-il)benzamida: El 4-(4-(etilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo (0,9323 g, 2,68 mmol) se diluyó con HCl 4,0M en dioxano (8 mL) y se agitó por 30 minutos. El precipitado blanco grueso que se formó se diluyó con etil éter (10 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró bajo nitrógeno, se lavó con éter (5mL) y se secó al vacío para proporcionar clorhidrato de N-etil-3-metil-4-(piperazin-1-il)benzamida (0,7528 g, 2,65 mmol, 99% rindiendo) como un sólido blanco.

1H NMR (400 MHz, DMSO-*d*6) δ ppm 1,10 (t, *J*=7,20 Hz, 3 H) 2,29 (s, 3 H) 3,00 - 3,14 (m, 4 H) 3,16 - 3,32 (m, 6 H) 7,07 (d, *J*=8,34 Hz, 1 H)

7,62 - 7,71 (m, 2 H) 8,34 (t, *J*=5,43 Hz, 1 H) 9,17 (br. s., 2 H). ESI-MS: m/z 248,2 $(M+H)^+$.

Compuesto 114: (S)-N-etil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol), clorhidrato de N-etil-3-metil-4-(piperazin-1-il)benzamida (133 mg, 0,469 mmol), yoduro de (cianometil)trimetilfosfonio (167 mg, 0,686 mmol) y N,N-diisopropiletilamina (374 µl, 2,143 mmol) en propiononitrilo (Volumen: 1287 µl) y se calentaron en un frasco cerrado a 90°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente y se purificó utilizando HPLC (ACN en agua 20-70% solución tampón de NH_4HCO_3,). Las fracciones se concentraron al vacío y el sólido resultante se llevó a una suspensión con MeCN caliente (5 mL), se enfrió a temperatura ambiente, se recogió por filtración, se lavó con agua (2 mL) y se secó al vacío para proporcionar (S)-N-etil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida (70,3 mg, 0,152 mmol, rindiendo 35,4%) como un sólido beige claro.
^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1,09 (t, *J*=7,20 Hz, 3 H) 1,33 - 1,57 (m, 3 H) 1,64 (d, *J*=12,13 Hz, 1 H) 1,85 (d, *J*=11,37 Hz, 1 H) 2,04 (d, *J*=12,13 Hz, 1 H) 2,26 (s, 3 H) 2,52 - 2,70 (m, 5 H) 2,87 (br. s., 4 H) 3,19 - 3,29 (m, 2 H) 3,37 - 3,43 (m, 2 H) 3,84 (dd, *J*=11,49, 2,65 Hz, 1 H) 4,50 (d, *J*=12,88 Hz, 1 H) 6,98 (d, *J*=1,52 Hz, 1 H) 7,01 (d, *J*=8,34 Hz, 1 H) 7,62 (d, *J*=8,59 Hz, 1 H) 7,65 (dd, *J*=9,35, 1,26 Hz, 2 H) 8,26 (t, *J*=5,43 Hz, 1 H) 10,49 (s, 1 H); [M+H] calculado para $C_{26}H_{34}N_6O_2$, 463; encontrado, 463.

Compuesto 115: (S)-N-ciclopropil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 115A: 4-(4-(ciclopropilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo: A ciclopropilamina (0,389 mL, 5,62 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (1,346 g, 7,02 mmol), y 1H-benzo[d][1,2,3]triazol-1-ol hidrato (1,075 g, 7,02 mmol) en DMF (Volumen: 6,4 mL) se agregó 4-metilmorfolina (2,57 mL, 23,41 mmol) a 23°C. La reacción se agitó a 23°C por 2 horas. La mezcla de reacción se diluyó con agua (50 mL) y el producto se extrajo con EtOAc (3 x 50 mL). Los extractos orgánicos se combinaron, se lavaron con HCl 1N (25 mL), $NaHCO_3$ saturado (25 mL), H_2O (25 mL), salmuera (25 mL), se secaron sobre $MgSO_4$, se filtraron, se lavaron con EtOAc, y se secaron *al vacío* para proporcionar 4-(4-(ciclopropilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo (1,53 g, 4,26 mmol, rindiendo 91%) como un sólido amarillo claro. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,51 - 0,60 (m, 2 H) 0,60 - 0,70 (m, 2 H) 1,42 (s, 9 H) 2,28 (s, 3 H) 2,77 - 2,87 (m, 5 H) 3,41 - 3,53 (m, 4 H) 7,02 (d, *J*=8,08 Hz, 1 H) 7,61 (dd, *J*=8,21, 1,89 Hz, 1 H) 7,64 (d, *J*=1,77 Hz, 1 H) 8,25 (d, *J*=4,29 Hz, 1 H). ESI-MS:m/z 360,3 $(M+H)^+$. mp=111,0-115,4°C.

Compuesto 115B: N-ciclopropil-3-metil-4-(piperazin-1-il)benzamida: A 4-(4-(ciclopropilcarbamoil)-2-metilfenil)piperazina-1-carboxilato de ter-butilo (1,490 g, 4,15 mmol) se agregó solución de ácido

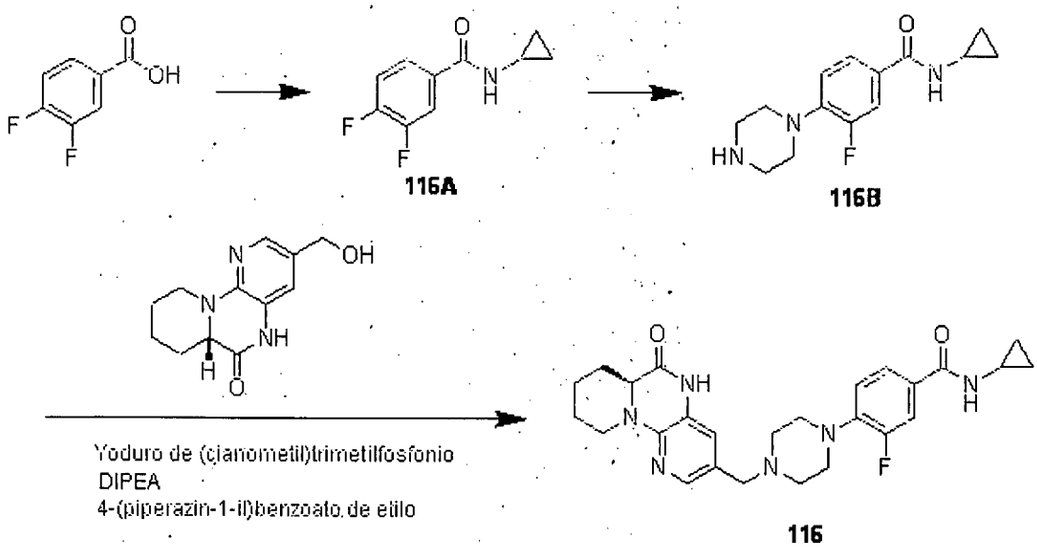
clorhídrico (8,72 mL, 34,9 mmol) en dioxano a 23°C. La reacción se agitó a 23°C por 30 minutos. La suspensión resultante se diluyó con Et_2O (10 mL), se filtró, se lavó con Et_2O (3 x 5 mL), y el sólido resultante se secó *al vacío* para proporcionar diclorhidrato de N-ciclopropil-3-metil-4-(piperazin-1-il)benzamida (1,37 g, 4,15 mmol, rindiendo 100%) como un sólido blanquecino. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,51 - 0,61 (m, 2 H) 0,61 - 0,70 (m, 2 H) 2,28 (s, 3 H) 2,82 (tq, *J*=7,41, 3,99 Hz, 1 H) 3,02 - 3,13 (m, 4 H) 3,14 - 3,29 (m, 4 H) 7,05 (d, *J*=8,34 Hz, 1 H) 7,62 - 7,69 (m, 2 H) 8,32 (d, *J*=4,29 Hz, 1 H) 9,38 (br. s., 2 H). ESI-MS : m/z 260,2 $(M+H)^+$. mp=171,5-172,8°C.

Compuesto 115: (S)-N-ciclopropil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (100 mg, 0,429 mmol), diclorhidrato de N-ciclopropil-3-metil-4-(piperazin-1-il)benzamida (143 mg, 0,430 mmol), yoduro de (cianometil)trimetilfosfonio (167 mg, 0,686 mmol) y N,N-diisopropiletilamina (374 µl, 2,143 mmol) en propiononitrilo (Volumen: 1287 µl) y se calentaron en un frasco cerrado a 90°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente y se purificó utilizando HPLC (ACN en agua 20-70%, solución tampón de NH_4HCO_3). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de MeCN (20 mL), se recogió por filtración, se lavó con agua (2 mL) y se secó al vacío para proporcionar (S)-N-ciclopropil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)- piperazin-1-il)benzamida (50,7 mg, 0,107 mmol, rindiendo 24,92%) como un sólido café claro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,49 - 0,59 (m, 2 H) 0,60 - 0,71 (m, 2 H) 1,33 - 1,57 (m, 3 H) 1,64 (d, *J*=12,88 Hz, 1 H) 1,85 (d, *J*=12,63 Hz, 1 H) 2,04 (d, *J*=12,88 Hz, 1 H) 2,25 (s, 3 H) 2,42 - 2,56 (m, 4 H) 2,60 (td, *J*=12,63, 2,78 Hz, 1 H) 2,76 - 2,93 (m, 5 H) 3,38 (s, 2 H) 3,84 (dd, *J*=11,37, 2,78 Hz, 1 H) 4,50 (d, *J*=13,14 Hz, 1 H) 6,98 (d, *J*=2,02 Hz, 1 H) 7,00 (d, *J*=8,34 Hz, 1 H) 7,56 - 7,63 (m, 2 H) 7,66

(d, J=2,02 Hz, 1 H) 8,22 (d, J=4,29 Hz, 1 H) 10,49 (s, 1 H); [M+H] calculado para $C_{27}H_{34}N_6O_2$, 475; encontrado, 475.

Compuesto 116: (S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]piratin-3-il)metil)piperazin-1-il)benzamida



Compuesto 116A: N-ciclopropil-3,4-difluorobenzamida: Utilizando ciclopropilamina y ácido 3,4-difluorobenzoico en el procedimiento general para el acoplamiento de aminas a ácidos carboxílico, el compuesto del título se obtuvo (rindiendo 89%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,52 - 0,63 (m, 2 H) 0,63 - 0,74 (m, 2 H) 2,83 (tq, J=7,42, 3,98 Hz, 1 H) 7,52 (dt, J=10,55, 8,37 Hz, 1 H) 7,66 - 7,75 (m, 1 H) 7,85 (ddd, J=11,68, 7,89, 2,15 Hz, 1 H) 8,42 - 8,60 (m, 1 H). ESI-MS:m/z 198,1 $(M+H)^+$. mp = 104,1-108,4°C.

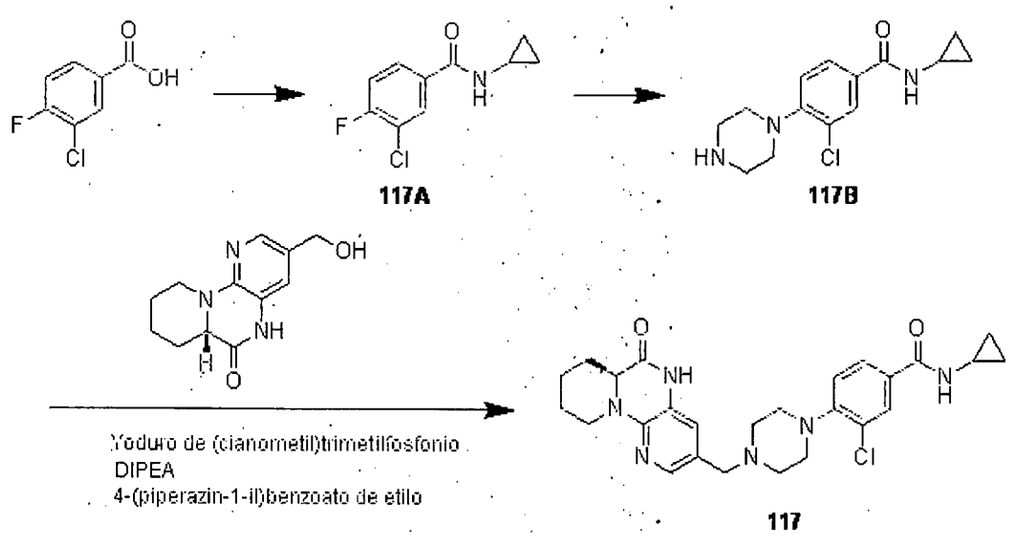
Compuesto 116B: N-ciclopropil-3-fluoro-4-(piperazin-1-il)benzamida: Utilizando N-ciclopropil-3,4-difluorobenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, el compuesto del título se obtuvo (rindiendo 33%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,51 - 0,61 (m, 2 H) 0,61 - 0,71 (m, 2 H) 2,55 - 2,68 (m, 1 H) 2,71 - 2,91 (m, 5 H) 2,92 - 3,09 (m, 4 H)

6,97 - 7,09 (m, 1 H) 7,51 - 7,65 (m, 2 H) 8,27 (d, *J*=4,04 Hz, 1 H). ESI-MS:m/z 264,2 $(M+H)^+$. mp = 140,9-143,1°C.

Compuesto 116: (S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (150 mg, 0,643 mmol), N-ciclopropil-3-fluoro-4-(piperazin-1-il)benzamida (203 mg, 0,772 mmol), yoduro de (cianometil)trimetilfosfonio (250 mg, 1,029 mmol) y N,N-diisopropiletilamina (562 µl, 3,22 mmol) en propiononitrilo (Volumen: 1.931 µl) y se calentaron en un frasco cerrado a 100°C por 4 horas. La mezcla de reacción se volvió una solución café oscura con precipitado. Se enfrió a temperatura ambiente y el precipitado se recogió por filtración, se lavó con MeCN (2 mL) y se suspendió en MeCN con calentamiento y sonicación. La suspensión se enfrió a temperatura ambiente, y el precipitado se recogió por filtración, se lavó con MeCN (2 mL) y se secó al vacío para proporcionar (S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida (265 mg, 0,554 mmol, 86% rindiendo) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ 10,48 (s, 1H), 8,31 (d, J = 4,3 Hz, 1H), 7,53 - 7,69 (m, 4H), 7,02 (t, J = 8,8 Hz, 1H), 6,97 (d, J = 2,0 Hz, 1H), 4,50 (br. d, J = 12,9 Hz, 1H), 3,84 (dd, J = 11,2, 2,7 Hz, 1H), 3,37 (s, 2H), 3,01 - 3,13 (m, 4H), 2,80 (tq, J = 7,4, 3,9 Hz, 1H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,44 - 2,51 (m, 4H), 2,04 (br. d, J = 12,9 Hz, 1H), 1,85 (br. d, J = 12,4 Hz, 1H), 1,64 (br. d, J = 12,6 Hz, 1H), 1,33 - 1,56 (m, 3H), 0,61 - 0,71 (m, 2H), 0,50 - 0,60 (m, 2H); [M+H] calculado para $C_{26}H_{31}FN_6O_2$, 479; encontrado, 479.

Compuesto 117: (S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 117A: 3-cloro-N-ciclopropil-4-fluorobenzamida: Utilizando ciclopropilamina y ácido 3-cloro-4-fluorobenzoico en el procedimiento general para el acoplamiento de aminas a ácidos carboxílico, se obtuvo el compuesto del título (rindiendo 89%) como un sólido blanco. ^{1}H NMR (DMSO-d_6, 400MHz): δ = 8,56 (d, J=3,5 Hz, 1 H), 8,03 (dd, J=7,3, 2,3 Hz, 1 H), 7,85 (ddd, J=8,6, 4,8, 2,3 Hz, 1 H), 7,52 (t, J=9,0 Hz, 1 H), 2,83 (tq, J=7,4, 3,9 Hz, 1 H), 0,66 - 0,75 (m, 2 H), 0,53 - 0,61 ppm (m, 2 H). ESI-MS: m/z 214,0 $(M+H)^+$.

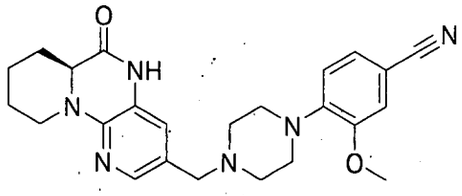
Compuesto 117B: 3-cloro-N-ciclopropil-4-(piperazin-1-il)benzamida: Utilizando 3-cloro-N-ciclopropil-4-fluorobenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, se obtuvo el compuesto del título (rindiendo 77%) como un sólido blanco. ESI-MS: m/z 280,2 $(M+H)^+$.

Compuesto 117: (S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (150 mg, 0,643 mmol), 3-cloro-N-ciclopropil-4-(piperazin-1-il)benzamida (216 mg, 0,772 mmol), yoduro de (cianometil)trimetilfosfonio (250 mg,

1,029 mmol) y N,N-diisopropiletilamina (562 µl, 3,22 mmol) en propiononitrilo (Volumen: 1.931 µl) y se calentaron en un frasco cerrado a 100°C por 4 horas. La mezcla de reacción se volvió una solución café oscura con un precipitado. Se enfrió a temperatura ambiente y el precipitado se recogió por filtración, se lavó con MeCN (2 mL) y se suspendió en MeCN (15 mL) con calentamiento y sonicación. Luego se enfrió a temperatura ambiente, el precipitado se recogió por filtración, se lavó con MeCN (2 mL) y se secó al vacío para proporcionar (S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida (272,4 mg, 0,550 mmol, rindiendo 86%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) δ 10,49 (s, 1H), 8,39 (d, J = 4,3 Hz, 1H), 7,85 (d, J = 2,0 Hz, 1H), 7,75 (dd, J = 8,3, 2,0 Hz, 1H), 7,66 (s, 1H), 7,16 (d, J = 8,6 Hz, 1H), 6,97 (d, J = 1,8 Hz, 1H), 4,50 (d, J = 12,9 Hz, 1H), 3,84 (dd, J = 11,4, 2,8 Hz, 1H), 3,38 (s, 2H), 3,02 (br. s., 4H), 2,77 - 2,88 (m, J = 0,8 Hz, 1H), 2,60 (td, J = 12,6, 2,5 Hz, 1H), 2,49 - 2,55 (m, J = 3,5, 1,8, 1,8 Hz, 4H), 2,04 (br. d, J = 12,6 Hz, 1H), 1,86 - 1,87 (m, 0H), 1,84 (br. s., 1H), 1,64 (br. d, J = 12,6 Hz, 1H), 1,32 - 1,57 (m, 3H), 0,61 - 0,72 (m, 2H), 0,51 - 0,61 (m, 2H); [M+H] calculado para $C_{26}H_{31}ClN_6O_2$, 495; encontrado, 495.

Compuesto 118: (S)-3-metoxi-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo

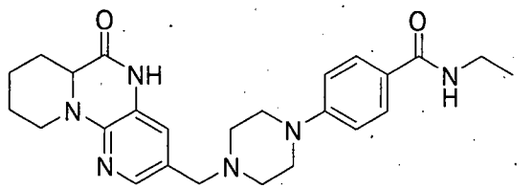


Se suspendieron (S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (150 mg, 0,643 mmol), clorhidrato de 3-metoxi-4-(piperazin-1-il)benzonitrilo (163 mg, 0,643 mmol), yoduro de (cianometil)trimetilfosfonio (250 mg, 1,029 mmol) y N,N-diisopropiletilamina (562 µl, 3,22 mmol) en propiononitrilo (Volumen: 1931 µl) y se calentaron en un frasco cerrado a 100°C por 2 horas. La mezcla de reacción se volvió una solución café oscura. Se diluyó con MeCN (4 mL) y se concentraron al vacío a alrededor de 3

mL. El precipitado resultante se filtró, se recristalizó de MeCN (5 mL) y se secó al vacío para proporcionar (S)-3-metoxi-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo (125 mg, 0,289 mmol, rindiendo 44,9%) como un sólido blanquecino.

^{1}H NMR (DMSO-d_6) δ 10,48 (s, 1H), 7,65 (d, J = 2,0 Hz, 1H), 7,30 - 7,36 (m, 2H); 6,93 - 6,98 (m, 2H), 4,50 (d, J = 12,9 Hz, 1H), 3,79 - 3,87 (m, 4H), 3,34 - 3,40 (m, 2H), 3,07 (br. s., 4H), 2,60 (td, J = 12,7, 2,7 Hz, 1H), 2,47 (br. s., 4H), 2,02 (br. s., 1H), 1,85 (d, J = 12,1 Hz, 1H), 1,64 (d, J = 12,4 Hz, 1H), 1,32 - 1,57 (m, 3H); [M+H] calculado para $C_{24}H_{28}N_6O_2$, 433; encontrado, 433.

Compuesto 119: N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida

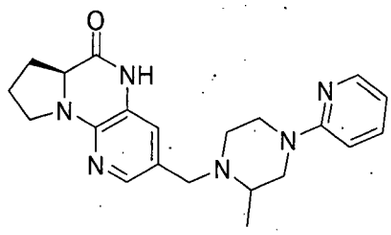


Se suspendieron 3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (50 mg, 0,214 mmol), N-etil-4-(piperazin-1-il)benzamida (55,0 mg, 0,236 mmol), yoduro de (cianometil)trimetilfosfonio (67,7 mg, 0,279 mmol) y N,N-diisopropiletilamina (187 µl, 1,072 mmol) en propiononitrilo (Volumen: 644 µl) y se calentaron en un frasco cerrado a 90°C por 1 hora. Se enfrió a temperatura ambiente, el precipitado resultante se filtró, se lavó con MeCN (5 mL) y se secó al vacío para proporcionar N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida (56 mg, 0,125 mmol, rindiendo 58,2%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) □ 10,43 (s, 1H), 8,12 (t, J = 5,6 Hz, 1H), 7,70 (d, J = 9,1 Hz, 2H), 7,66 (d, J = 2,0 Hz, 1H), 6,98 (d, J = 2,0 Hz, 1H), 6,92 (d, J = 9,1 Hz, 2H), 4,47 - 4,55 (m, 1H), 3,83 (dd, J = 11,4, 2,8 Hz, 1H), 3,32 - 3,40 (m, 2H), 3,18 - 3,28 (m, 6H), 2,61 (td, J = 12,6, 2,5 Hz, 1H), 2,43 - 2,49 (m, 4H), 2,04 (d, J = 13,1 Hz, 1H), 1,80 - 1,91 (m, 2H), 1,64 (d, J = 12,6 Hz, 2H), 1,33 - 1,58 (m, 3H),

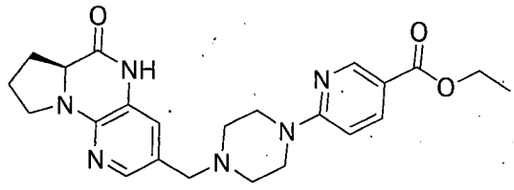
1,09 (d, J = 14,4 Hz, 3H); [M+H] calculado para $C_{25}H_{32}N_6O_2$, 449; encontrado, 449.

Compuesto 120: (6aS)-3-((2-metil-4-(piridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



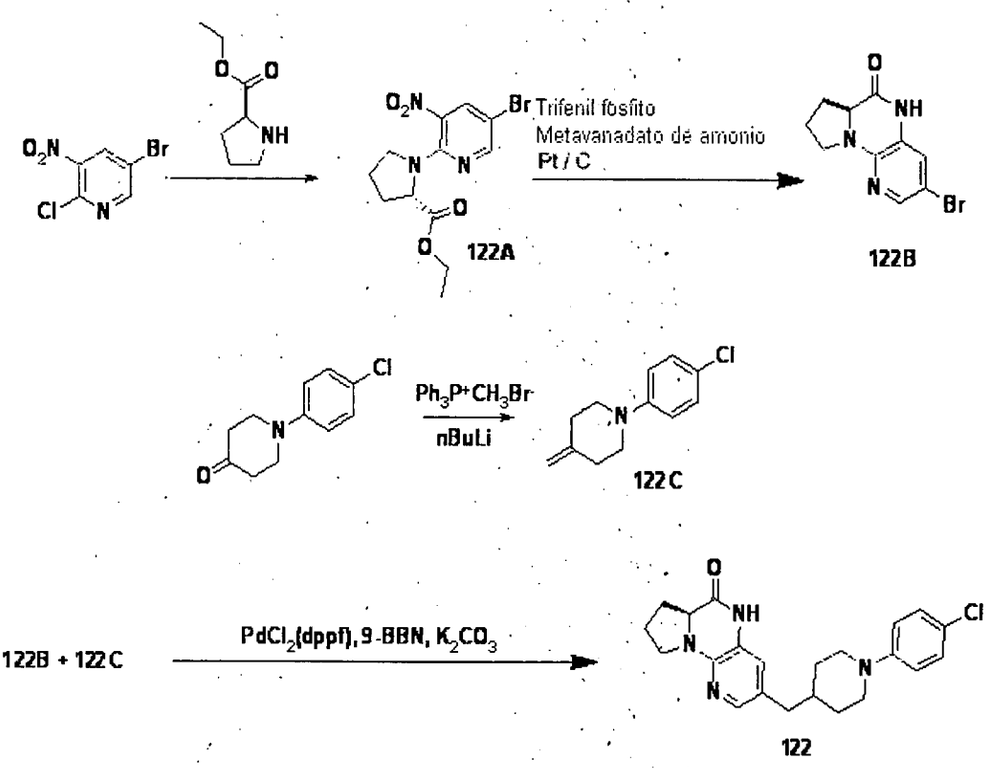
Se preparó el compuesto 120 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó 3-metil-1-(piridin-2-il)piperazina en lugar de clorhidrato de 1-(4-clorofenil)piperazina. [M+H] calculado para $C_{21}H_{26}N_6O$, 379; encontrado, 379.

Compuesto 121: 6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo



Se preparó el compuesto 121 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó 6-(piperazin-1-il)nicotinato de etilo en lugar de clorhidrato de 1-(4-clorofenil)piperazina. [M+H] calculado para $C_{23}H_{28}N_6O_3$, 437; encontrado, 437.

Compuesto 122: (S)-3-((1-(4-clorofenil)piperidin-4-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



Compuesto 122A: 1-(5-bromo-3-nitropiridin-2-il)pirrolidin-2-carboxilato de (S)-etilo: El 5-bromo-2-cloro-3-nitropiridina (5,94 g, 25 mmol) y pirrolidin-2-carboxilato de(S)-etilo (7,52 g, 52,5 mmol) se combinaron y se agitaron a 90°C por 10 minutos en un frasco cerrado. El material crudo se purificó por columna cromatográfica evaporativa (EtOAc en hexanos 20-30%, para proporcionar 1-(5-bromo-3-nitropiridin-2-il)pirrolidin-2-carboxilato de (S)-etilo (8,43 g, 24,49 mmol, rindiendo 98%) como un aceite amarillo viscoso. [M+H] calculado para $C_{12}H_{14}BrN_3O_4$, 344; encontrado, 344.

Compuesto 122B: (S)-3-bromo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: El 1-(5-bromo-3-nitropiridin-2-il)pirrolidin-2-carboxilato de (S)-etilo (8,6 g, 24,99 mmol) se disolvió en diclorometano (Volumen: 125 ml) y a ésta solución se agregó trifenil fosfito (0,078 g, 0,250 mmol), metavanadato de amonio (0,175 g, 1,499 mmol) y Pt/C (5% en peso) (0,975 g, 0,250 mmol). La mezcla de reacción se hidrogenó a 80 psi a 25°C por 4 horas. La mezcla de reacción se filtró a través de celite utilizando DCM y MeOH para completar la transferencia y lavar el tapón de celite. Los

filtrados combinados y lavados se concentraron al vacío y cristalizaron con etil éter (75 mL). El precipitado se filtró y se secó al vacío para proporcionar (S)-3-bromo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (2,87 g, 10,70 mmol, rindiendo 42,8%) como un sólido beige ligero.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,82 - 2,03 (m, 3 H) 2,11 - 2,26 (m, 1 H) 3,27 - 3,47 (m, 1 H) 3,49 - 3,63 (m, 1 H) 4,01 - 4,11 (m, 1 H) 7,06(d, *J*=2,27 Hz, 1 H) 7,77 (d, *J*=2,02 Hz, 1 H) 10,57 (s, 1 H). [M+H] calculado para $C_{10}H_{10}BrN_3O$, 268; encontrado, 268.

Compuesto 122C: 1-(4-clorofenil)-4-metilenpiperidina: Se suspendió el bromuro de metiltrifenilfosfonio (1,429 g, 4,00 mmol) en THF (Razón: 1,667, Volumen: 2,5 ml) y se enfrió a -78°C. Se agregó gota a gota n-butillitio (0,960 ml, 2,400 mmol) durante 3 minutos y la suspensión amarilla resultante se agitó a -78°C por 10 minutos. Una solución de 1-(4-clorofenil)piperidin-4-ona (0,419 g, 2 mmol) en THF (Razón: 1,000, Volumen: 1,5 ml) se agregó gota a gota durante 3 minutos y la suspensión roja oscura se agitó a -78°C por 10 minutos y luego se dejó lentamente calentar a 5°C durante 1 hora. La reacción se agitó a 5°C por 4 horas y se detuvo con agua (4 mL). Ésta se extrajo con etil éter (2 X 5 mL) y los extractos se lavaron con agua (4 X 5 mL). Las aguas de lavado combinadas se volvieron a extraer con etil éter (5 mL) y los extractos orgánicos combinados se lavaron con salmuera (5 ml), se secaron con ($MgSO_4$), se filtraron y se concentraron al vacío. Se proporcionó por columna cromatográfica evaporativa (SiO_2 40 g, hexanos:acetato de etilo 9:1) el 1-(4-clorofenil)-4-metilenpiperidina (0,196 g, 0,944 mmol, rindiendo 47,2%) como un aceite amarillo transparente. [M+H] calculado para $C_{12}H_{14}Cl$, 208; encontrado, 208.

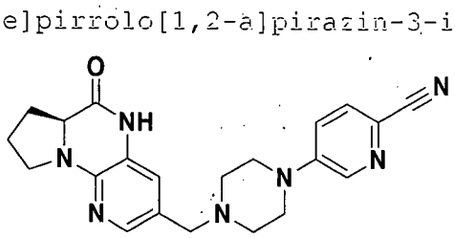
Compuesto 122: (S)-3-((1-(4-clorofenil)piperidin-4-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: El 1-(4-clorofenil)-4-metilenpiperidina (70 mg, 0,337 mmol) se diluyó con una solución THF 0,5M de 9-BBN (0,674 mL, 0,337 mmol) bajo nitrógeno y agitada a 75°C por 1 hora. La mezcla de reacción se agregó luego a una suspensión de (S)-3-bromo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (90 mg, 0,337

mmol), aducto $PdCl_2(dppf)-CH_2Cl_2$ (8,26 mg, 10,11 µmol) y carbonato de potasio (93 mg, 0,674 mmol) en DMF (1,0 mL) y agua (0,1 mL) y se agitó a 60°C por 4 horas.

La mezcla se enfrió, se diluyó con agua (10 mL) y el material rojo resultante separado, se lavó con agua, se disolvió en acetato de etilo (10 mL), se secó con ($MgSO_4$), se filtró y se concentró al vacío. Por columna cromatográfica evaporativa (SiO_2 12 g, acetato de etilo) se proporcionó el producto deseado como un sólido amarillo. Se suspendió en MeOH (5 mL) y el precipitado se filtró y se secó al vacío para entregar el producto como un sólido blanco (16 mg, rindiendo 12%).

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1,11 - 1,30 (m, 2 H) 1,43 - 1,58 (m, 0 H) 1,63 (d, *J*=12,13 Hz, 1 H) 1,80 - 2,03 (m, 2 H) 2,06 - 2,25 (m, 1 H) 2,29 - 2,44 (m, 2 H) 2,53 - 2,64 (m, 2 H) 3,35 - 3,44 (m, 1 H) 3,51 - 3,62 (m, 1 H) 3,65 (d, *J*=12,13 Hz, 2 H) 3,87 - 3,98 (m, 1 H) 6,82 (d, *J*=1,77 Hz, 1 H) 6,91 (d, *J*=9,09 Hz, 2 H) 7,19 (d, *J*=9,09 Hz, 2 H) 7,54 (d, *J*=1,77 Hz, 1 H) 10,40 (s, 1 H). [M+H] calculado para $C_{22}H_{25}ClN_4O$, 397; encontrado, 397.

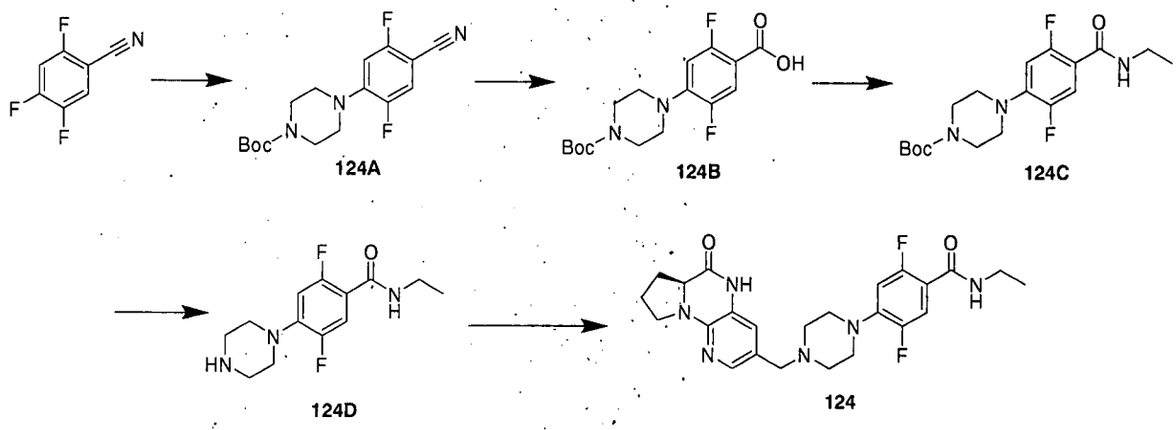
Compuesto 123: (S)-5-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)picolinonitrilo



Se preparó el compuesto 123 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 1, excepto que se utilizó 5-(piperazin-1-il)picolinonitrilo en lugar de clorhidrato de 1-(4-clorofenil)piperazina.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,84 - 2,02 (m, 3 H) 2,09 - 2,24 (m, 1 H) 2,39 - 2,48 (m, 4 H) 3,34 - 3,48 (m, 7 H) 3,53 - 3,64 (m, 1 H) 3,94 - 4,03 (m, 1 H) 6,97 (d, *J*=1,77 Hz, 1 H) 7,34 (dd, *J*=8,97, 2,91 Hz, 1 H) 7,61 (d, *J*=1,52 Hz, 1 H) 7,74 (d, *J*=8,84 Hz, 1 H) 8,40 (d, *J*=2,78 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{21}H_{23}N_7O$, 390; encontrado, 390.

Compuesto 124: (S)-N-etil-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 124A: 4-(4-ciano-2,5-difluorofenil)piperazina-1-carboxilato de ter-butilo: La piperazina-1-carboxilato de ter-butilo (0,931 g, 5 mmol) y 2,4,6-trifluorobenzonitrilo (0,785 g, 5,00 mmol) se combinaron, se agregó carbonato de potasio (0,898 g, 6,50 mmol) y la mezcla de reacción se agitó a 90°C por 1 día. La mezcla se trituró con acetato de etilo (3 X 5 mL) y los extractos orgánicos combinados se filtraron. Estos se concentraron a alrededor de 5-10 mL y se sometieron a columna cromatográfica evaporativa sobre sílica gel (SiO_2 120 g, hexanos:acetato de etilo de 1:0 a 4:1) para proporcionar 4-(4-ciano-2,5-difluorofenil)piperazina-1-carboxilato de ter-butilo (1,363 g, 4,22 mmol, rindiendo 84%) como un sólido blanco.
^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1,41 (s, 9 H) 3,12 - 3,27 (m, 4 H) 3,45 (d, *J*=4,80 Hz, 4 H) 7,12 (dd, *J*=11,87, 7,07 Hz, 1 H) 7,80 (dd, *J*=12,88, 6,32 Hz, 1 H).

Compuesto 124B: ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-2,5-difluorobenzoico: El 4-(4-ciano-2,5-difluorofenil)- piperazina-1-carboxilato de ter-butilo (20 mg, 0,062 mmol) se disolvió en etanol (1 mL) y se trató con agua (0,2 mL) y NaOH al 50% (0,2 mL, 2,500 mmol). La mezcla de reacción se agitó a 90°C por 1 hora, se diluyó con agua (2 mL) y se acidificó con HCl 1N a pH<4. El sólido se filtró, se lavó con agua y se secó al vacío para proporcionar el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-2,5-difluorobenzoico

(21,0 mg, 0,061 mmol, rindiendo 99%) como un sólido blanco. ESI-MS : m/z 343 $(M+H)^+$.

Compuesto 124C: 4-(4-(etilcarbamoil)-2,5-difluorofenil)piperazina-1-carboxilato de ter-butilo: Se suspendieron el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-2,5-difluorobenzoico (0,021 g, 0,061 mmol) y el clorhidrato etilamina (7,50 mg, 0,092 mmol) en DMF (Volumen: 0,7 mL) y se trató con DIPEA (0,054 mL, 0,307 mmol) y hexafluorofosfato(V) de 2-(3H-[1,2,3]triazolo[4,5-b]piridin-3-il)-1,1,3,3-tetrametilisouronio (0,047 g, 0,123 mmol). La mezcla de reacción se agitó a temperatura ambiente por 15 minutos y se diluyó con agua. El precipitado se filtró, se lavó con agua y se secó al vacío para proporcionar 4-(4-(etilcarbamoil)-2,5-difluorofenil)piperazina-1-carboxilato de ter-butilo (20,1 mg, 0,054 mmol, rindiendo 89%). ESI-MS : m/z 370 $(M+H)^+$.

Compuesto 124D: N-etil-2,5-difluoro-4-(piperazin-1-il)benzamida: El 4-(4-(etilcarbamoil)-2,5-difluorofenil)- piperazina-1-carboxilato de ter-butilo (0,020 g, 0,054 mmol) se diluyó con HCl 4,0M en dioxano (3 mL) y se agitó por 30 minutos. El precipitado blanco grueso que se formó se diluyó con etil éter (10 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró bajo nitrógeno y se secó al vacío para proporcionar el clorhidrato N-etil-2,5-difluoro-4-(piperazin-1-il)benzamida (16,2 mg, 0,053 mmol, rindiendo 98%) como un sólido blanco. ESI-MS : m/z 270 $(M+H)^+$.

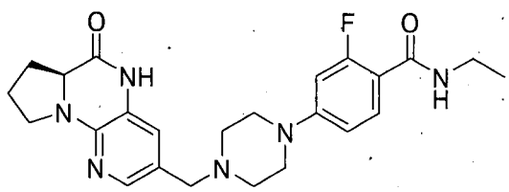
Compuesto 124: (S)-N-etil-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (10,76 mg, 0,049 mmol), clorhidrato de N-etil-2,5-difluoro-4-(piperazin-1-il)benzamida (15 mg, 0,049 mmol), yoduro de (cianometil)trimetilfosfonio (17,88 mg, 0,074 mmol) y N,N-diisopropiletilamina (0,043 mL, 0,245 mmol) en propiononitrilo (Volumen: 0,2 mL) y se calentaron en un frasco cerrado a 90°C por 2 horas. La mezcla de reacción se volvió una solución café oscura. Se

enfrió a temperatura ambiente, se diluyó con diclorometano (2 mL) y metanol (0,3 mL), y se purificó utilizando columna cromatográfica evaporativa sobre sílica gel (SiO_2 12 g, diclorometano-metanol 100:0-90:10). El sólido resultante se suspendió en éter (1 mL), se agitó hasta que resultó una suspensión fina, se filtró y el sólido se recristalizó de MeOH-agua (1:7, 4 mL) y se secó al vacío para proporcionar (S)-N-etil-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzamida (8,5 mg, 0,018 mmol, rindiendo 36,8%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,02 (t, J=7,20 Hz, 3 H) 1,76 - 1,97 (m, 3 H) 2,11 (m, J=6,44, 4,17 Hz, 1 H) 2,36 - 2,42 (m, 4 H) 3,03 (br. s., 4 H) 3,12 - 3,22 (m, 2 H) 3,28 - 3,37 (m, 3 H) 3,46 - 3,59 (m, 1 H) 3,86 - 3,97 (m, 1 H) 6,81 (dd, J=12,63, 7,07 Hz, 1 H) 6,91 (d, J=1,77 Hz, 1 H) 7,30 (dd, J=13,64, 6,82 Hz, 1 H) 7,55 (d, J=1,52 Hz, 1 H) 7,95 - 8,04 (m, 1 H) 10,38 (s, 1 H).

[M+H] calculado para $C_{24}H_{28}F_2N_6O_2$, 471; encontrado, 471.

Compuesto 125: (S)-N-etil-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida.

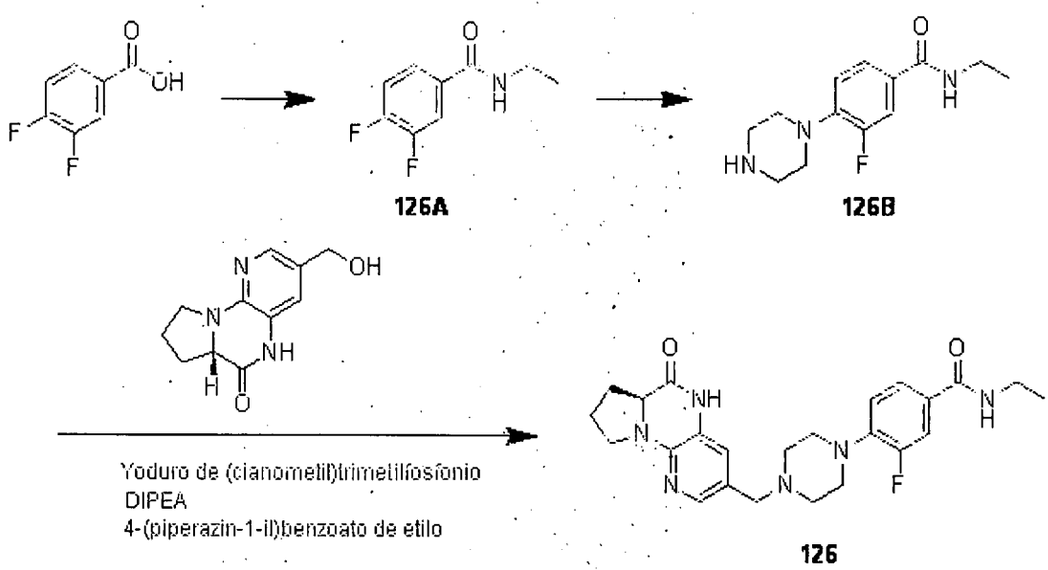


Se suspendieron el (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (76 mg, 0,348 mmol), clorhidrato de N-etil-2-fluoro-4-(piperazin-1-il)benzamida (100 mg, 0,348 mmol), yoduro de (cianometil)trimetilfosfonio (127 mg, 0,521 mmol) y N,N-diisopropiletilamina (0,303 ml, 1,738 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 120°C por 3 horas. La mezcla de reacción se volvió una suspensión café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 10-95%). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-

metanol (5:1, 6 mL) y se secó al vacío para proporcionar (S)-N-etil-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (28,5 mg, 0,063 mmol, rindiendo 18,12%) como un sólido color café.

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1,13 (t; *J*=7,20 Hz, 3 H) 1,83 - 2,02 (m, 3 H) 2,18 (dd, *J*=6,44, 4,17 Hz, 1 H) 2,44 - 2,49 (m, 4 H) 2,81 - 3,01 (m, 4 H) 3,23 - 3,32 (m, 2 H) 3,34 - 3,44 (m, 3 H) 3,52 - 3,64 (m, 1 H) 3,93 - 4,01 (m, 1 H) 6,91 (td, *J*=8,21, 2,53 Hz, 1 H) 6,97 (d, *J*=1,77 Hz, 1 H) 7,00 (dd, *J*=11,37, 2,53 Hz, 1 H) 7,62 (d, *J*=1,52 Hz, 1 H) 7,67 (dd, *J*=8,46, 7,20 Hz, 1 H) 8,86 (t, *J*=5,43 Hz, 1 H) 10,45 (s, 1 H). [M+H] calculado para $C_{24}H_{29}FN_6O_2$, 453; encontrado, 453.

Compuesto 126: (S)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida.



Compuesto 126A: 3,4-difluoro-N-etilbenzamida: Utilizando clorhidrato de etanamina y ácido 3,4-difluorobenzoico en el procedimiento general para el acoplamiento de aminas a ácidos carboxílico, se obtuvo el compuesto del título (rindiendo 56%) como un sólido blanquecino.

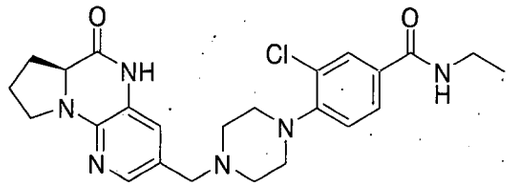
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,12 (t, *J*=7,20 Hz, 3 H) 3,28 (qd, *J*=7,24, 5,56 Hz, 2 H) 7,55 (dt, *J*=10,48, 8,40 Hz, 1 H) 7,73 (m, *J*=7,33, 4,74, 2,08, 1,14, 1,14 Hz, 1 H) 7,88 (ddd, *J*=11,75, 7,83,

2,15 Hz, 1 H) 8,58 (t, *J*=4,93 Hz, 1 H). ESI-MS: m/z 186,1 $(M+H)^+$. Mp = 94,1-96,2°C.

Compuesto 126B: 3-fluoro-N-etil-4-(piperazin-1-il)benzamida: Utilizando 3,4-difluoro-N-etilbenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, se obtuvo el compuesto del título (rindiendo 80%) como un sólido blanco. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,10 (t, *J*=7,20 Hz, 3 H) 2,31 (br. s., 1 H) 2,79 - 2,87 (m, 4 H) 2,95 - 3,03 (m, 4 H) 3,26 (qd, *J*=7,20, 5,68 Hz, 2 H) 7,03 (t, *J*=8,59 Hz, 1 H) 7,55 - 7,65 (m, 2 H) 8,35 (t, *J*=5,43 Hz, 1 H). ESI-MS: m/z 252,2 $(M+H)^+$. mp = 142,4-144,9°C.

Compuesto 126: (S)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (126): Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de N-etil-3-fluoro-4-(piperazin-1-il)benzamida (131 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, 10-95% ACN en agua). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-metanol (5:1, 6 mL) y se secó al vacío para proporcionar (S)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (82,3 mg, 0,182 mmol, rindiendo 39,9%) como un sólido amarillo verdoso. ^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 0,98 - 1,08 (m, 3 H) 1,77 - 1,96 (m, 3 H) 2,04 - 2,18 (m, 1 H) 2,35 - 2,43 (m, 4 H) 2,93 - 3,07 (m, 4 H) 3,13 - 3,23 (m, 2 H) 3,28 - 3,38 (m, 3 H) 3,47 - 3,57 (m, 1 H) 3,88 - 3,95 (m, 1 H) 6,92 (d, *J*=2,02 Hz, 1 H) 6,97 (t, *J*=8,84 Hz, 1 H) 7,47 - 7,57 (m, 3 H) 8,28 (t, *J*=5,56 Hz, 1 H) 10,37 (s, 1 H). [M+H] calculado para $C_{24}H_{29}FN_6O_2$, 453; encontrado, 453.

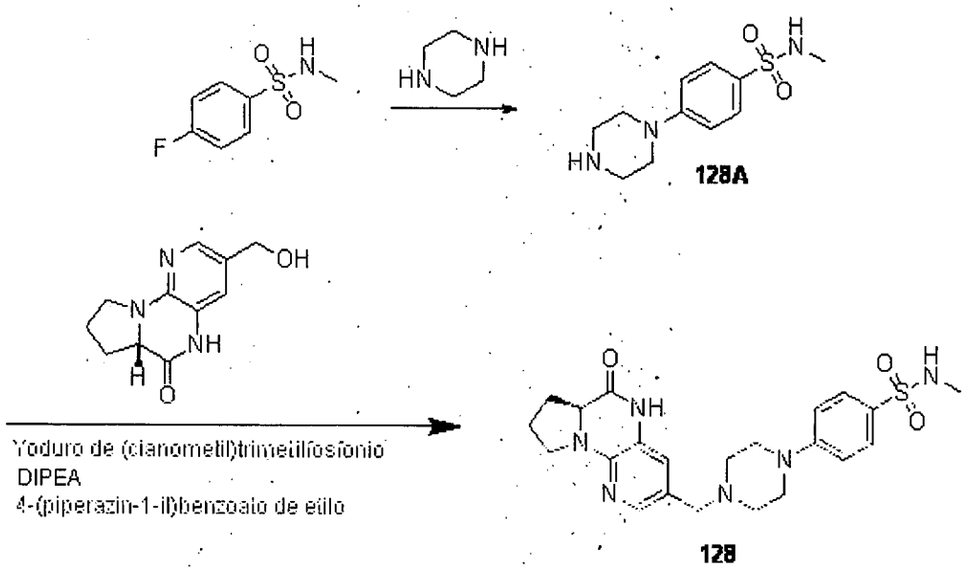
Compuesto 127: (S)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Se suspendieron el (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]- pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de 3-cloro-N-etil-4-(piperazin-1-il)benzamida (139 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, 10-95% ACN en agua). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-metanol (5:1, 6mL) y se secó al vacío para proporcionar (S)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]- pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (75,6 mg, 0,161 mmol, 35,3% rindiendo) como un sólido de color tostado.

^{1}H NMR (400 MHz, DMSO-*d6*) δ ppm 1,03 (t, *J*=7,20 Hz, 3 H) 1,76 - 1,93 (m, 3 H) 2,06 - 2,17 (m, 1 H) 2,44 - 2,51 (m, 4 H) 2,96 (br. s., 4 H) 3,14 - 3,23 (m, 2 H) 3,28 - 3,38 (m, 3 H) 3,46 - 3,58 (m, 1 H) 3,88 - 3,97 (m, 1 H) 6,92 (d, *J*=2,02 Hz, 1 H) 7,10 (d, *J*=8,34 Hz, 1 H) 7,56 (d, *J*=1,77 Hz, 1 H) 7,70 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,81 (d, *J*=2,27 Hz, 1 H) 8,37 (t, *J*=5,43 Hz, 1 H) 10,38 (s, 1 H). [M+H] calculado para $C_{24}H_{29}ClN_6O_2$, 469; encontrado, 469.

Compuesto 128: (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)bencenosulfonamida



128A

128

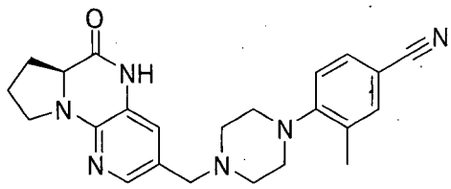
Compuesto 128A: N-metil-4-(piperazin-1-il)bencenosulfonamida: El 4-fluoro-N-metilbencenosulfonamida (189 mg, 0,999 mmol) y piperazina (430 mg, 4,99 mmol) se combinaron y la mezcla de reacción se agitó a 120°C por 2 horas. Se diluyó con agua (5 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró, se lavó con agua (5x3 mL) y se secó al vacío para proporcionar N-metil-4-(piperazin-1-il)bencenosulfonamida (222 mg, 0,869 mmol, rindiendo 87%) como un sólido blanco. ESI-MS : m/z 256 $(M+H)^+$.

Compuesto 128: (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)bencenosulfonamida: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]- pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), N-metil-4-(piperazin-1-il)bencenosulfonamida (116 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 10-95%). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-metanol (2:1, 6 mL) y

se secó al vacío para proporcionar (S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-a]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)bencenosulfonamida (110 mg, 0,241 mmol, rindiendo 52,8%) como un sólido color tostado.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,88 - 2,04 (m, 3 H) 2,15 - 2,27 (m, 1 H) 2,38 (d, J=4,80 Hz, 3 H) 2,51 (d, J=4,29 Hz, 4 H) 3,32 (br. s., 4 H) 3,38 - 3,49 (m, 3 H) 3,57 - 3,69 (m, 1 H) 3,97 - 4,07 (m, 1 H) 7,02 (d, J=1,52 Hz, 1 H) 7,07 (d, J=9,09 Hz, 2 H) 7,15 (q, J=4,72 Hz, 1 H) 7,59 (d, J=8,84 Hz, 2 H) 7,66 (d, J=1,77 Hz, 1 H) 10,48 (s, 1 H). [M+H] calculado para $C_{24}H_{29}ClN_6O_2$, 457; encontrado, 457.

Compuesto 129: (S)-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo

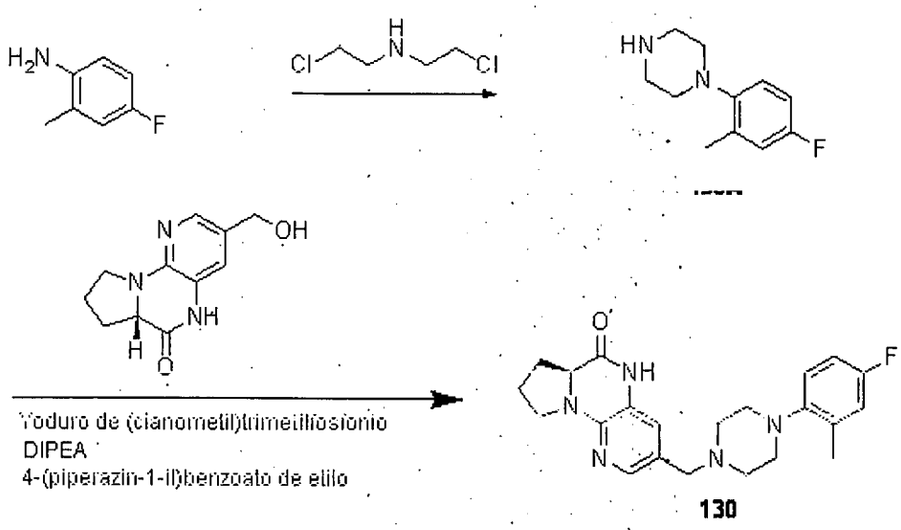


Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), 3-metil-4-(piperazin-1-il)benzonitrilo (92 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 10-95%). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua (6 mL) y se secó al vacío para proporcionar (S)-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzonitrilo (90,1 mg, 0,224 mmol, rindiendo 49,1%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-$d6$) δ ppm 1,85 - 2,01 (m, 3 H) 2,12 - 2,21 (m, 1 H) 2,24 (s, 3 H) 2,43 - 2,55 (m, 4 H) 2,85 - 2,97 (m, 4 H) 3,35 - 3,44 (m, 3 H) 3,53 - 3,63 (m, 1 H) 3,95 - 4,03 (m, 1 H) 6,98 (d,

J=2,02 Hz, 1 H) 7,05 - 7,12 (m, 1 H) 7,54 - 7,60 (m, 2 H) 7,62 (d, J=1,77 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{23}H_{26}N_6O$, 403; encontrado, 403.

Compuesto 130: (S)-3-((4-(4-fluoro-2-metilfenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona



130

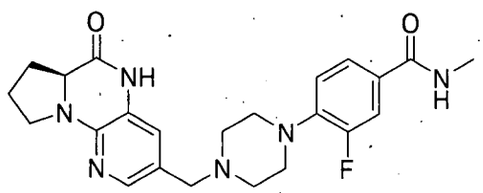
Compuesto 130A: 1-(4-fluoro-2-metilfenil)piperazina: El clorhidrato de Bis(2-cloroetil)amina (1,79 g, 10,03 mmol) y 4-fluoro-2-metilanilina (1,26 g, 10,07 mmol) se disolvieron en 2-propanol (Volumen: 10 mL) y se agitaron en un frasco cerrado a 100°C durante la noche. La mezcla de reacción se diluyó con i-PrOH (10 mL) y se enfrió a 10°C. El precipitado resultante se filtró y se purificó utilizando HPLC (ACN en agua 10-80%, solución tampón de TFA). Las fracciones se concentraron al vacío, se suspendieron en éter (3 mL) y se trató con HCl 4N en dioxano (1 mL). El precipitado se filtró y se secó al vacío para proporcionar el diclorhidrato de 1-(4-fluoro-2-metilfenil)piperazina (150 mg, 0,561 mmol, rindiendo 5,60%). ESI-MS : m/z 195 $(M+H)^+$.

Compuesto 130: (S)-3-((4-(4-fluoro-2-metilfenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456

mmol), diclorhidrato de 1-(4-fluoro-2-metilfenil)piperazina (122 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-3-((4-(4-fluoro-2-metilfenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (102,3 mg, 0,259 mmol, rindiendo 56,7%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,80 - 2,02 (m, 3 H) 2,09 - 2,20 (m, 1 H) 2,23 (s, 3 H) 2,37 - 2,49 (m, 4 H) 2,77 (br. s., 4 H) 3,34 - 3,44 (m, 3 H) 3,52 - 3,65 (m, 1 H) 3,93 - 4,03 (m, 1 H) 6,88 - 7,07 (m, 4 H) 7,62 (s, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{22}H_{26}FN_5O$, 396; encontrado, 396.

Compuesto 131: (S)-3-fluoro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida

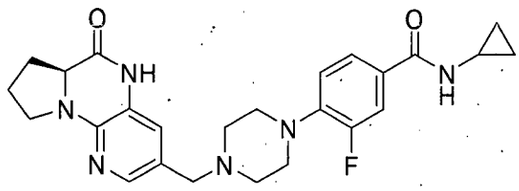


Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de 3-fluoro-N-metil-4-(piperazin-1-il)benzamida (125 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron

al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-3-fluoro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido- [3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)- benzamida (128,5 mg, 0,293 mmol, rindiendo 64,2%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1,83 - 2,03 (m, 3 H) 2,09 - 2,25 (m, 1 H) 2,50 (m, 4 H) 2,75 (d, J=4,29 Hz, 3 H) 2,96 - 3,14 (m, 4 H) 3,35 - 3,45 (m, 3 H) 3,53 - 3,65 (m, 1 H) 3,93 - 4,05 (m, 1 H) 6,98 (d, J=1,77 Hz, 1 H) 7,04 (t, J=8,59 Hz, 1 H) 7,51 - 7,67 (m, 3 H) 8,27 - 8,38 (m, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{23}H_{27}FN_6O_2$, 439; encontrado, 439.

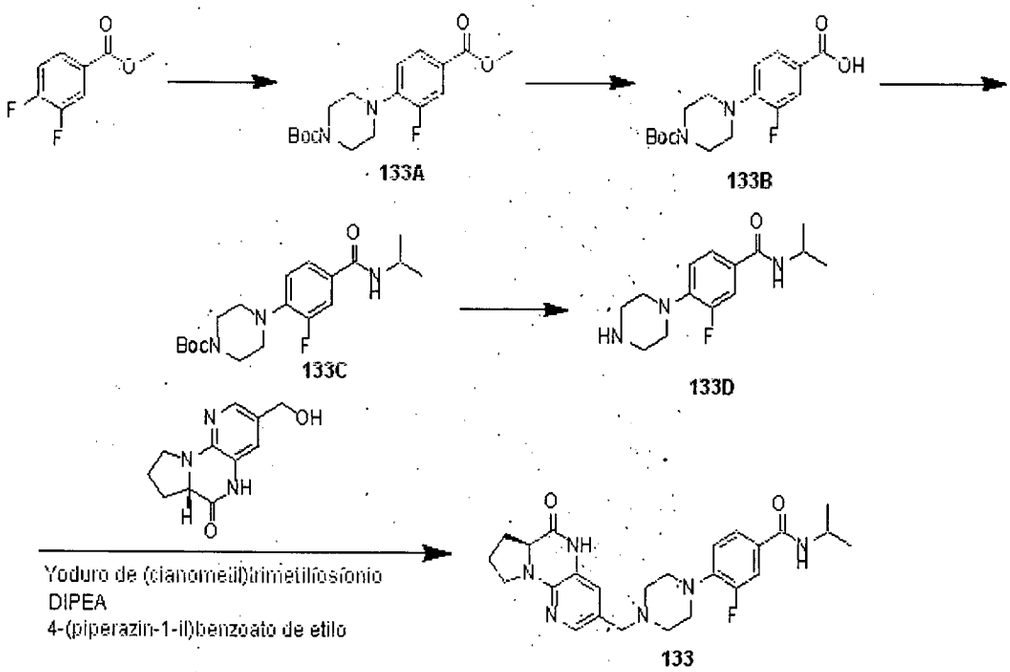
Compuesto 132: (S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de N-ciclopropil-3-fluoro-4-(piperazin-1-il)benzamida (137 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidro- pirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (85,3 mg, 0,184 mmol, rindiendo 40,3%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0,45 - 0,61 (m, 2 H) 0,61 - 0,76 (m, 2 H) 1,83 - 2,05 (m, 3 H) 2,08 - 2,25 (m, 1 H) 2,44 - 2,49 (m, 4 H) 2,80 (td, *J*=7,33, 3,79 Hz, 1 H) 3,08 (br. s., 4 H) 3,54 - 3,66 (m, 1 H) 3,91 - 4,06 (m, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,02 (t, *J*=8,84 Hz, 1 H) 7,49 - 7,69 (m, 3 H) 8,31 (d, *J*=4,04 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{25}H_{29}FN_6O_2$, 465; encontrado, 465.

Compuesto 133: (S)-3-fluoro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 133A: 4-(2-fluoro-4-(metoxicarbonil)fenil)piperazina-1-carboxilato de ter-butilo: El Carbonato de potasio (5,56 g, 40,3 mmol) y piperazina-1-carboxilato de ter-butilo (6,92 g, 37,2 mmol) se combinaron, se agregó 3,4-difluorobenzoato de metilo (5,33 g, 31,0 mmol) y la mezcla de reacción se agitó a 90°C por 1 dia. La mezcla se trituró con acetato de etilo (3 X 5 mL) y los extractos orgánicos combinados se filtraron. Éstos se concentraron hasta alrededor de 5-10 mL y se sometieron a columna cromatográfica evaporativa sobre sílica gel (SiO_2 120 g, hexanos:acetato de etilo 1:0 a 4:1) para proporcionar 4-(2-fluoro-4-(metoxicarbonil)fenil)- piperazina-1-

carboxilato de ter-butilo (4,702 g, 13,90 mmol, rindiendo 44,9%) como un sólido blanco. ESI-MS : m/z 339 $(M+H)^+$.

Compuesto 133B: ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-fluorobenzoico: El 4-(2-fluoro-4-(metoxicarbonil)fenil)piperazina-1-carboxilato de ter-butilo (4,6 g, 13,59 mmol) se suspendió en 1,4-Dioxano (Volumen: 68,0 ml) y se trató con LiOH 1N (68,0 ml, 68,0 mmol). La mezcla de reacción se agitó a temperatura ambiente por 23 horas. La mezcla de reacción se concentró al vacío hasta que se retiró la mayor parte de dioxano y se acidificó con HCl (4,5 N) hasta que resultó un precipitado grueso. Se recogió por filtración, se lavó con agua y se secó al vacío para proporcionar el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-fluorobenzoico (4,40 g, 13,57 mmol, rindiendo 100%) como un sólido café. ESI-MS : m/z 325 $(M+H)^+$.

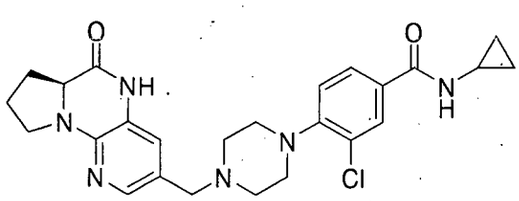
Compuesto 133C: 4-(2-fluoro-4-(isopropilcarbamoil)fenil)piperazina-1-carboxilato de ter-butilo: Se suspendieron el ácido 4-(4-(ter-butoxicarbonil)piperazin-1-il)-3-fluorobenzoico (1,1 g, 3,39 mmol), propan-2-amina (0,241 g, 4,07 mmol), clorhidrato de N1-((etilimino)metilen)-N3,N3-dimetilpropan-1,3-diamina (0,975 g, 5,09 mmol) y 1H-benzo[d][1,2,3]triazol-1-ol hidrato (0,779 g, 5,09 mmol) en DMF (Volumen: 13,57 ml) y se agregó 4-metilmorfolina (1,864 ml, 16,96 mmol). La mezcla de reacción se agitó a temperatura ambiente por 2 horas. Se diluyó con agua (50 mL) y se extrajo con acetato de etilo (3X100 mL). Los extractos orgánicos combinados se lavaron con salmuera (3x50 mL), se secaron con ($MgSO_4$) y se concentraron al vacío para proporcionar 4-(2-fluoro-4-(isopropilcarbamoil)fenil)-piperazina-1-carboxilato de ter-butilo (1,11 g, 3,04 mmol, rindiendo 89%) como un sólido blanquecino. ESI-MS : m/z 366 $(M+H)^+$.

Compuesto 133D: 3-fluoro-N-isopropil-4-(piperazin-1-il)benzamida (133D): El 4-(2-fluoro-4-(isopropilcarbamoil)-fenil)piperazina-1-carboxilato de ter-butilo (1,10 g, 3,01 mmol) se diluyó con HCl 4,0M en dioxano (3 mL) y se agitó por 30 minutos. Se formó un precipitado blanco grueso se diluyó con etil éter (10 mL) y se agitó hasta que resultó una suspensión fina. El precipitado se filtró bajo nitrógeno

y se secó al vacío para proporcionar clorhidrato de 3-fluoro-N-isopropil-4-(piperazin-1-il)benzamida como un sólido blanco. ESI-MS : m/z 302 $(M+H)^+$.

Compuesto 133: (S)-3-fluoro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)-metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroxi-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de 3-fluoro-N-isopropil-4-(piperazin-1-il)benzamida (138 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-3-fluoro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (71,4 mg, 0,153 mmol, rindiendo 33,6%) como un sólido amarillo claro.
^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 1,14 (d, J=6,57 Hz, 6 H) 1,82 - 2,01 (m, 3 H) 2,12 - 2,24 (m, 1 H) 2,46 - 2,50 (m, 4 H) 2,98 - 3,15 (m, 4 H) 3,35 - 3,44 (m, 3 H) 3,54 - 3,64 (m, 1 H) 3,92 - 4,14 (m, 2 H) 6,98 (d, J=1,77 Hz, 1 H) 7,03 (t, J=8,84 Hz, 1 H) 7,56 - 7,66 (m, 3 H) 8,09 (d, J=7,83 Hz, 1 H) 10,45 (s, 1 H). [M+H] calculado para $C_{25}H_{31}FN_6O_2$, 467; encontrado, 467.

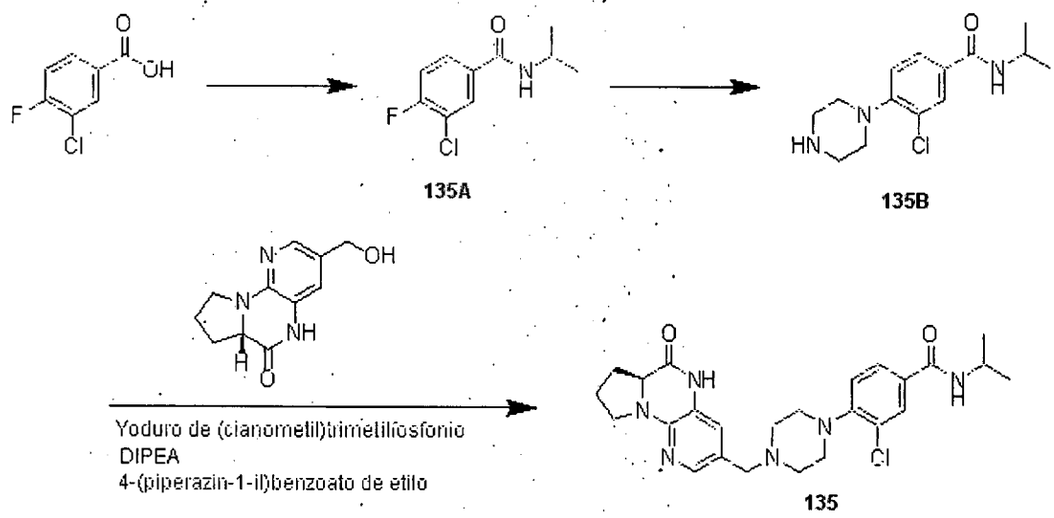
Compuesto 134: (S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Se suspendieron (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), 3-cloro-N-ciclopropil-4-(piperazin-1-il)benzamida (128 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 25-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 15 mL) y se secó al vacío para proporcionar(S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidro- pirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (120,4 mg, 0,250 mmol, rindiendo 54,9%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 0,50 - 0,60 (m, 2 H) 0,61 - 0,72 (m, 2 H) 1,84 - 2,01 (m, 3 H) 2,12 - 2,23 (m, 1 H) 2,51 - 2,57 (m, 4 H) 2,77 - 2,86 (m, 1 H) 3,02 (br. s., 4 H) 3,35 - 3,46 (m, 3 H) 3,54 - 3,64 (m, 1 H) 3,95 - 4,03 (m, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,16 (d, *J*=8,34 Hz, 1 H) 7,63 (d, *J*=1,77 Hz, 1 H) 7,75 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,85 (d, *J*=2,02 Hz, 1 H) 8,39 (d, *J*=4,04 Hz, 1 H) 10,45 (s, 1 H). [M+H] calculado para $C_{25}H_{29}ClN_6O_2$, 481; encontrado, 481.

Compuesto 135: (S)-3-cloro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 135A: 3-cloro-4-fluoro-N-isopropilbenzamida: Utilizando clorhidrato de isopropilamina y ácido 3-cloro-4-fluorobenzoico en el procedimiento general para el acoplamiento de aminas a ácidos carboxílico, se obtuvo el compuesto del título (rindiendo 81%) como un sólido blanco. ESI-MS: m/z 216 $(M+H)^+$.

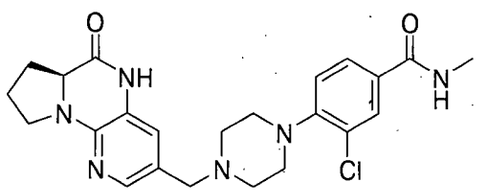
Compuesto 135B: 3-cloro-N-isopropil-4-(piperazin-1-il)benzamida: Utilizando 3-cloro-4-fluoro-N-isopropilbenzamida en el procedimiento general para reacciones de sustitución nucleofílica aromática, se obtuvo el compuesto del título (rindiendo 51%) como un sólido blanquecino. ESI-MS: m/z 282,2 $(M+H)^+$.

Compuesto 135: (S)-3-cloro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)-metil)piperazin-1-il)benzamida: Se suspendieron (S)-3-(hidroxi-metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), 3-cloro-N-isopropil-4-(piperazin-1-il)benzamida (129 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propionitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en

agua 25-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 15 mL) y se secó al vacío para proporcionar (S)-3-cloro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidro-pirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)-benzamida (122,1 mg, 0,253 mmol, rindiendo 55,4%) como un sólido tostado claro.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,14 (d, J=6,57 Hz, 6 H) 1,84 - 2,03 (m, 3 H) 2,12 - 2,25 (m, 1 H) 2,50 - 2,59 (m, 4 H) 3,02 (br. s., 4 H) 3,35 - 3,45 (m, 3 H) 3,53 - 3,64 (m, 1 H) 3,94 - 4,09 (m, 2 H) 6,98 (d, J=1,52 Hz, 1 H) 7,17 (d, J=8,59 Hz, 1 H) 7,63 (d, J=1,77 Hz, 1 H) 7,77 (dd, J=8,34, 2,02 Hz, 1 H) 7,89 (d, J=2,02 Hz, 1 H) 8,18 (d, J=7,58 Hz, 1 H) 10,45 (s, 1 H). [M+H] calculado para $C_{25}H_{31}ClN_6O_2$, 483; encontrado, 483.

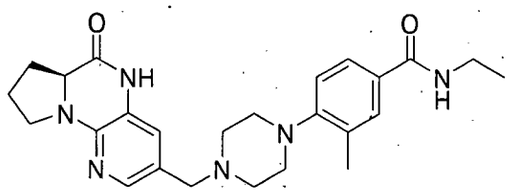
Compuesto 136: (S)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzamida



Se suspendieron el (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de 3-cloro-N-metil-4-(piperazin-1-il)benzamida (132 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido- [3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (53,1 mg, 0,117 mmol, rindiendo 25,6%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,83 - 2,02 (m, 3 H) 2,10 - 2,24 (m, 1 H) 2,51 (br. s., 4 H) 2,75 (d, *J*=4,55 Hz, 3 H) 3,03 (br. s., 4 H) 3,36 - 3,45 (m, 3 H) 3,52 - 3,65 (m, 1 H) 3,93 - 4,03 (m, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,17 (d, *J*=8,34 Hz, 1 H) 7,63 (d, *J*=1,77 Hz, 1 H) 7,75 (dd, *J*=8,34, 2,02 Hz, 1 H) 7,86 (d, *J*=2,02 Hz, 1 H) 8,41 (q, *J*=4,13 Hz, 1 H) 10,45 (s, 1 H). [M+H] calculado para $C_{23}H_{27}ClN_6O_2$, 455; encontrado, 455.

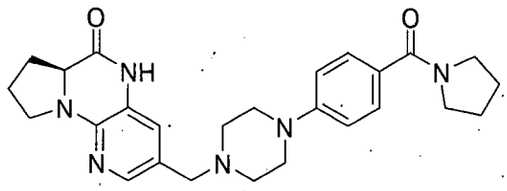
Compuesto 137: (S)-N-etil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Se suspendieron el (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,456 mmol), clorhidrato de N-etil-3-metil-4-(piperazin-1-il)benzamida (129 mg, 0,456 mmol), yoduro de (cianometil)trimetilfosfonio (166 mg, 0,684 mmol) y N,N-diisopropiletilamina (0,398 ml, 2,281 mmol) en propiononitrilo (Volumen: 1,370 ml) y se calentaron en un frasco cerrado a 90-120°C por 4 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (básico, ACN en agua 45-95%, básico). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (2:1, 6 mL) y se secó al vacío para proporcionar (S)-N-etil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (128,5 mg, 0,286 mmol, rindiendo 62,8%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1,83 - 2,03 (m, 3 H) 2,09 - 2,25 (m, 1 H) 2,50 (m, 4 H) 2,75 (d, *J*=4,29 Hz, 3 H) 2,96 - 3,14 (m, 4 H) 3,35 - 3,45 (m, 3 H) 3,53 - 3,65 (m, 1 H) 3,93 - 4,05 (m, 1 H) 6,98 (d, *J*=1,77 Hz, 1 H) 7,04 (t, *J*=8,59 Hz, 1 H) 7,51 - 7,67 (m, 3 H) 8,27 - 8,38 (m, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{25}H_{32}N_6O_2$, 449; encontrado, 449.

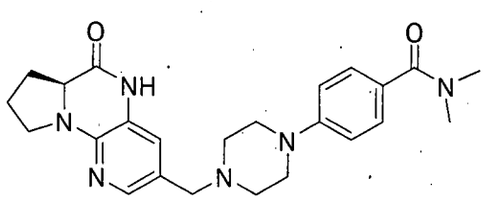
Compuesto 138: (S)-3-((4-(4-(pirrolidin-1-carbonil)fenil)-piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]-pirrolo[1,2-a]pirazin-6(5H)-ona



En un frasco de 1 dram, se suspendió el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil) piperazin-1-il)benzoico (100 mg, 0,245 mmol) en DMF (Volumen: 1,227 mL) luego se agregó pirrolidina (0,024 mL, 0,295 mmol), HATU (140 mg, 0,368 mmol) y N-metilmorfolina (0,108 mL, 0,982 mmol). El rxn se agitó a temperatura ambiente durante la noche. La mezcla se purificó por HPLC-MS preparativa (modo acídico, 15-35%). El pH de las fracciones combinadas se ajustó a pH = 8-9 y se extrajeron con EtOAc (3x30 ml), se lavaron con salmuera, se secaron con $MgSO_4$, se filtraron y se concentraron a sequedad. El resíduo se suspendió con agua/ACN (1:1), y se concentró al vacío para proporcionar el compuesto del título como un sólido esponjoso blanco (29 mg, rindiendo 26%). Punto de fusión = 121,3°C.

^{1}H NMR (400 MHz, DMSO-*d*6) □ ppm 1,73 - 1,87 (m, 4 H) 1,87 - 2,01 (m, 3 H) 2,14 - 2,21 (m, 1 H) 2,43 - 2,49 (m, 4 H) 3,15 - 3,23 (m, 4 H) 3,35 (br. s., 2 H) 3,37 - 3,49 (m, 5 H) 3,54 - 3,65 (m, 1 H) 3,95 - 4,04 (m, 1 H) 6,91 (d, *J*=9,09 Hz, 2 H) 6,99 (d, *J*=2,02 Hz, 1 H) 7,42 (d, *J*=8,84 Hz, 2H) 7,62 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{26}H_{32}N_6O_2$, 461; encontrado, 461.

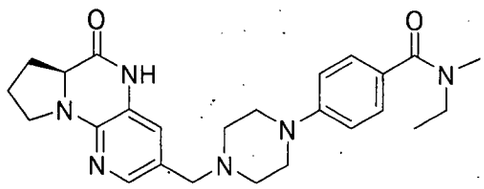
Compuesto 139: (S)-N,N-dimetil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



En un frasco de 1 dram, el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzoico (100 mg, 0,245 mmol) se suspendió en DMF (Volumen: 1,227 mL) luego se agregó clorhidrato de dimetilamina (24,02 mg, 0,295 mmol), HATU (140 mg, 0,368 mmol) y N-metilmorfolina (0,108 mL, 0,982 mmol). La reacción se agitó a temperatura ambiente durante la noche. La mezcla se purificó por HPLC-MS preparativa (modo acídico, 15-35%). El pH de las fracciones combinadas se ajustó a pH = 8-9 y se extrajeron con EtOAc (3x30 ml), se lavaron con salmuera, se secaron con $MgSO_4$, se filtraron y se concentraron a sequedad. El resíduo se suspendió con agua/ACN (1:1), y se concentró al vacío para proporcionar el compuesto del título como un sólido esponjoso blanco (21 mg, rindiendo 19%). Punto de fusión = 99,2°C.

^{1}H NMR (400 MHz, DMSO-*d*6) δ ppm 1,85 - 2,04 (m, 3 H) 2,12 - 2,21 (m, 1 H) 2,43 - 2,49 (m, 4 H) 2,94 (s, 6 H) 3,14 - 3,23 (m, 4 H) 3,35 - 3,43 (m, 3 H) 3,54 - 3,64 (m, 1 H) 3,94 - 4,03 (m, 1 H) 6,92 (d, *J*=9,09 Hz, 2 H) 6,99 (d, *J*=1,77 Hz, 1 H) 7,29 (d, *J*=8,84 Hz, 2 H) 7,62 (d, *J*=1,52 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{24}H_{30}N_6O_2$, 435; encontrado, 435.

Compuesto 140: (S)-N-etil-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida

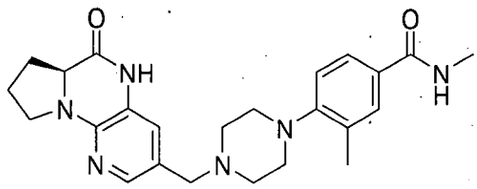


En un frasco de 1 dram, el ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)-piperazin-1-il)benzoico (100 mg, 0,245 mmol) se suspendió en DMF (Volumen: 1,227 mL) luego se agregó N-metiletanamina (0,025 mL, 0,295 mmol), HATU (140 mg, 0,368 mmol) y N-metilmorfolina (0,108 mL, 0,982 mmol). La reacción se agitó a temperatura ambiente durante la noche. La mezcla se purificó por HPLC-MS preparativo (modo acídico, 15-35%). El pH de las fracciones combinadas se ajustó a pH = 8-9 y se extrajeron con EtOAc (3x30 ml), se lavaron con salmuera, se secaron

con $MgSO_4$, se filtraron y se concentraron a sequedad. El resíduo se suspendió con agua/ACN (1:1), y se concentró al vacío para proporcionar el compuesto del título como un sólido blanco esponjoso (18 mg, rindiendo 17%). Punto de fusión = 91,9°C.

^{1}H NMR (400 MHz, DMSO-*d*6) □ ppm 1,09 (t, *J*=7,07 Hz, 3 H) 1,24 (br. s., 3 H) 1,85 - 2,04 (m, 3 H) 2,13 - 2,21 (m, 1 H) 2,43 - 2,48 (m, 3 H) 2,90 (s, 3 H) 3,14 - 3,22 (m, 4 H) 3,34 - 3,43 (m, 3 H) 3,54 - 3,64 (m, 1 H) 3,95 - 4,02 (m, 1 H) 6,92 (d, *J*=8,84 Hz, 2 H) 6,99 (d, *J*=2,02 Hz, 1 H) 7,25 (d, *J*=8,59 Hz, 2 H) 7,62 (d, *J*=1,77 Hz, 1 H) 10,44 (s, 1 H). [M+H] calculado para $C_{25}H_{32}N_6O_2$, 449; encontrado, 449.

Compuesto 141: (S)-N,3-dimetil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida

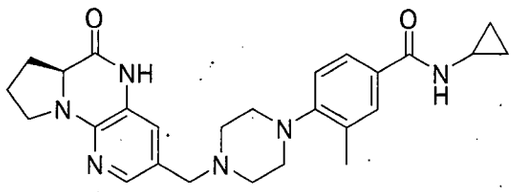


Se suspendieron el (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (300 mg, 1,368 mmol), [Reactantes], yoduro de (cianometil)-trimetilfosfonio (499 mg, 2,053 mmol) y N,N-diisopropiletilamina (1195 µl, 6,84 mmol) en propiononitrilo (Volumen: 4109 µl) y se calentaron en un frasco cerrado a 120°C por 2 horas. La mezcla de reacción se volvió una solución café oscura. Se enfrió a temperatura ambiente, se concentró al vacío, se disolvió en DMSO (2 mL) y se purificó utilizando HPLC (solución tampón de NH_4HCO_3, ACN en agua 20-70%). Las fracciones se concentraron al vacío y el sólido resultante se recristalizó de agua-MeOH (1:1, 5 mL), y luego de ACN (30 mL), y se secó al vacío para proporcionar (S)-N,3-dimetil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (232,7 mg, 0,536 mmol, rindiendo 39,1%) como un sólido tostado claro.

^{1}H NMR (DMSO-d_6) δ 10,40 (s, 1H), 8,19 (q, J = 4,0 Hz, 1H), 7,57 - 7,66 (m, 3H), 6,95 - 7,04 (m, 2H), 3,93 - 4,02 (m, 1H), 3,54 - 3,64 (m, 1H), 3,38 (s, 3H), 2,87 (br. s., 4H), 2,74 (d, J = 4,5 Hz, 3H),

2,49 - 2,55 (m, 4H), 2,25 (s, 3H), 2,11 - 2,22 (m, 1H), 1,80 - 2,02 (m, 3H). [M+H] calculado para $C_{24}H_{30}N_6O_2$, 435; encontrado, 435.

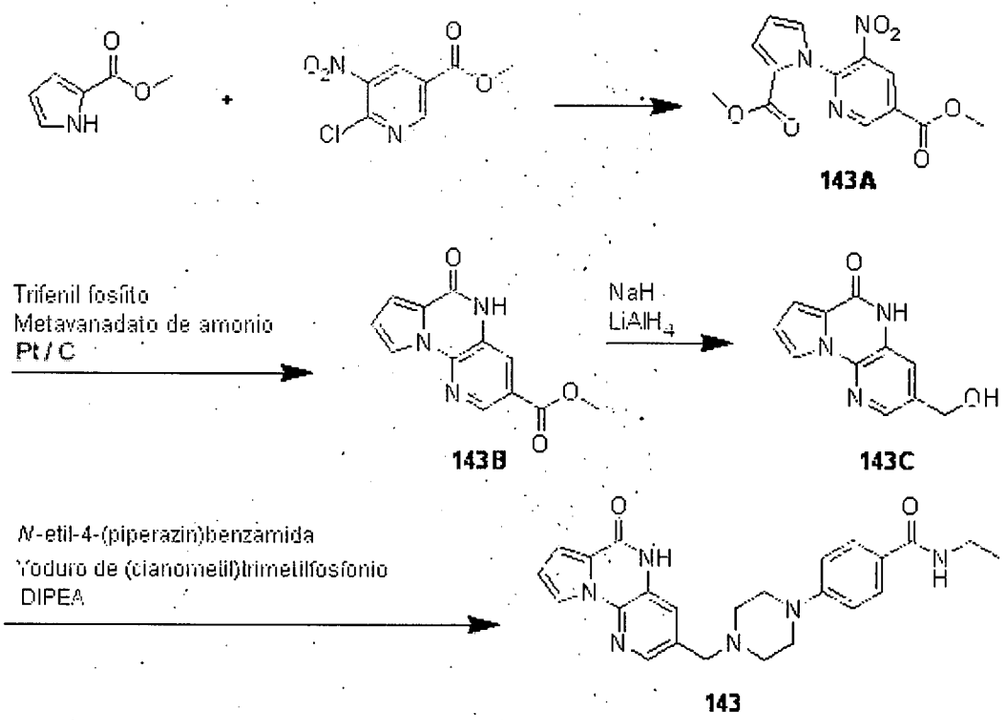
Compuesto 142: (S)-N-ciclopropil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



A una suspensión de (S)-3-(hidroximetil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (0,1 g, 0,456 mmol), diclorhidrato de N-ciclopropil-3-metil-4-(piperazin-1-il)benzamida (0,179 g, 0,538 mmol), y yoduro de (cianometil)trimetilfosfonio (0,188 g, 0,775 mmol) en propiononitrilo (Volumen: 2,0 mL), se agregó N-etil-N-isopropilpropan-2-amina (0,556 mL, 3,19 mmol) a 23°C. La reacción se agitó a 90°C por 8 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró, y se lavó con propiononitrilo (3 x 1 mL). El sólido resultante se reconstituyó en DMSO (Volumen: 3,0 mL) y se purificó mediante LCMS preparativa de masa de gatillo utilizando un gradiente de eluyente de ACN:NH_4HCO_3 10 mM (acuoso) 25-65%. Las fracciones recolectadas se combinaron y el ACN se eliminó mediante evaporación rotatoria hasta proporcionar una suspensión. La suspensión se filtró, se lavó con H_2O (3 x 10 mL), y el sólido resultante se secó *al vacío* para proporcionar (S)-N-ciclopropil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida (0,0624 g, 0,135 mmol, rindiendo 29,7%) como un sólido blanquecino.

^{1}H NMR (400 MHz, DMSO-d_6) □ ppm 0,50 - 0,59 (m, 2 H) 0,60 - 0,70 (m, 2 H) 1,86 - 2,00 (m, 3 H) 2,14 - 2,20 (m, 1 H) 2,25 (s, 3 H) 2,47 - 2,50 (m, 4 H) 2,76 - 2,93 (m, 5 H) 3,34 - 3,44 (m, 3 H) 3,55 - 3,63 (m, 1 H) 3,93 - 4,02 (m, 1 H) 6,96 - 7,04 (m, 2 H) 7,56 - 7,67 (m, 3 H) 8,22 (d, *J*=4,29 Hz, 1 H) 10,45 (s, 1 H). ESI-MS : m/z 461,4 $(M+H)^+$. mp = 226,7-233,5°C.

Compuesto 143: N-etil-4-(4-((6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida



Compuesto 143A: 6-(2-(metoxicarbonil)-1H-pirrol-1-il)-5-nitronicotinato de metilo: El 1H-pirrol-2-carboxilato de etilo (5,78 g, 46,2 mmol) se disolvió en DMSO y se enfrió a 10°C. Se agregó NaH en dos porciones durante 5 minutos. La mezcla de reacción se agitó a 10°C por 10 minutos y se agregó lentamente 6-cloro-5-nitronicotinato de metilo (5 g, 23,09 mmol) en DMSO (10 mL) durante 3 minutos. La mezcla de reacción roja se dejó enfriar a temperatura ambiente y se agitó durante la noche. Se enfrió a 0°C y se detuvo con agua (12 mL) y se diluyó con salmuera (50 mL). La mezcla se lavó con EtOAc (2 X 25 mL) y la capa acuosa se acidificó a pH = 2 con HCl 4,5N. Se extrajo con EtOAc (1 X 100 mL) y la capa orgánica se secó con (Na_2SO_4), se filtró y se concentró al vacío para proporcionar un sólido amarillo, el cual se disolvió en MeOH (100 mL) y se enfrió a 0°C. Se agregó lentamente cloruro de tionilo (45 mL, 617 mmol) durante 5 minutos. La mezcla de reacción se agitó a 0°C por 1 hora y luego a temperatura ambiente durante la noche. Se concentró al vacío y el sólido resultante se trituró con acetato de etilo (300 mL). El sólido se

recogió por filtración y el filtrado se concentró al vacío. Luego se lavó con etil éter para proporcionar 6-(2-(metoxicarbonil)-1H-pirrol-1-il)-5-nitronicotinato de metilo (5,04 g, 16,51 mmol, rindiendo 92%) como un sólido amarillo, [M+H] calculado para $C_{13}H_{11}N_3O_6$, 306; encontrado, 306.

Compuesto 143B: 6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-carboxilato de metilo: El 6-(2-(metoxicarbonil)-1H-pirrol-1-il)-5-nitronicotinato de metilo (5,00 g, 16,38 mmol) se disolvió en diclorometano (Volumen: 82 ml) y á ésta solución se agregó trifenil fosfito (0,051 g, 0,164 mmol), metavanadato de amonio (0,115 g, 0,983 mmol) y Pt/C (5% en peso) (0,639 g, 0,164 mmol). La mezcla de reacción se hidrogenó a 100 psi a 25°C por 36 horas. La mezcla de reacción se filtró a través de un tapón corto de celite y el tapón y el precipitado se lavaron bien con metanol (100 mL) y luego MeOH:DCM (100 mL, 1:1). Los sólidos (celite y Pt/C) se extrajeron en forma continua con mezcla de MeOH/DCM (1:1) en un extractor Soxlet por 2 días. Los extractos se combinaron con los primeros filtrados, se concentraron al vacío, se cristalizaron con MeOH (100 mL) y el sólido resultante se recogió por filtración y se suspendió en etil éter (200 mL). El sólido se recogió por filtración y se secó al vacío para proporcionar el 6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-carboxilato de metilo (2,15 g, 8,84 mmol, rindiendo 54,0%) como un sólido gris.

^{1}H NMR (DMSO-d_6) δ 11,49 (s, 1H), 8,69 (s, 1H), 8,15 (br. s., 1H), 8,11 (s, 1H), 7,16 (d, J = 2,5 Hz, 1H), 6,78 (t, J = 3,0 Hz, 1H), 3,91 (s, 3H). [M+H] calculado para $C_{12}H_9N_3O_3$, 244; encontrado, 244.

Compuesto 143C: 3-(hidroximetil)pirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona: Se suspendió el 6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-carboxilato de metilo (2,0 g, 8,22 mmol) en THF (Volumen: 27,4 ml) bajo atmósfera de nitrógeno y se enfrió a 0°C. Se agregó hidruro de sodio (0,658 g, 16,45 mmol) en varias porciones durante 7 minutos. La mezcla de reacción se agitó a 0°C por 10 minutos, a temperatura ambiente por 20 minutos y se enfrió por debajo de -50°C. Se agregó hidruro de aluminio y litio (7,40 ml, 14,80 mmol) durante

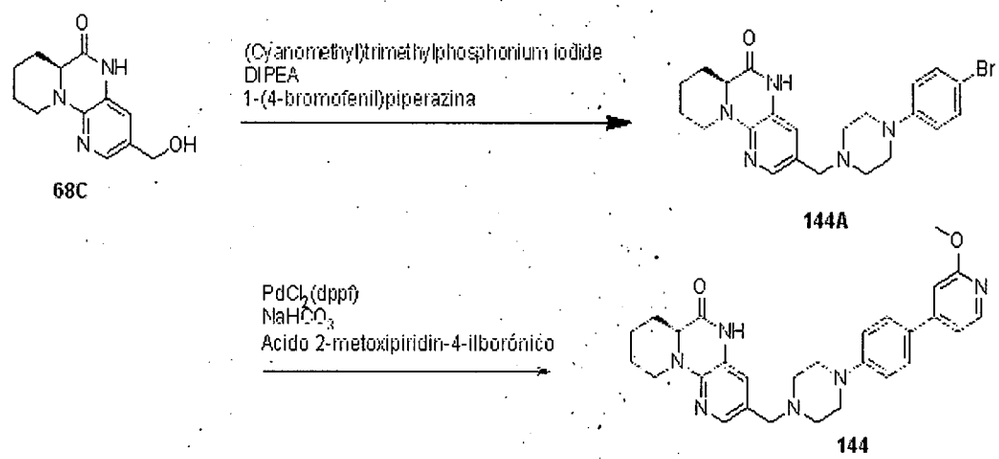
el período de 5 minutos y la reacción se mantuvo a una temperatura entre -30 y -20°C por 1 hora. La mezcla se enfrió por debajo de -40°C y se agregó MeOH (6 mL). Se agregó agua (5 mL) y luego más MeOH (50 mL). La mezcla de reacción se agitó a temperatura ambiente por 10 minutos. El precipitado resultante se filtró, se suspendió en MeOH (100 mL) y se volvió a filtrar. El sólido se suspendió en MeOH:DCM se calentó durante la noche (1:1, 200 mL) y se filtró en caliente. Éste sólido se disolvió en MeOH/DCM (100 mL, 3:1) y se cargó sobre sílica gel (12 g) luego se purificó mediante columna cromatográfica evaporativa sobre sílica gel (SiO_2 220 g, gradiente DCM:MeOH 100:1-85:15) para proporcionar 3-(hidroximetil)pirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (854 mg, 3,97 mmol, rindiendo 48,3%) como un sólido blanco.

^{1}H NMR (DMSO-d6) δ 11,36 (br. s., 1H), 8,14 (d, J = 1,8 Hz, 1H), 8,10 (dd, J = 2,8, 1,5 Hz, 1H), 7,61 - 7,66 (m, 1H), 7,09 (dd, J = 3,8, 1,5 Hz, 1H), 6,71 (dd, J = 3,7, 2,9 Hz, 1H), 5,42 (br. s., 1H), 4,53 - 4,64 (m, 2H). [M+H] calculado para $C_{11}H_9N_3O_2$, 216; encontrado, 216.

Compuesto 143: N-etil-4-(4-((6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)-benzamida: Se suspendieron el 3-(hidroximetil)piridó[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona (100 mg, 0,465 mmol), N-etil-4-(piperazin-1-il)benzamida (119 mg, 0,511 mmol), yoduro de (cianometil)trimetilfosfonio (158 mg, 0,651 mmol) y N,N-diisopropiletilamina (406 µl, 2,323 mmol) en propiononitrilo (Volumen: 1395 µl) y se calentaron en un pequeño frasco cerrado por 7 horas a 90-120°C (la temperatura se aumento por 10°C después de 4, 5 y 6 horas. Se agregó una porción adicional de yoduro de (cianometil)trimetilfosfonio (43,3 mg) después de 4 horas. La mezcla de reacción se enfrió a temperatura ambiente, se filtró y el precipitado se lavó con MeCN (5 mL) para proporcionar un sólido blanquecino (168,4 mg). El sólido se calentó a reflujo en EtOH (15 mL) por 5 minutos y se dejó enfriar a temperatura ambiente. Se filtró y se secó al vacío para proporcionar N-etil-4-(4-((6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)- piperazin-1-il)benzamida (112,5 mg, 0,261 mmol, rindiendo 56,2%) como un sólido blanco.

^{1}H NMR (DMSO-d_6) □ 11,31 (s, 1H), 8,08 - 8,17 (m, 3H), 7,71 (d, J = 8,8 Hz, 2H), 7,66 (d, J = 1,8 Hz, 1H); 7,09 (dd, J = 3,7, 1,6 Hz, 1H), 6,93 (d, J = 8,8 Hz, 2H), 6,72 (dd, J = 3,7, 2,9 Hz, 1H), 3,62 (s, 2H), 3,20 - 3,28 (m, 6H), 2,52 - 2,59 (m, 4H), 1,09 (t, J = 7,2 Hz, 3H). [M+H] calculado para $C_{24}H_{26}N_6O_2$, 431; encontrado, 431.

Compuesto 144: (S)-3-((4-(4-(2-metoxipiridin-4-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



68C

144A

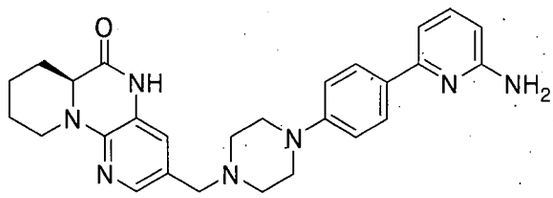
144

Compuesto 144A: (S)-3-((4-(4-bromofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: El compuesto 144 se preparó utilizando un procedimiento análogo a aquél descrito con relación al compuesto 68, excepto que se utilizó 1-(4-bromofenil)piperazina en lugar de clorhidrato de 4-(4-clorofenil)-1,2,3,6-tetrahidropiridina para proporcionar un sólido blanco: [M+H] calculado para $C_{22}H_{26}BrN_5O$, 456; encontrado, 456.

Compuesto 144: (S)-3-((4-(4-(2-metoxipiridin-4-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona: (S)-3-((4-(4-bromofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona (,04 mmol), ácido 2-metoxipiridin-4-ilborónico (0,060 mmol), aducto $PdCl_2(dppf)$-CH_2Cl_2 (3,27 mg, 4,00 µmol), bicarbonato de sodio (0,500 ml, 0,500 mmol), dioxano (Volumen: 1 ml) y un agitador de barra, se selló en un frasco de microonda de 5 mL. Se calentó el frasco a 135°C por 30

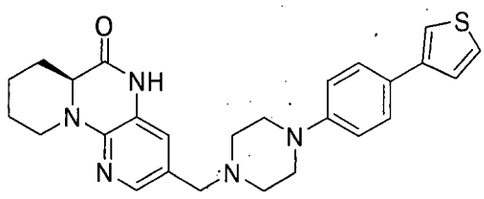
minutos. La capa acuosa se eliminó del frasco, la mezcla de reacción se filtró en un frasco de 1,8 mL para someter a HPLC. La mezcla de reacción se purificó por LCMS para proporcionar un sólido amarillo: [M+H] calculado para $C_{29}H_{32}N_6O_2$, 485; encontrado, 485.

Compuesto 145: (S)-3-((4-(4-(6-aminopiridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



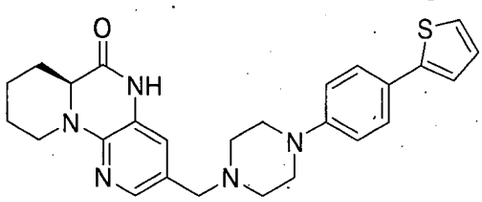
Se preparó el compuesto 145 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó 6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridin-2-amina en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_7O$, 470; encontrado, 470.

Compuesto 146: (S)-3-((4-(4-(tiofen-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



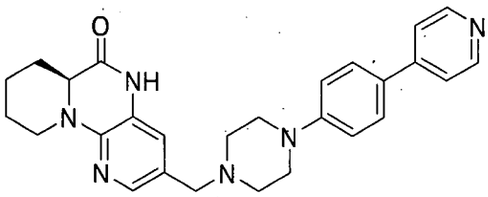
Se preparó el compuesto 146 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido tiofen-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{29}N_5OS$, 460; encontrado, 460.

Compuesto 147: (S)-3-((4-(4-(tiofen-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



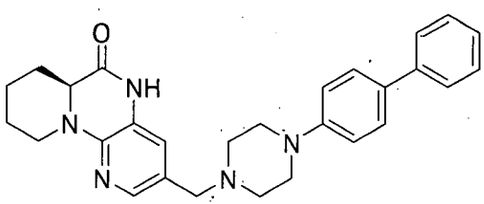
Se preparó el compuesto 147 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó el ácido tiofen-2-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{29}N_5OS$, 460; encontrado, 460.

Compuesto 148: (S)-3-((4-(4-(piridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se preparó el compuesto 148 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido piridin-4-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{30}N_6O$, 455; encontrado, 455.

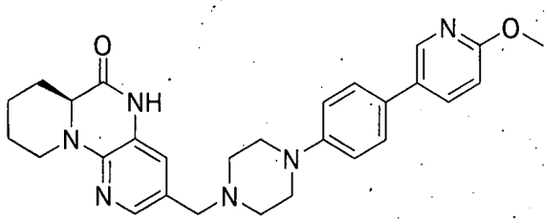
Compuesto 149: (S)-3-((4-(bifenil4-il)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se preparó el compuesto 149 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que

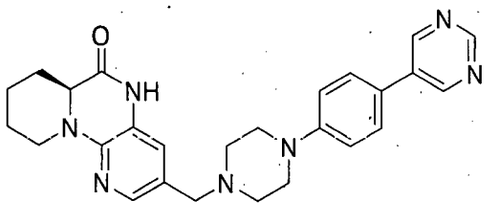
se utilizó ácido fenilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{31}N_5O$, 454; encontrado, 454.

Compuesto 150: (S)-3-((4-(4-(6-metoxipiridin-3-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



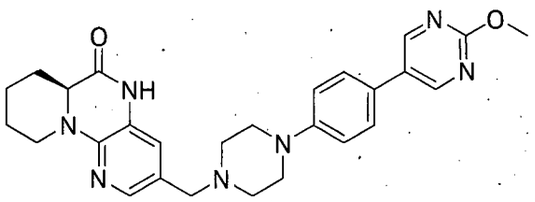
Se preparó el compuesto 150 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 6-metoxipiridin-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O_2$, 485; encontrado, 485.

Compuesto 151: (S)-3-((4-(4-(pirimidin-5-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



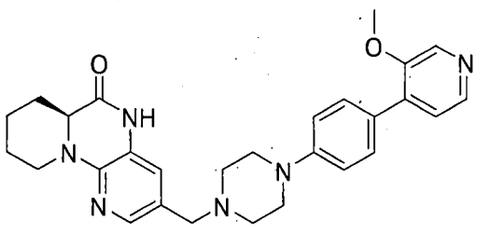
Se preparó el compuesto 151 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido pirimidin-5-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{29}N_7O$, 456; encontrado, 456.

Compuesto 152: (S)-3-((4-(4-(2-metoxipirimidin-5-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



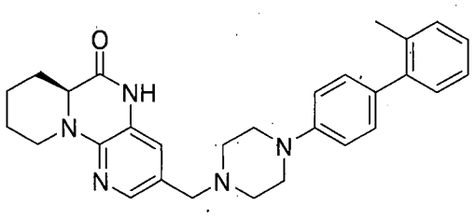
Se preparó el compuesto 152 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 2-metoxipirimidin-5-ilborónico en lugar de 2-metoxipiridin-4-ilborónico para proporcionar un sólido verde como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_7O_2$, 486; encontrado, 486.

Compuesto 153: (S)-3-((4-(4-(3-metoxipiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



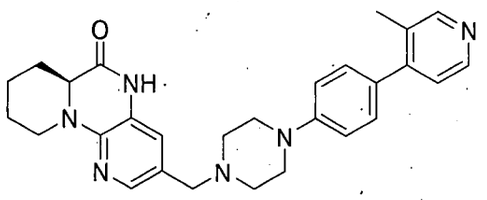
Se preparó el compuesto 153 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 3-metoxipiridin-4-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O_2$, 485; encontrado, 485.

Compuesto 154: (S)-3-((4-(2'-metilbifenil4-il)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



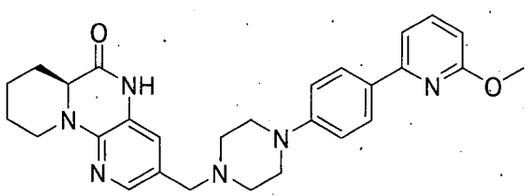
Se preparó el compuesto 154 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido o-tolilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido gris como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{29}H_{33}N_5O$, 468; encontrado, 468.

Compuesto 155: (S)-3-((4-(4-(3-metilpiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



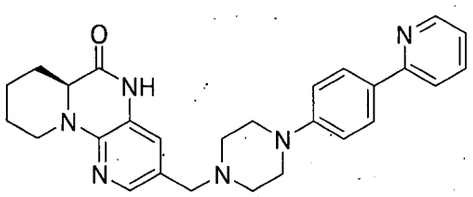
Se preparó el compuesto 155 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 3-metilpiridin-4-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O$, 469; encontrado, 469.

Compuesto 156: (S)-3-((4-(4-(6-metoxipiridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



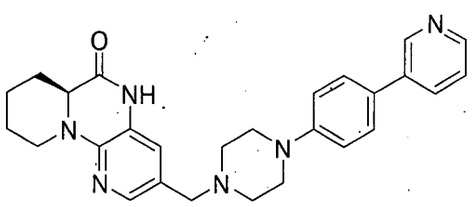
Se preparó el compuesto 156 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó 2-metoxi-6-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O_2$, 485; encontrado, 485.

Compuesto 157: (S)-3-((4-(4-(piridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



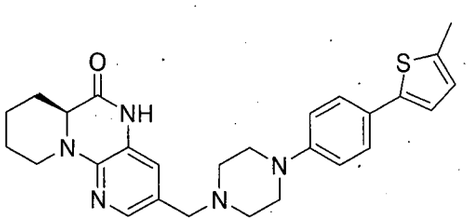
Se preparó el compuesto 157 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó 2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido amarillo como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{30}N_6O$, 455; encontrado, 455.

Compuesto 158: (S)-3-((4-(4-(piridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



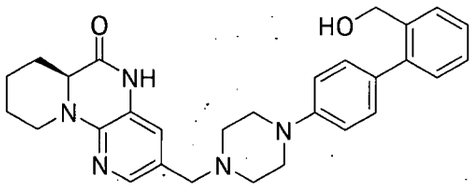
Se preparó l compuesto 158 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido piridin-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{30}N_6O$, 455; encontrado, 455.

Compuesto 159: (S)-3-((4-(4-(5-metiltiofen-2-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



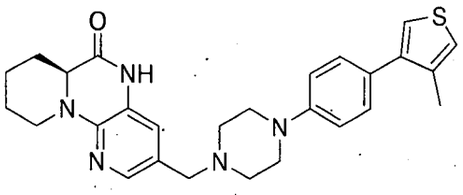
Se preparó el compuesto 159 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 5-metiltiofen-2-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_5OS$, 474; encontrado, 474.

Compuesto 160: (S)-3-((4-(2'-(hidroximetil)bifenil4-il)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



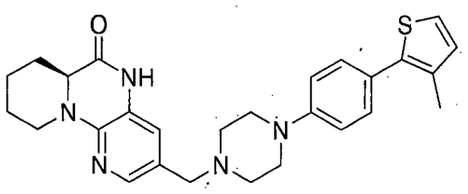
Se preparó el compuesto 160 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó benzo[c][1,2]oxaborol-1(3H)-ol en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido gris como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{29}H_{33}N_5O_2$, 484; encontrado, 484.

Compuesto 161: (S)-3-((4-(4-(4-metiltiofen-3-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



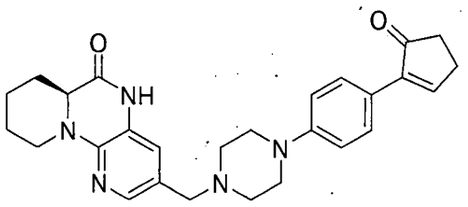
Se preparó el compuesto 161 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 4-metiltiofen-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_5OS$, 474; encontrado, 474.

Compuesto 162: (S)-3-((4-(4-(3-metiltiofen-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



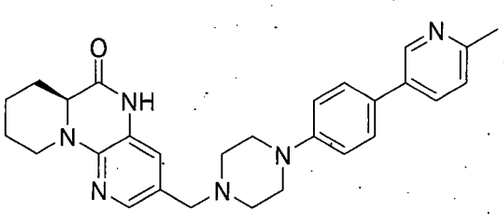
Se preparó el compuesto 162 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó 3-metiltiofen-2-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido amarillo como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_5OS$, 474; encontrado, 474.

Compuesto 163: (S)-3-((4-(4-(5-oxociclopent-1-enil)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



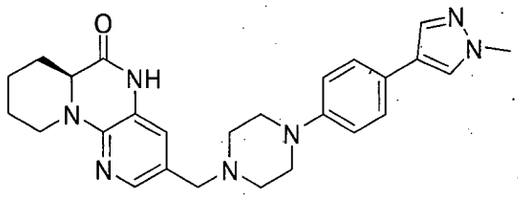
Se preparó el compuesto 163 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 5-oxociclopent-1-enilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{27}H_{31}N_5O_2$, 458; encontrado, 458.

Compuesto 164: (S)-3-((4-(4-(6-metilpiridin-3-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



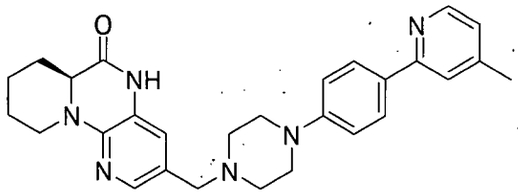
Se preparó el compuesto 164 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 6-metilpiridin-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido negro como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O$, 469; encontrado, 469.

Compuesto 165: (S)-3-((4-(4-(1-metil-1*H*-pirazol-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



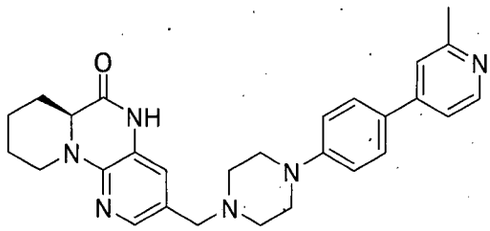
Se preparó el compuesto 165 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 1-metil-1H-pirazol-4-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido blanco como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{31}N_7O$, 458; encontrado, 458.

Compuesto 166: (S)-3-((4-(4-(4-metilpiridin-2-il)fenil)-piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



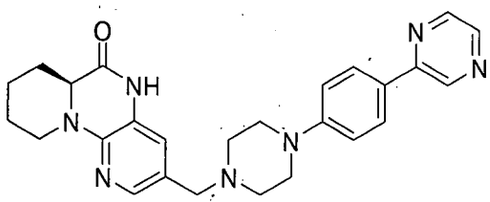
Se preparó el compuesto 166 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó 4-metil-2-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)piridina en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido café como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{32}N_6O$, 469; encontrado, 469.

Compuesto 167: (S)-3-((4-(4-(2-metilpiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



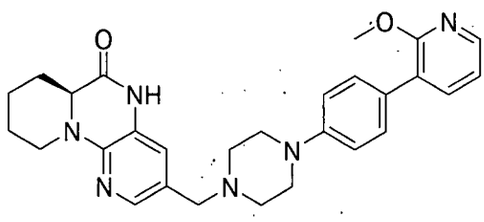
Se preparó el compuesto 167 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 2-metilpiridin-4-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido amarillo como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O$, 469; encontrado, 469.

Compuesto 168: (S)-3-((4-(4-(pirazin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se preparó el compuesto 168 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido pirazin-2-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar un sólido de color tostado como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{26}H_{29}N_7O$, 456; encontrado, 456.

Compuesto 169: (S)-3-((4-(4-(2-metoxipiridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona



Se preparó el compuesto 169 utilizando un procedimiento análogo a aquél descrito con relación al compuesto 144, excepto que se utilizó ácido 2-metoxipiridin-3-ilborónico en lugar de ácido 2-metoxipiridin-4-ilborónico para proporcionar sólido verde como la sal de TFA después de la purificación por HPLC-MS: [M+H] calculado para $C_{28}H_{32}N_6O_2$, 485; encontrado, 485.

Ensayos Biológicos

Se puede probar actividad de los compuestos como inhibidores de PARP *in vitro*, *in vivo* o en una línea celular. Más adelante se proporcionan descripciones de un ensayo de actividad enzimática PARP *in vitro* para la actividad contra PARP y un ensayo de quicio-potentiación celular PARP.

Ensayo enzimático PARP

Constante de Disociación (K_D) de Resonancia de Plasmonde Superficie

Preparación de Enzima

El dominio catalítico de PARP Humana se clonó y se preparó como se describe en Kinoshita, T.; Nakanishi, I.; Warizaya, M.; Iwashita, A.; Kido, Y.; Hattori, K. and Fujii, T. 2006 FEBS Letters 556, 43-46. Se almacenó la enzima purificada a -80°C en Tris 25 mM (hidroximetil)aminometano (Tris) pH 7,4, NaCl 150 mM, ditiotreitol 2 mM (DTT) a una concentración de 6 mg/ml.

Ensayos Biacore

Se realizaron ensayos de afinidad Biacore para los compuestos de prueba en un Biacore T100 (GE Healthcare) como sigue. Se activó una series de Sensor S Chip CM5 (número de catálogo BR-1006-68, GE Healthcare) para el acoplamiento de amida con un Kit de Acoplamiento de Amina (número de catálogo BR-1000-50, GE Healthcare) como se describe por el fabricante. La fase móvil del tampón consistió de

tampón Biacore HBS-P (número de catálogo BR-1003-68, GE Healthcare) complementado con dimetilsulfóxido 1% v/v (DMSO), Tris cloruro de (2-carboxietil)fosfina 0,5 mM (TCEP), y $MgCl_2$ 5 mM. Las muestras de enzima (2 µl/6 mg/ml) almacenadas a -80°C fueron diluidas a 0,080 mg/ml con ácido 4-morfolinetanosulfónico (MES) 10 mM pH 6,5 y luego montado en el chip Biacore CM5 activado a un caudal de 10 µl/min durante 240 segundos. Si fue exitosamente montado, se observó una señal de aproximadamente 8.000 unidades reflectivas. Los compuestos de ensayo fueron 9 veces diluidos seriadamente 2 veces en tampón de fase mócil (indicado más abajo) a DMSO final de 1% v/v para generar una gradiente de concentración que estime el rango de sus K_Ds anticipadas. Se dió 1 minuto de exposición al Biacore PARP montado (fase de asociación) a diversas concentraciones de compuestos de ensayo para observar un equilibrio en estado estacionario o uno en velocidad o transcurso. Se suguió la exposición con una fase de disociación de 5 minutos. Las fase de asociación y disociación ocurrieron a una tasa de flujo de 50 µl /min y a una temperatura de 25°C.

Análisis de unión Biacore

Modelo de equilibrio rápido: Si el compuesto de ensayo que se une, refleja un equilibrio rápido, se genera un gráfico de respuesta en estado estacionario versus concentración y la ecuación $Rmax*[compuesto]/([compuesto]+K_D)$ se ajusta al perfil. Los parámetros Rmax (response en la saturación) y K_D (Constante de unión) fueron calculados a través de un ajuste no linear de mínimos cuadrados de la ecuación a los datos a través del uso del programa de análisis Biacore T100.

Modelo de unión lenta:

Si la unión del compuesto de ensayo no logró el equilibrio dentro del primer minuto de exposición, la constante de velocidad de asociación y la constante de velocidad de disociación para el compuesto de ensayo se calcularon a través del análisis simultáneo de la familia de las curvas de progreso obtenidas del experimento de gradiente de concentración. La optimización del parámetro se hizo a

través de un análisis no linear de mínimos cuadrados de la Respuesta de la fase de asociación= Rmax*(1-exp(-(k_{on}[cmpd]+k_{off})*t)) y de la Respuesta de la fase de disociación = Rmax*exp(-(k_{on}[cmpd]+k_{off})*t) mediante el uso del programa de análisis Biacore T100. La constante de unión K_D se calculó a partir de la definición $K_D = k_{off}/k_{on}$

Constante de Inhibición (IC_{50}) de PARP ELISA

La inhibición de la actividad catalítica de PARP se determinó mediante el uso de un kit de ensayo de ELISA en base colorimétrica PARP/Apoptosis (número de catálogo 4684-096-K HT, Trevigen). A cada pocillo recubierto en histona en la placa de 96 pocillo suministrada por el fabricante (número de catálogo 4677-096-P) se agregó 39 µl de tampón PARP (número de catálogo 4671-096-02) y 1 µl de compuesto de ensayo disuelto en DMSO (diluido de manera seriada 3-veces 11 veces). Después de mezclar, se agrega 5 µl de PARP 0,1 nM (número de catálogo 4684-096-01) y se deja que la solución repose a temperatura ambiente durante 10 minutos. Se inicia la catálisis PARP con la adición de 5 µl de β-nicotinamida adenina dinucleotido (NAD+) 100 uM (número de catálogo 4684-096-02) con ADN activado (número de catálogo 4671-096-06). Después de 10 minutos de catálisis se detuvo la reacción mediante aspiración de solvente seguido por irrigación de los pocillos de ensayo 4 veces con solución salina tamponada de fosfato (PBS) que contiene t-Octilfenoxipolietoxietanol 0,1% (Triton® X-100). Se agregan anticuerpo monoclonal anti-poli ADP ribosa (PAR) de ratón, conjugado de inmunoglobulina G antiratón de cabra (IgG)-peroxidasa de rábano picante (HRP) y sustrato HRP de acuerdo a the las especificaciones del fabricante para generar una señal colorimétrica proporcional a la de la la actividad catalítica de PARP. Se calculó un IC_{50} para el compuesto de ensayo a partir de la ecuación Absorbancia = (Amax-basal)/(1+([cmpd]/IC_{50})^n)+ajuste basal a los 12 puntos de la gradiente de concentración del compuesto a través de minimos cuadrados no lineares.

Determinación del Factor de Potentiación (PF_{50}) a partir del ensato de Quimiopotenciación Celular PARP

La línea celular Jurkat se mantuvo de acuerdo a las instrucciones del proveedor (American Type Culture Collection (Rockville, MD)). Se sembraron las células en microplacas de cultivo de tejido de 96 pocillos a 10.000 células por pocillo y se cultivaron durante 24 horas antes de la adición de los compuestos, TMZ (Temozolomida) o vehículo DMSO (dimetilsulfóxido). Luego de 96 horas de tratamiento, la conversión de MTS ([3-(4,5-dimetiltiazol-2-il)-5-(3-carboxi-metoxifenil)-2-(4-sulfofenil)-2H-tetrazolio, sal interna], Promega, Madison, WI) a través de las células metabólicamente activas se determinó a través de la medición de la $OD_{490\ nm}$ con un lector de microplacas Spectramax (Molecular Devices, San Diego, CA). Para generar las curvas concentración-respuesta, se trataron las células en duplicado con un rango de diluciones seriadas de compuesto (la concentración final de DMSO fue 0,5%) en ausencia o presencia del quimioreactivo TMZ 100 µM. El porcentaje de células viables por pocillo se calculó por corrección del basal y se normalizó contra las células tratadas con DMSO. Los valores de EC_{50} para la inhibición de la viabilidad celular se calcularon utilizando el programa de ajuste de curva XLfit4 MicroSoft Excel. El factor de quimiopotenciación PF_{50} se calculó como la razón de los valores EC_{50} de las células co-tratadas sin y con TMZ, respectivamente.

Se debe destacar que ua diversidad de otros sistemas y de huéspedes de expresión son también adecuados para la expresión de PARP, tal como se apreciaría fácilmente por una persona experta en el arte.

La TABLA 1 lisa los valores de pK_D, pIC_{50} y PF_{50} para compuestos seleccionados de la presente invención. Aquí, $pIC_{50} = -\log(IC_{50})$ y $pK_D = -\log(K_D)$ donde IC_{50} y K_D se expresan en concentración molar.

TABLA 1: Valores de pK_D, pIC_{50} y PF_{50} de Compuestos Ejemplificados contra PARP

COMPUESTO	pK_D	pIC_{50}	PF_{50}
1			> 500
2	> 7,5		> 2000
3	6,1 - 7,5		> 10
4		7,4 - 7,8	> 2000
5	> 7,5	7,4 - 7,8	> 5000
6A			≥ 0
6		≥ 7,9	> 10
7			> 10
8			> 10
9			≥ 0
10	> 7,5	≥ 7,9	> 5000
11		7,4 - 7,8	> 10
12		7,4 - 7,8	> 10
13		7,4 - 7,8	> 5000
14			> 500
15			> 500
16			> 500
17			> 2000
18			> 10
19			≥ 0
20			≥ 0
21			> 2000
22			> 10
23			≥ 0
24		7,4 - 7,8	> 5000
25			≥ 0
26			> 10
28			≥ 0
29		≤ 7,3	> 500
31			≥ 0
32			≥ 0

COMPUESTO	pK_D	pIC_{50}	PF_{50}
34			≥ 0
35			≥ 0
36			≥ 0
37		≤ 7,3	> 2000
38			≥ 0
39			≥ 0
40			> 10
41			≥ 0
42		≤ 7,3	> 500
45		7,4 - 7,8	> 10
46			≥ 0
47		≤ 7,3	> 10
48			≥ 0
49			≥ 0
50			≥ 0
51			≥ 0
52	> 7,5		≥ 0
53	6,1 - 7,5	≤ 7,3	≥ 0
54	≤ 6		
56	> 7,5		≥ 0
57	> 7,5		≥ 0
58	≤ 6		
59	> 7,5		≥ 0
60	≤ 6		
61	≤ 6		
63	6,1 - 7,5		≥ 0
64	> 7,5		≥ 0
65	≤ 6	≥ 7,9	> 10
66	≤ 6	7,4 - 7,8	> 10
67	> 7,5	7,4 - 7,8	≥ 0
68		≥ 7,9	> 5000
69		≥ 7,9	> 10
70		≤ 7,3	≥ 0
71		≥ 7,9	> 500

COMPUESTO	pK_D	pIC_{50}	PF_{50}
72		≥ 7,9	> 500
73		≥ 7,9	> 2000
74		≥ 7,9	> 10
75		7,4 - 7,8	> 500
76			≥ 0
77		7,4 - 7,8	> 10
78			> 10
79			> 10
80	> 7,5	≤ 7,3	≥ 0
81	6,1 - 7,5	≤ 7,3	≥ 0
82	6,1 - 7,5	≤ 7,3	≥ 0
83	≤ 6	7,4 - 7,8	≥ 0
84	6,1 - 7,5	≥ 7,9	≥ 0
85	6,1 - 7,5	7,4 - 7,8	≥ 0
86	> 7,5	7,4 - 7,8	> 500
87		7,4 - 7,8	> 10
88	> 7,5	≥ 7,9	≥ 0
89			> 10
90		≥ 7,9	> 10
91			> 2000
92			> 5000
93			≥ 0
94		≤ 7,3	≥ 0
95		≤ 7,3	≥ 0
96		≤ 7,3	
97			≥ 0
98			> 5000
99			> 5000
100			> 10
101		≤ 7,3	> 10
102		7,4 - 7,8	≥ 0
103		7,4 - 7,8	≥ 0
104		≤ 7,3	≥ 0
105		7,4 - 7,8	> 10

COMPUESTO	pK_D	pIC_{50}	PF_{50}
106		≥ 7,9	> 5000
107		7,4 - 7,8	> 2000
108		≥ 7,9	> 500
109		7,4 - 7,8	> 2000
110		7,4 - 7,8	> 5000
111		7,4 - 7,8	> 5000
112		≥ 7,9	> 10
113		≤ 7,3	> 2000
114		≤ 7,3	> 2000
115		7,4 - 7,8	> 2000
116		≥ 7,9	> 5000
117		7,4 - 7,8	> 5000
118		≥ 7,9	> 5000
120		≤ 7,3	≥ 0
121		7,4 - 7,8	≥ 0
122		≤ 7,3	≥ 0
123		7,4 - 7,8	> 10
124		≤ 7,3	≥ 0
125		≤ 7,3	≥ 0
126		7,4 - 7,8	> 5000
127		7,4 - 7,8	> 500
128		≤ 7,3	≥ 0
129		7,4 - 7,8	> 500
130		7,4 - 7,8	> 2000
131		≥ 7,9	> 500
132		≥ 7,9	> 2000
133		7,4 - 7,8	> 2000
134		7,4 - 7,8	> 5000
135		7,4 - 7,8	> 5000
136		≥ 7,9	> 5000
137		≥ 7,9	> 5000
138		≤ 7,3	≥ 0
139		≤ 7,3	≥ 0
140		≤ 7,3	≥ 0

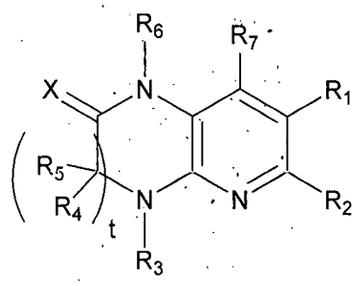
COMPUESTO	pK_D	pIC_{50}	PF_{50}
141		≥ 7,9	> 500
142		≥ 7,9	> 2000
144		≤ 7,3	
145		≤ 7,3	
146		7,4 - 7,8	
147		≤ 7,3	
148		7,4 - 7,8	
149		≤ 7,3	
150		≤ 7,3	
151		≤ 7,3	
152		7,4 - 7,8	
153		≤ 7,3	
154		≤ 7,3	
155		≤ 7,3	
156		≤ 7,3	
157		≤ 7,3	
158		≤ 7,3	
159		≤ 7,3	
160		≤ 7,3	
161		≤ 7,3	
162		≤ 7,3	
163		≤ 7,3	
164		7,4 - 7,8	
165		7,4 - 7,8	
166		7,4 - 7,8	
167		7,4 - 7,8	
168		7;4 - 7,8	
169		≤ 7,3	

Será aparente para aquellos expertos en el arte que diversas modificaciones y variaciones se pueden realizar a los compuestos, composiciones, kits, y métodos de la presente invención sin apartarse del espíritu o espectro de la invención. Por lo cual, se pretende que la presente invención cubra las modificaciones y

variaciones de esta invención con la condición que estas se encuentren dentro del espectro de las cláusulas anexas y sus equivalentes.

REIVINDICACIONES

1. Un compuesto que tiene la fórmula:



o una sal farmacéuticamente aceptable de lo mismo, CARACTERIZADO porque

t se selecciona del grupo que consiste de 1 y 2;

X se selecciona del grupo que consiste de O, S y NR_8;

R_1 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), aminoalquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_1 es $-L_1-R_{13}$;

L_1 está ausente o es un conector que provee una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{13} y el anillo al cual L_1 está unido, donde los átomos del conector que proporcionan la separación son cada uno seleccionado de manera independiente del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

R_2 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_3 se selecciona del grupo que consiste de hidrógeno, carboniloxi, alcoxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_3 es $-L_2-R_{18}$;

L_2 está ausente o es un conector que provee una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{18} y el anillo al cual L_2 se encuentra unido, donde los átomos del conector que proporcionan la separación son cada uno seleccionado de

manera independiente del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

cada R_4 se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

cada R_5 se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

o R_3 y uno de R_4 y R_5, junto a los átomos a los cuales se encuentran unidos, forman un anillo sustituido o no sustituido seleccionado de heterocicloalquilo(C3-5) y heteroarilo(C3-4), el residuo de heterocicloalquilo posee 1 o 2 heteroátomos seleccionados de N, O, y S, con la condición que al menos uno de los heteroátomos es un átomo de nitrógeno, y el residuo de heteroarilo posee 1 o 2 nitrógeno heteroátomos;

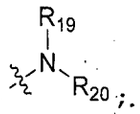
R_6 se selecciona del grupo que consiste de hidrógeno, carboniloxi, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_7 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}),

bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_8 se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{13} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_{13} posee la fórmula:

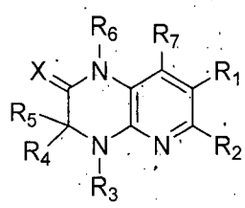


R_{18} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})) alquilo(C_{1-5}), hetero-cicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{19} y R_{20} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir, o R_{19} y R_{20} se toman juntos para formar un anillo sustituido o sin sustituir;

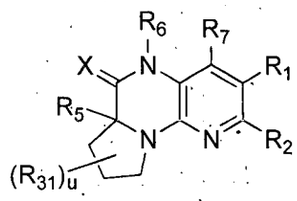
con las condiciones de (a) si R_1 es hidrógeno, cloro, metilo, 3,4-difluorofenilo, o 1-cloro-3-metil-1-oxopentan-3-il-aminocarbonilo, entonces R_6 es hidrógeno, y (b) si el sustituyente R_3 y los sustituyentes R_4 y R_5 están unidos a átomos de nitrógeno y de carbono adyacentes, respectivamente, entonces al menos uno de R_3, R_4, y R_5 no es hidrógeno.

2. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1, CARACTERIZADO porque es de la fórmula:



en la cual R_1, R_2, R_3, R_4, R_5, R_6, R_7-, y X son como se define en la reivindicación 1.

3. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 2, CARACTERIZADO porque es de la fórmula:



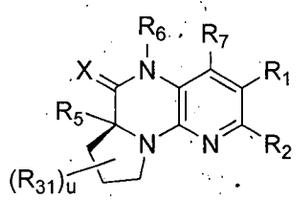
en la cual R_1, R_2, R_5, R_6, R_7, y X son como se define en la reivindicación 1;

u se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

cada R_{31} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}),

sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

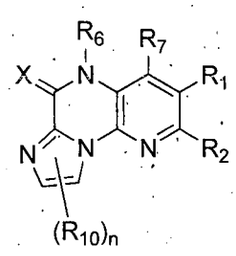
4. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 3, CARACTERIZADO porque es de la fórmula:



o un estereoisómero de los mismo, donde R_1, R_2, R_5, R_6, R_7, y X son como se define en la reivindicación 1, y u y R_{31} son como se define en la reivindicación 3.

5. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 3 o la reivindicación 4, CARACTERIZADO porque cada R_{31} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, y un alquilo(C_{1-3}) sustituido o sin sustituir.

6. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1, CARACTERIZADO porque es de la fórmula:



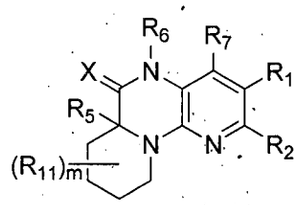
donde R_1, R_2, R_6, R_7, y X son como se define en la reivindicación 1;

n se selecciona del grupo que consiste de 0, 1 y 2; y

cada R_{10} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), hetero-cicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

7. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 6, CARACTERIZADO porque cada R_{10} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, y un alquilo(C_{1-3}) sustituido o sin sustituir.

8. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1, CARACTERIZADO porque es de la fórmula:

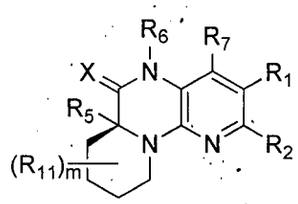


donde R_1, R_2, R_5, R_6, R_7, y X son como se define en la reivindicación 1;

m se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8; y

cada R_{11} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

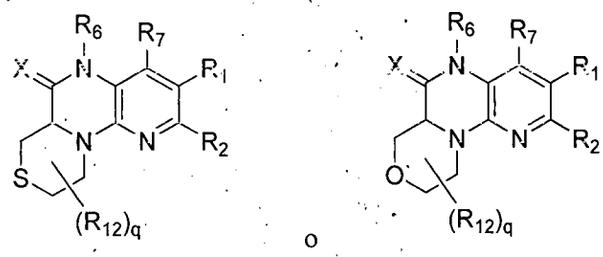
9. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 8, CARACTERIZADO porque es de la fórmula:



o un estereoisómero de los mismos, donde R_1, R_2, R_5, R_6, R_7, y X son como se define en la reivindicación 1, y m y R_{11} son como se define en la reivindicación 8.

10. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 8 o la reivindicación 9, CARACTERIZADO porque cada R_{11} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, y un alquilo(C_{1-3}) sustituido o sin sustituir.

11. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1, CARACTERIZADO porque es de la fórmula



donde R_1, R_2, R_6, R_7, y X son como se define en la reivindicación 1;

q se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5 y 6; y

cada R_{12} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

12. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 11, CARACTERIZADO porque cada R_{12} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, y un alquilo(C_{1-3}) sustituido o sin sustituir.

13. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1 o la reivindicación 2,

CARACTERIZADO porque R_3 se selecciona de alquilo(C_{1-3}) y aril(C_{1-6})alquilo, cada uno sustituido o sin sustituir.

14. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 1 o la reivindicación 2, CARACTERIZADO porque R_3 es $-L_2-R_{18}$, y

L_2 está ausente o es un conector seleccionado del grupo que consiste de $-(CR_{14}R_{15})_r-$, $-CO-$, $-CS-$, $-C(=NR_{16})-$, $-NR_{17}-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$, y las combinaciones de lo mismo;

r se selecciona del grupo que consiste de 1, 2 y 3;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilo-alquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonil-alquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})

alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{16} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{17} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12}) alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), biciclo-aril(C_{9-12})alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, biciclo-arilo(C_{9-}

$_{12}$) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

15. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 14, CARACTERIZADO porque L_2 es -$CR_{14}R_{15}$-.

16. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 14, CARACTERIZADO porque L_2 es -CH_2-.

17. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a una cualquiera de las reivindicaciones 14 a 16, CARACTERIZADO porque R_{18} es un fenilo sustituido o sin sustituir.

18. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a una cualquiera de las reivindicaciones 1, 2, y 14 a 17, CARACTERIZADO porque R_4 y R_5 son cada uno seleccionado de manera independiente de hidrógeno, halógeno, y alquilo(C_{1-3}) sustituido o sin sustituir.

19. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque X es O.

20. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a una cualquiera de las reivindicaciones 1 a 18, CARACTERIZADO porque X es NR_8, y R_8 se selecciona del grupo que consiste de hidrógeno y un alquilo(C_{1-3}) sustituido o sin sustituir.

21. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque R_1 es -L_1-R_{13}, y

L_1 está ausente o es un conector seleccionado del grupo que consiste de -$(CR_{14}R_{15})_r$-, -CO-, -CS-, -C(=NR_{16})-, -NR_{17}-, -O-, -S-, -SO-, -SO_2-, y las combinaciones de lo mismo;

R_{13} es como se define en la reivindicación 1;

r se selecciona del grupo que consiste de 1, 2 y 3;

R_{14} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_{15} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoàlquilo(C_{1-10}), cicloalquil(C_{3-12}) alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), bicicloalquilo(C_{9-12}), hetero-bicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

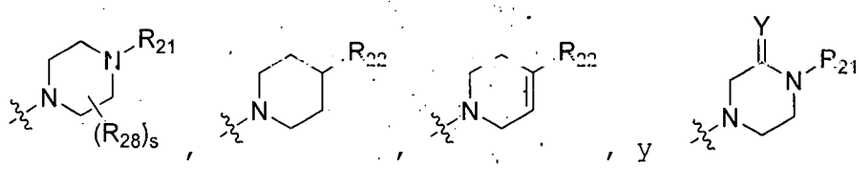
R_{16} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tio-carbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinil-alquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{17} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir.

22. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 21, CARACTERIZADO porque R_{14}, R_{15}, R_{16}, y R_{17} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, halógeno, y un alquilo(C_{1-3}) sustituido o sin sustituir.

23. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 21, CARACTERIZADO porque L_1 es -CH_2-.

24. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque R_{13} se selecciona de:



donde

s se selecciona del grupo que consiste de 0, 1, 2, 3, 4, 5, 6, 7 y 8;

Y se selecciona del grupo que consiste de O y S;

R_{21} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir; y

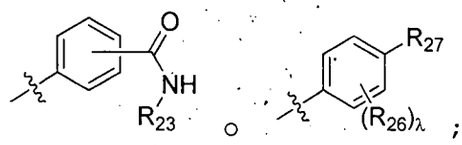
R_{22} y cada R_{28} son independientemente seleccionados del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}),

sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

25. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 24, CARACTERIZADO porque cada R_{28} se selecciona del grupo que consiste de hidrógeno, halógeno, y alquilo(C_{1-3}) sustituido o sin sustituir.

26. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 24, CARACTERIZADO porque R_{21} o R_{22} se selecciona de fenilo y piridinilo, cada uno sustituido o sin sustituir.

27. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 24, CARACTERIZADO porque R_{21} o R_{22} posee la fórmula:



;

donde

λ se selecciona del grupo que consiste de 0, 1, 2, 3 y 4;

R_{23} se selecciona del grupo que consiste de hidrógeno, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}),

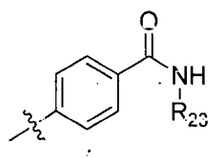
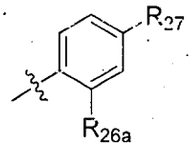
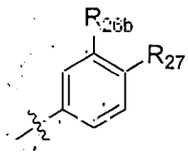
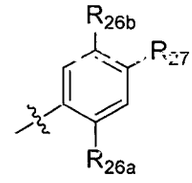
ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y heterobiciclo-arilo(C_{4-12}), cada uno sustituido o sin sustituir;

cada R_{26} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}),

bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

28. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 27, CARACTERIZADO porque R_{21} o R_{22} se selecciona de:

donde

R_{23} y R_{27} son como se define en la reivindicación 27;

R_{26a} y R_{26b} son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{4-12}), heteroariloxi(C_{1-10}), carbonilo, oxi-carbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), halo-alquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12}) alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{4-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir.

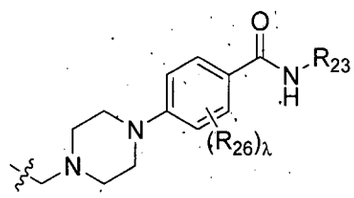
29. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a la reivindicación 27 o la reivindicación 28, CARACTERIZADO porque

R_{23} se selecciona de hidrógeno, alquilo(C_{1-3}), y cicloalquilo(C_{3-6});

R_{26}, R_{26a}, y R_{26b} son cada uno seleccionado de manera independiente de hidrógeno y halógeno, y de alquilo(C_{1-3}) y alcoxi(C_{1-3}), cada uno sustituido o sin sustituir; y

R_{27} se selecciona de -CO-NH-R_{23}.

30. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a una cualquiera de las reivindicaciones 1 a 20, CARACTERIZADO porque R_1 posee la fórmula:



donde

λ se selecciona del grupo que consiste de 0, 1 y 2;

R_{23} se selecciona del grupo que consiste de alquilo(C_{1-3}) y cicloalquilo(C_{3-6}); y

cada R_{26} se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, alquilo(C_{1-3}) y alcoxi(C_{1-3}).

31. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque R_2 se selecciona del grupo que consiste de hidrógeno, halógeno, y alquilo(C_{1-3}) sustituido o sin sustituir.

32. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque R_6 y R_7 son cada uno seleccionado de manera independiente del grupo que consiste de hidrógeno y un alquilo(C_{1-3}) sustituido o sin sustituir.

33. El compuesto o la sal farmacéuticamente aceptable del mismo de acuerdo a cualquiera de las reivindicaciones precedentes, CARACTERIZADO porque R_6 es hidrógeno.

34. El compuesto de acuerdo a la reivindicación 1, CARACTERIZADO porque se selecciona de los siguientes compuestos:

(S)-3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo;

(S)-N-metil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo;

ácido (S)-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotínico;

(S)-N-etil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

(S)-N-ciclopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

(S)-N-isopropil-6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

(S)-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo;

ácido (S)-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoico;

(S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-3-((4-(2,4-difluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-cloro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-2,3-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-2,6-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-3,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-3-fluoro-5-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)picolinonitrilo;

(S)-3-((4-fenilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-fluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-acetilfenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(piridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((bencil(metil)amino)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(3-metoxifenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-m-tolilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(3-metoxifenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-metoxifenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-p-tolilpiperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(pirimidin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(3-hidroxifenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-hidroxifenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(5-(trifluorometil)piridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-bromofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(3-fluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(1H-benzo[d]imidazol-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-yodofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(benzo[d]oxazol-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(5-cloropiridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-(((4-metoxibencil)(metil)amino)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(1,3,5-triazin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-metilo;

(S)-3-((4-(3,5-difluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-cloro-3-fluorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-(trifluorometil)fenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(R)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(R)-3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(R)-3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)piperidin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-3,4-dimetil-7-((4-fenilpiperidin-1-il)metil)-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-3,4-dimetil-7-((3-oxo-4-fenilpiperazin-1-il)metil)-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-fluorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-3,4-dimetil-7-((4-fenil5,6-dihidropiridin-1(2H)-il)metil)-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(3-clorofenil)piperazin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)piperazin-1-il)metil)-3,4-dimetil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

4-isopropil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[3,2-b]pirazin-7-carboxilato de (S)-metilo;

(S)-7-(hidroximetil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)piperazin-1-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)piperidin-1-il)metil)-4-isopropil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

(S)-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-etil-3-metil-3,4-dihidropirido[3,2-b]pirazin-2(1H)-ona;

4-etil-3-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de (S)-metilo;

(S)-4-etil-7-(hidroximetil)-3-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)imidazo[1,2-a]pirido[3,2-e]pirazin-6(5H)-ona;

3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)imidazo[1,5-a]pirido[3,2-e]pirazin-6(5H)-ona;

3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de metilo;

3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

3-((4-(4-clorofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

3-((4-(4-clorofenil)piperidin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-carboxilato de (S)-metilo;

(S)-3-(hidroximetil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-clorofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-clorofenil)piperidin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo;

(S)-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo;

ácido (S)-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzoico;

(S)-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-isopropil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo;

ácido (S)-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotínico;

(S)-N-metil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

(S)-N-etil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

(S)-N-ciclopropil-6-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)nicotinamida;

7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-metil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo;

7-(hidroximetil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

7-((4-(4-clorofenil)piperazin-1-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

7-((4-(4-clorofenil)piperidin-1-il)metil)-4-metil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-bencil-7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-bencil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo;

4-bencil-7-(hidroximetil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-bencil-7-((4-(4-clorofenil)piperazin-1-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-bencil-7-((4-(4-clorofenil)piperidin-1-il)metil)-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de metilo;

3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

3-((4-(4-clorofenil)piperidin-1-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

(R)-6-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo;

6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-carboxilato de (R)-metilo;

(R)-3-(hidroximetil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

(R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(R)-3-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-6a,7,9,10-tetrahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-6(5H)-ona;

(R)-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (R)-etilo;

ácido (R)-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzoico;

3-((4-(4-clorofenil)piperazin-1-il)metil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona;

6-oxo-5,6,6a,7,9,10-hexahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-3-carboxilato de metilo;

3-(hidroximetil)-6a,7,9,10-tetrahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-6(5H)-ona;

7-((4-(4-clorofenil)-5,6-dihidropiridin-1(2H)-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

4-isopropil-2-oxo-1,2,3,4-tetrahidropirido[2,3-b]pirazin-7-carboxilato de metilo;

7-(hidroximetil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

7-((4-(4-clorofenil)piperazin-1-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

7-((4-(4-clorofenil)piperidin-1-il)metil)-4-isopropil-3,4-dihidropirido[2,3-b]pirazin-2(1H)-ona;

7-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-2-metil-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona;

2-ter-butil ester 7-metil ester del ácido 10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2,7-dicarboxílico;

ter-butil ester del ácido 7-Hidroximetil-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico;

ter-butil ester del ácido 7-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-10-oxo-1,3,4,9,10,10a-hexahidro-2,4a,5,9-tetraaza-fenantren-2-carboxílico;

7-[4-(4-cloro-fenil)-piperazin-1-ilmetil]-1,3,4,10a-tetrahidro-2H,9H-2,4a,5,9-tetraaza-fenantren-10-ona;

(R)-N-metil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(R)-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

6-(4-((6-oxo-5,6,6a,7,9,10-hexahidro-[1,4]oxazino[4,3-a]pirido[3,2-e]pirazin-3-il)metil)piperazin-1-il)nicotinonitrilo;

4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzoato de (S)-etilo;

(S)-4-(4-((6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

6-oxo-6,6a,7,8-tetrahidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-3-carboxilato de (S)-metilo;

(S)-3-(hidroximetil)-7,8-dihidro-5H-azeto[1,2-a]pirido[3,2-e]pirazin-6(6aH)-ona;

4-(4-((6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-il)metil)piperazin-1-il)benzonitrilo;

6-oxo-6,7,7a,8,9,10-hexahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-3-carboxilato de metilo;

3-(hidroximetil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-6(7H)-ona;

3-((4-(4-clorofenil)piperazin-1-il)metil)-7a,8,9,10-tetrahidro-5H-pirido[3,2-b]pirrolo[1,2-d][1,4]diazepin-6(7H)-ona;

4-((S)-3-metil-4-((R)-6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(R)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(R)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(R)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,9,10-hexahidropirido[3,2-e][1,4]tiazino[4,3-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-fluoro-N-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N,3-dimetil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-3-metil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-metoxi-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

N-etil-4-(4-((6-oxo-6,6a,7,8,9,10-hexahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-3-il)metil)piperazin-1-il)benzamida;

(6aS)-3-((2-metil-4-(piridin-2-il)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

6-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)nicotinato de (S)-etilo;

(S)-3-((1-(4-clorofenil)piperidin-4-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-bromo-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-5-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)picolinonitrilo;

(S)-N-etil-2,5-difluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-2-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-etil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)bencenosulfonamida;

(S)-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzonitrilo;

(S)-3-((4-(4-fluoro-2-metilfenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-fluoro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-3-fluoro-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-fluoro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-ciclopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-isopropil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-cloro-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-3-((4-(4-(pirrolidin-1-carbonil)fenil)piperazin-1-il)metil)-6a,7,8,9-tetrahidropirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-N,N-dimetil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-etil-N-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N,3-dimetil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

(S)-N-ciclopropil-3-metil-4-(4-((6-oxo-5,6,6a,7,8,9-hexahidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

N-etil-4-(4-((6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-il)metil)piperazin-1-il)benzamida;

6-oxo-5,6-dihidropirido[3,2-e]pirrolo[1,2-a]pirazin-3-carboxilato de metilo;

3-(hidroximetil)pirido[3,2-e]pirrolo[1,2-a]pirazin-6(5H)-ona;

(S)-3-((4-(4-(2-metoxipiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-bromofenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(6-aminopiridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(tiofen-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(tiofen-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(piridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(bifenil4-il)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(6-metoxipiridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(pirimidin-5-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(2-metoxipirimidin-5-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(3-metoxipiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(2'-metilbifenil4-il)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(3-metilpiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(6-metoxipiridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(piridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(piridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(5-metiltiofen-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(2'-(hidroximetil)bifenil-4-il)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(4-metiltiofen-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(3-metiltiofen-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(5-oxociclopent-1-enil)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(6-metilpiridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(1-metil-1H-pirazol-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(4-metilpiridin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(2-metilpiridin-4-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(pirazin-2-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

(S)-3-((4-(4-(2-metoxipiridin-3-il)fenil)piperazin-1-il)metil)-7,8,9,10-tetrahidro-5H-dipirido[1,2-a:3',2'-e]pirazin-6(6aH)-ona;

un estereoisómero de cualquiera de los compuestos antes mencionados; y una sal farmacéuticamente aceptable de cualquiera de los compuestos antes mencionados.

35. Una composición farmacéutica CARACTERIZADA porque comprende un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones anteriores; y un excipiente farmacéuticamente aceptable.

36. Uso de un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones 1 a 34, CARACTERIZADO porque sirve para preparar un medicamento.

37. El uso de un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones 1 a 34, CARACTERIZADO porque sirve para preparar un medicamento útil para el tratamiento de una enfermedad o condición para la cual la actividad PARP contribuye a la patología y/o sintomatología de la enfermedad o condición.

38. Un método para tratar una enfermedad o condición en un individuo para la cual la actividad PARP contribuye a la patología y/o sintomatología de la enfermedad o condición, CARACTERIZADO porque el método comprende administrar al individuo una cantidad efectiva de un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones 1 a 34.

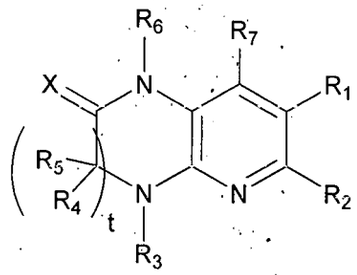
39. Un método para tratar una enfermedad o condición en un individuo, CARACTERIZADO porque el método comprende administrar al individuo una cantidad efectiva de un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones 1 a 34, donde la enfermedad o condición se selecciona de cáncer, enfermedades cardiovasculares, enfermedades metabólicas, enfermedades inflamatorias, daños por reperfusión, condiciones isquémicas, y enfermedades neurodegenerativas.

40. Una combinación de una cantidad efectiva de un compuesto o la sal farmacéuticamente aceptable del mismo como se define en cualquiera de las reivindicaciones 1 a 34, CARACTERIZADO porque además comprende al menos un agente farmacéuticamente activo.

RESUMEN

Inhibidores de Poli (ADP-ribosa) Polimerasa (PARP)

Se describen compuestos de la siguiente fórmula:



en la cual R_1, R_2, R_3, R_4, R_5, R_6, R_7, X, y t se definen en la memoria descriptiva. También se describen las composiciones farmacéuticas, los kit, y artículos de manufactura, que contienen los compuestos, métodos e intermediarios útiles para preparar los compuestos, y los métodos para utilizar los compuestos para tratar enfermedades, desórdenes, y condiciones relacionadas con la actividad PARP.

Industria y Comercio
SUPERINTENDENCIA

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

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(54) Titulo: **INHIBIDORES DE POLI (ADP-RIBOSA) POLIMERASA (PARP)**

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
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(71)Solicitante(s) **TAKEDA PHARMACEUTICAL COMPANY LIMITED**

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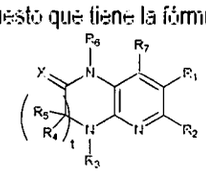
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(54) Titulo: **INHIBIDORES DE POLI (ADP-RIBOSA) POLIMERASA (PARP)**

Reivindicación(es):

1. Un compuesto que tiene la fórmula:



o una sal farmacéuticamente aceptable de lo mismo, CARACTERIZADO porque

t se selecciona del grupo que consiste de 1 y 2;

X se selecciona del grupo que consiste de O, S y NR_3;

R_1 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{6-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), aminoalquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{6-12}), heteroarilo(C_{4-10}), bicicloarilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_1 es $-L_1-R_{13}$;

L_1 está ausente o es un conector que provee una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{13} y el anillo al cual L_1 está unido, donde los átomos del conector que proporcionan la separación son cada uno seleccionado de manera independiente del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

R_2 se selecciona del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{6-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxialquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonilalquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), aza-alquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), cicloalquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})alquilo(C_{1-5}), bicicloaril(C_{9-12})-alquilo(C_{1-5}), heterobicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterociclo-alquilo(C_{3-12}), bicicloalquilo(C_{9-12}), heterobiciclo-alquilo(C_{3-12}), arilo(C_{6-12}), heteroarilo(C_{4-10}), biciclo-arilo(C_{9-12}) y heterobicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir;

R_3 se selecciona del grupo que consiste de hidrógeno, carboniloxi, alcoxi(C_{1-10}), carbonilo, oxicarbonilo, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ciclo-alquil(C_{3-12})alquilo(C_{1-5}), heterocicloalquil(C_{3-12})-alquilo(C_{1-10}), arilalquilo(C_{1-10}), heteroaril(C_{1-10})-alquilo(C_{1-5}), bicicloaril(C_{9-12})alquilo(C_{1-5}), hetero-bicicloaril(C_{8-12})alquilo(C_{1-5}), heteroalquilo(C_{1-10}), cicloalquilo(C_{3-12}), heterocicloalquilo(C_{3-12}), biciclo-alquilo(C_{9-12}), heterobicicloalquilo(C_{3-12}), arilo(C_{6-12}), hetero(C_{1-10})arilo, bicicloarilo(C_{9-12}) y hetero-bicicloarilo(C_{4-12}), cada uno sustituido o sin sustituir; o R_3 es $-L_2-R_{16}$;

L_2 está ausente o es un conector que provee una separación de 1, 2, 3, 4, 5 o 6 átomos entre R_{16} y el anillo al cual L_2 se encuentra unido, donde los átomos del conector que proporcionan la separación son cada uno seleccionado de manera independiente del grupo que consiste de carbono, oxígeno, nitrógeno, y azufre;

cada R_4 se selecciona de manera independiente del grupo que consiste de hidrógeno, halógeno, nitro, ciano, tio, oxi, hidroxi, carboniloxi, alcoxi(C_{1-10}), ariloxi(C_{6-12}), heteroariloxi(C_{1-10}), carbonilo, oxicarbonilo, amido, amino, alquilamino(C_{1-10}), sulfonamido, imino, sulfonilo, sulfinilo, alquilo(C_{1-10}), haloalquilo(C_{1-10}), hidroxi-alquilo(C_{1-10}), carbonilalquilo(C_{1-10}), tiocarbonil-alquilo(C_{1-10}), sulfonilalquilo(C_{1-10}), sulfinilalquilo(C_{1-10}), azaalquilo(C_{1-10}), oxaalquilo(C_{1-10}), oxoalquilo(C_{1-10}), iminoalquilo(C_{1-10}), ...

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 654

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISION A TRAMITE - NUEVAS CREACIONES

PATENTE DE INVENCION [ ] **MODELO DE UTILIDAD** [ ] **Art. 33 Decisión 486/00**

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

Completa [ ] Incompleta [ ]

PATENTE DE INVENCION PCT [X] **MODELO DE UTILIDAD PCT** [ ] **Art. 33 Decisión 486/00 Circular Única**

- [X] Indicación que se solicita una PCT
- [X] Datos de identificación del solicitante o de la persona que presenta la solicitud
- [X] Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- [ ] Dibujos de ser estos pertinentes
- [X] Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa [X] Incompleta [ ]

DISEÑO INDUSTRIAL [ ] **(Art. 119 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

ESQUEMA DE TRAZADO [ ] **(Art. 92 Decisión 486/00)**

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

Completa [ ] Incompleta [ ]

Industria y Comercio
SUPERINTENDENCIA

Prosperidad para todos

Bogotá D.C.,
2020

Doctor(a)
MARGARITA CASTELLANOS ABONDANO
Apoderado(a) y/o Representante de
TAKEDA PHARMACEUTICAL COMPANY LIMITED

REFERENCIA	Radicación No.	11 102248
	Solicitud internacional	PCT/US2010/021669
	Fecha inicio fase nacional	23/08/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	13714

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. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se consideraró abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (C)

02 SET. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11