



Libertad y Orden

REPÚBLICA DE COLOMBIA
DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT
PATE NTE DE INVENCION



Industria y Comercio
SUPERINTENDENCIA

07-3804

TITULO: COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS
INFLAMATORIOS.

SOLICITANTE: SCHERING CORPORATION

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, New Jersey
07033-0530, E.U.A.

APODERADO J. IAN RAISBECK

BOGOTÁ, 16 DE ENERO, 2007

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

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☒

Capítulo I.

☐

Capítulo II.

2

SOLICITANTE
(71)

Nombre: SCHERING CORPORATION

Dirección: 2000 Galloping Hill Road, Kenilworth,
New Jersey 07033-0530, E.U.A.

Nacionalidad o Domicilio: ESTADOUNIDENSE

Lugar de Constitución: ESTADOS UNIDOS DE
AMERICA

Teléfono: **Fax:**

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C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual

Número

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O APODERADO.

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C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual

Número 79.376.996

TP 135.799

INVENTOR (ES)
(72)

Nombre: VER PAGINA ADJUNTA

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5

PCT (86)

Solicitud Internacional No. PCT/US2005/024771

Fecha Julio 13, 2005

Publicación Internacional No. WO 2006/019768

Fecha Febrero 23, 2006

6

Título (54) COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS INFLAMATORIOS.

Clasificación Internacional (51) C07D 403/06.

Prioridad

SI

☒

N

☐

(33) País de Origen

US

(32) Fecha

Julio 16, 2004

(31) Número de Solicitud

60/588,502

9

Comprobante de pago No. 07-640

Fecha

Enero 4, 2007

10

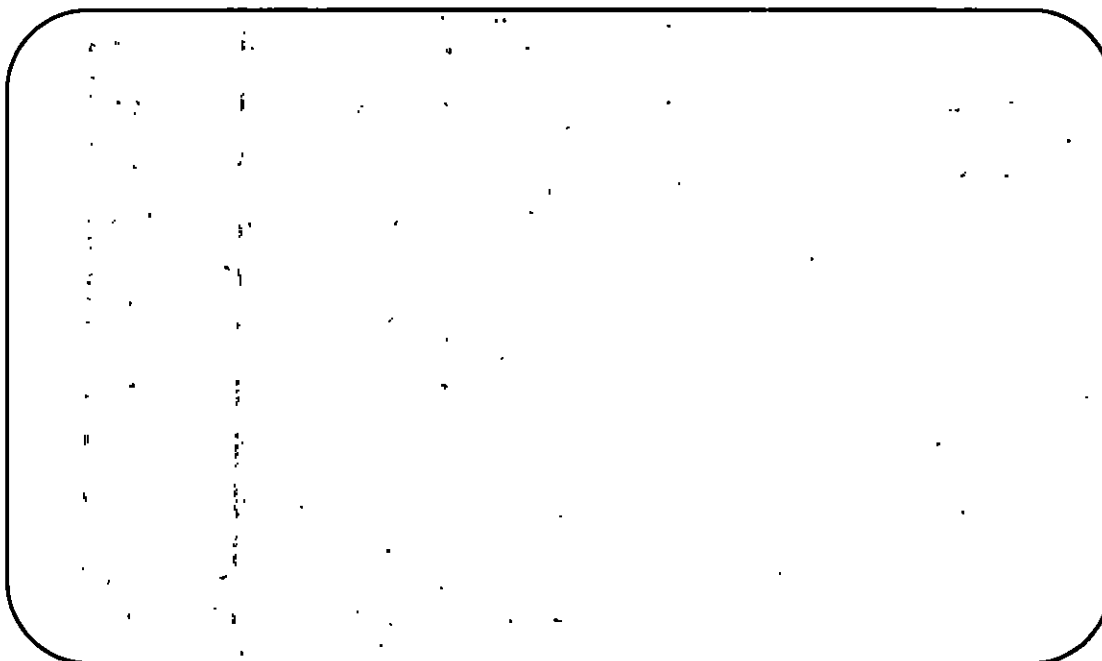
ANEXOS

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-057.472, Sustitución.
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12 x 12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK

FIRMA:

J. Ian Raisbeck

C.C. 79.376.996 Btá T.P. 135.799

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Rad: 07-003804- -00000-0000
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Eve: 376 FASENACIONALI
Act: 411 PRESENTACION Folios: 473

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FECHA : ENERO 4 DE 2007

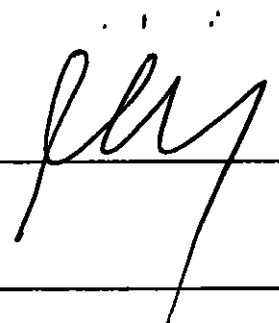
***** CONSIGNACION *****

DEPOSITANTE	TIPO PASO	BANCO	CUENTA	No. PASO	FECHA PASO	Vr. PASO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	56710700	04/01/2007	2,810,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : 
RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref.: Solicitud de Patente de invención Titulada: "COMPUESTOS PARA EL
TRATAMIENTO DE TRASTORNOS INFLAMATORIOS".

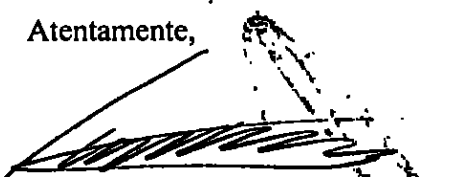
Solicitante: SCHERING CORPORATION.

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor J. IAN RAISBECK LLINAS, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,


CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA

EL ANTERIOR ESCRITO DIRIGIDO A:

Industria y Comercio

27

FUE PRESENTADO PERSONALMENTE
ANTE M. NOTARIO VEINTISIETE
DE LA CIUDAD DE BOGOTÁ D.C.

Carlos R. Olarte G.

C.C. 29.782.747 Bogotá T.P. 74295.

YO, EL NOTARIO, DEL CONTENIDO DEL ANTERIOR
DOCUMENTO Y QUE LA FIRMA QUE LO
ACOMPaña ES LA DE LA PERSONA POR EL
CUAL FUE PRESENTADO.

HCE:

26 OCT 2008

HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA



**APOSTILLA EN PODER DE REPRESENTACIÓN DE
SCHERING CORPORATION**

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
- Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguerite La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey
8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el Poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con
confrontación. Bogotá 5 septiembre, 2003.

copia archivo, para

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

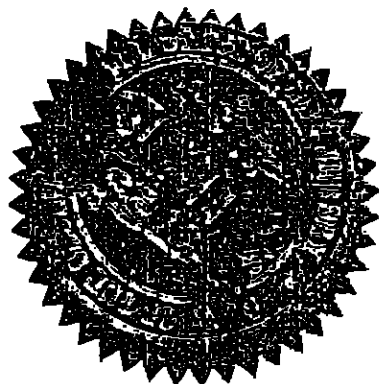
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 29TH DAY OF AUGUST 2003
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER
8. NO. A180345
9. SEAL/STAMP:
10. SIGNATURE



John E McCormac

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
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Power of Attorney

The undersigned,
SCHERING CORPORATION

domiciled in

2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Poder

El suscrito,

domiciliado en

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

Signature/Firma:


Edward H. Hazer, Senior Legal Director

Date/Fecha:

August 7, 2003

City/Country/Ciudad/Pais: **Kenilworth, New Jersey, U.S.A.**

OLARTE RAISBECK

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Notarial Certification

On this date, **August 7, 2003**

The undersigned Notary Public certifies:

1. That **Edward H. Mazer**

of legal age and domiciled in

119 Greenwood Drive, Millburn, New Jersey 07041, U.S.A.

signed the foregoing document.

2. That the grantor has executed the foregoing document as **Senior Legal Director of SCHERING CORPORATION**

3. That **SCHERING CORPORATION**

having its principal place of business located in

2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.S.A.

is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de

4. Que

con sede principal ubicada en

2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.S.A.

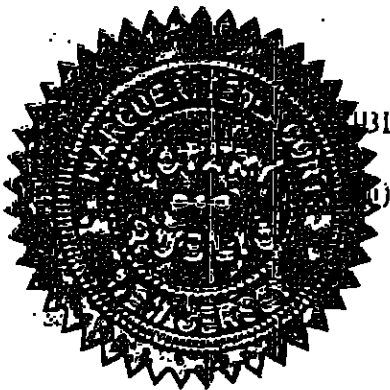
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

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

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

PUBLIC (Signature):

Marguerite La Corte
Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
23 February 2006 (23.02.2006)

PCT

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WO 2006/019768 A1

(51) International Patent Classification⁷: C07D 403/06,
417/14, 401/14, 409/14, 413/14, A61P 43/00, 29/00,
A61K 31/4178

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(21) International Application Number:
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(25) Filing Language: English

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(30) Priority Data:
60/588,502 16 July 2004 (16.07.2004) US

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
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European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

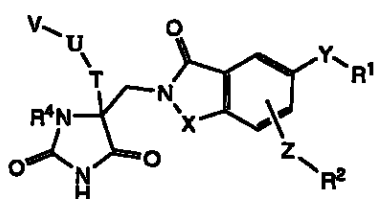
— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for all designations

Published:

— with international search report

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

(54) Title: HYDANTOIN DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISORDERS



(57) Abstract: This invention relates to compounds of Formula (1) or
a pharmaceutically acceptable salt, solvate or isomer thereof, which can
be useful for the treatment of diseases or conditions mediated by MMPs,
ADAMs, TACE, TNF- or combinations thereof.

WO 2006/019768 A1

HYDANTOIN DERIVATIVES FOR THE TREATMENT OF INFLAMMATORY DISORDERS

BACKGROUND OF THE INVENTION**Field of the Invention**

This invention relates generally to novel hydantoin derivatives that can inhibit matrix metalloproteinases (MMPs), a disintegrin and metalloproteinases (ADAMs) and/or tumor necrosis factor alpha - converting enzyme (TACE) and in so doing prevent the release of tumor necrosis factor alpha (TNF- α), pharmaceutical compositions comprising such compounds, and methods of treatment using such compounds.

Description

Osteo- and rheumatoid arthritis (OA and RA, respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A (1970) 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteinases. The available evidence supports the belief that it is the metalloproteinases that are responsible for the degradation of the extracellular matrix of articular cartilage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloproteinase) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Metalloproteinases (MPs) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

MMPs are a family of over 20 different enzymes that are involved in a variety of biological processes important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as RA and OA, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMPs (tissue inhibitor of MPs), which form inactive complexes with the MMP's.

Tumor necrosis factor alpha (TNF- α) is a cell-associated cytokine that is processed from a 26 kDa precursor form to a 17 kd active form. See Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. 2002 Jan; 34(1):1-5 and Moss ML, White JM, Lambert MH, Andrews RC. "TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 2001 Apr 1;6(8):417-426, each of which is incorporated by reference herein.

TNF- α has been shown to play a pivotal role in immune and inflammatory responses. Inappropriate or over-expression of TNF- α is a hallmark of a number of diseases, including RA, Crohn's disease, multiple sclerosis, psoriasis and sepsis. Inhibition of TNF- α production has been shown to be beneficial in many preclinical models of inflammatory disease, making inhibition of TNF- α production or signaling an appealing target for the development of novel anti-inflammatory drugs.

TNF- α is a primary mediator in humans and animals of inflammation, fever and acute phase responses, similar to those observed during acute infection and shock. Excess TNF- α has been shown to be lethal. Blocking the effects of TNF- α with specific antibodies can be beneficial in a variety of conditions, including autoimmune diseases such as RA (Feldman et al, Lancet, (1994) 344, 1105), non-insulin dependent diabetes mellitus (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) and Crohn's disease (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Compounds that inhibit the production of TNF- α are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that metalloproteases, such as TACE, are capable of converting TNF- α from its inactive to active form (Gearing et al Nature, 1994, 370, 555). Since excessive TNF- α production has been noted in several disease conditions also characterized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF- α production may also have a particular advantage in diseases where both mechanisms are involved.

One approach to inhibiting the harmful effects of TNF- α is to inhibit the enzyme, TACE before it can process TNF- α to its soluble form. TACE is a member of the ADAM family of type I membrane proteins and mediates the ectodomain shedding of various membrane-anchored signaling and adhesion proteins. TACE has become increasingly important in the study of several diseases, including inflammatory disease, because of its role in cleaving TNF- α from its "stalk" sequence and thus releasing the soluble form of the TNF- α protein (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

There are numerous patents and publications which disclose hydroxamate, sulphonamide, hydantoin, carboxylate and/or lactam based MMP inhibitors.

US 6,677,355 and US 6,534,491(B2), describe compounds that are hydroxamic acid derivatives and MMP inhibitors.

US 6,495,565 discloses lactam derivatives that are potential inhibitors of MMPs and/or TNF- α .

PCT Publications WO2002/074750, WO2002/096426, WO20040067996, WO2004012663, WO200274750 and WO2004024721 disclose hydantoin derivatives that are potential inhibitors of MMPs.

PCT Publications WO2004024698 and WO2004024715 disclose sulphonamide derivatives that are potential inhibitors of MMPs.

PCT Publications WO2004056766, WO2003053940 and WO2003053941 also describe potential inhibitors of TACE and MMPs.

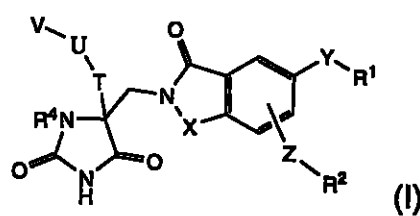
There is a need in the art for inhibitors of MMPs, ADAMs, TACE, and TNF- α , which can be useful as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibition of TNF- α , TACE and or other MMPs

can prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of OA and RA as well as many other auto-immune diseases.

SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of compounds as inhibitors of TACE, the production of TNF- α , MMPs, ADAMs or any combination thereof, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof using such compounds or pharmaceutical compositions.

In one embodiment, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in formula (I):



or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein:

X is selected from the group consisting of -S-, -C(R⁴)₂- or -N(R⁴)-;

T is selected from the group consisting of H (with U and V being absent), alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, and arylalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of T is unsubstituted or optionally independently substituted with one to four R¹⁰ moieties which can

be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

U is absent or present, and if present U is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, and $-N(R^4)C(S)N(R^4)-$;

V is absent or present, and if present V is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

Z is absent or present, and if present Z is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

n is 1 to 3;

R^1 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^1 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Y is present and Y is N, S or O, then R^1 is not halogen;

R^2 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^2 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Z is present and Z is N, S or O, then R^2 is not halogen;

each R^4 is the same or different and is independently selected from the group consisting of H and alkyl;

R^{10} is selected from the group consisting of $-OR^4$, $-N(R^4)_2$, $-S(O)-$, $-S(O)_2-$, $-N(R^4)S(O)_2-$, $-S(O)_2N(R^4)-$, $-O(\text{fluoroalkyl})$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of R^{10} is unsubstituted or optionally independently substituted with one to four R^{30} moieties which can be the same or different, each R^{30} moiety being independently selected from the group of R^{30} moieties below;

R^{20} is selected from the group consisting of halogen, alkyl, fluoroalkyl; and

R^{30} is selected from the group consisting of halogen, alkyl, and fluoroalkyl.

The compounds of Formula I can be useful as inhibitors of TACE and may be useful in the treatment and prevention of diseases associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof.

DETAILED DESCRIPTION OF THE INVENTION

In its several embodiments, the present invention provides a novel class of inhibitors of TACE, the production of TNF- α , MMPs, ADAMs or any combination thereof, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations

comprising one or more such compounds, and methods of treatment, prevention or amelioration of one or more of the symptoms of inflammation.

In one embodiment, the present invention provides compounds which are represented by structural Formula (I) above or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein the various moieties are as described above.

In another embodiment, the isomer referred to in the preceding paragraph is a stereoisomer.

In one embodiment, T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is $-O-$.

In another embodiment, T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present, and if present Z is $-O-$; and R^2 is selected from the group consisting of alkylaryl and alkylheteroaryl.

In another embodiment, T is alkyl or aryl; X is $-N(R^4)-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is $-O-$.

In another embodiment, X is $-CH_2-$ or $-N(R^4)-$.

In yet another embodiment, X is $-CH_2-$.

In still another embodiment, X is $-N(R^4)-$.

In another embodiment, R^4 is H.

In another embodiment, T is alkyl.

In yet another embodiment, T is $-CH_3$.

In still another embodiment, T is aryl and said aryl is unsubstituted or optionally independently substituted with one to five R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

In another embodiment, R^{10} is halogen.

In yet another embodiment, R^{10} is heteroaryl.

In still another embodiment, R^{10} is aryl.

In an embodiment U selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(O)-$, and $-N(R^4)S(O)_2-$.

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In yet another embodiment U is a covalent bond.

In still another embodiment U is $-N(R^4)-$.

In yet still another embodiment, U is $-N(R^4)C(O)-$.

In another embodiment, V is selected from the group consisting of aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, and cycloalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of any of said aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

In another embodiment, Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-C(O)-$ and $-O-$.

In yet another embodiment, Y is $-O-$.

In still another embodiment, Y is $-(C(R^4)_2)_n-$.

In yet still another embodiment, Y is $-C(O)-$.

In another embodiment, Y is a covalent bond.

In an embodiment, R^1 is selected from the group consisting of $-OR^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

In another embodiment, R^1 is H.

In yet another embodiment, R^1 is alkylaryl.

In still another embodiment, R^1 is alkyl.

In yet still another embodiment, R^1 is fluoroalkyl.

In a further embodiment, R^1 is halogen.

In another embodiment, R^1 is $-OR^4$.

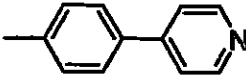
In another embodiment, where R^1 is $-OR^4$, R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_3$.

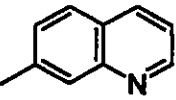
In another embodiment, where R^1 is $-OR^4$, R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{OH}$.

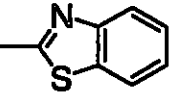
In another embodiment, where R^1 is $-OR^4$, R^4 is $-\text{CH}_2-$ .

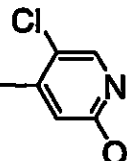
In another embodiment, the alkyl is $-\text{CH}_3$.

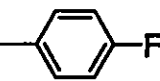
In still another embodiment, the alkyl is $-\text{CH}_2\text{CH}_3$.

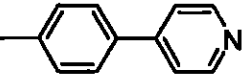
In another embodiment, in formula (I), T, U, and V are taken together to form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

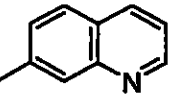
In another embodiment, in formula (I), T, U, and V are taken together to form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

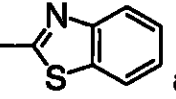
In another embodiment, in formula (I), T, U, and V are taken together to form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

In another embodiment, in formula (I), T, U, and V are taken together to form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

In another embodiment, in formula (I), T, U, and V are taken together to form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

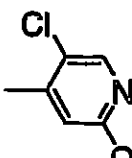
In another embodiment, in formula (I), T, U, and V are taken together to form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

In another embodiment, in formula (I), T, U, and V are taken together to form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

In another embodiment, in formula (I), T, U, and V are taken together to form  and R² is selected from the group consisting of F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, and $-\text{OCH}_2$ -.

In another embodiment, in formula (I), T, U, and V are taken together to

form  and R^2 is selected from the group consisting of F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, and $-\text{OCH}_2$ -.

In another embodiment, in formula (I), T, U, and V are taken together to

form  and R^2 is selected from the group consisting of F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, and $-\text{OCH}_2$ -.

In another embodiment, the fluoroalkyl is $-\text{CH}_2\text{CF}_3$.

In an embodiment, halogen is selected from the group consisting of $-\text{Br}$, $-\text{Cl}$ and $-\text{F}$.

In another embodiment, R^4 is $-\text{CH}_3$.

In yet another embodiment, alkyl of R^1 is substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties.

In another embodiment, R^{20} is aryl.

In another embodiment, Z is selected from the group consisting of a covalent bond, $-\text{N}(\text{R}^4)-$, $-(\text{C}(\text{R}^4)_2)_n-$, $-\text{C}(\text{O})-$ and $-\text{O}-$.

In yet another embodiment, Z is $-\text{O}-$.

In still another embodiment, Z is a covalent bond.

In yet still another embodiment, Z is $-\text{N}(\text{R}^4)-$.

In a further embodiment, Z is $-\text{C}(\text{O})-$.

In another embodiment, R^4 is alkyl.

In another embodiment, R^2 is selected from the group consisting of $-\text{OR}^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

In another embodiment wherein R^2 is $-\text{OR}^4$, R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_3$.

In another embodiment wherein R^2 is $-\text{OR}^4$, R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{OH}$.

In another embodiment wherein R^2 is $-\text{OR}^4$, R^4 is $-\text{CH}_2$ -.

In yet another embodiment, R^2 is hydrogen.

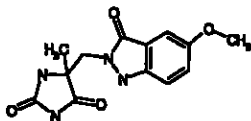
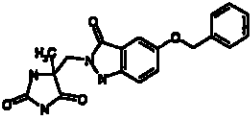
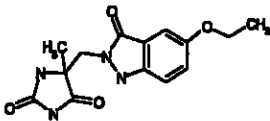
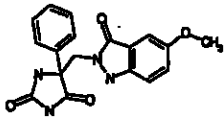
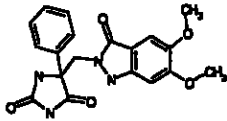
In still another embodiment, R^2 is alkyl.

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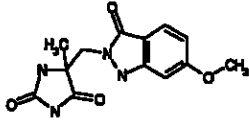
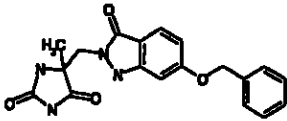
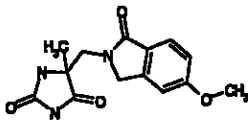
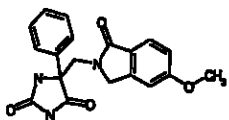
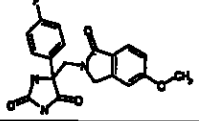
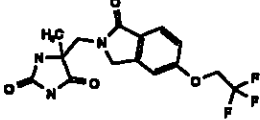
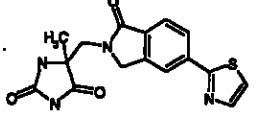
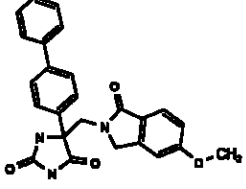
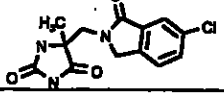
- In yet still another embodiment, R² is alkylaryl.
- In yet further embodiment, R² is fluoroalkyl.
- In another embodiment, R² is -CH₂CF₃.
- In yet another embodiment, R² is halogen.
- In another embodiment, R² is heteroaryl.
- In another embodiment, R⁴ is -CH₃.

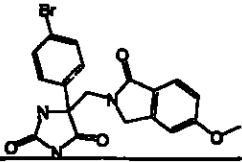
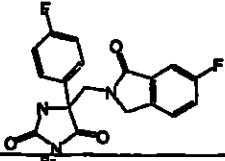
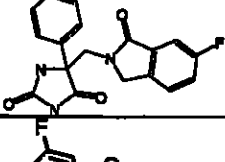
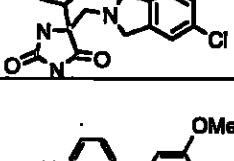
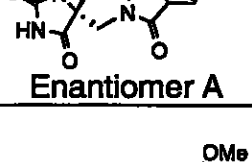
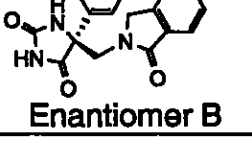
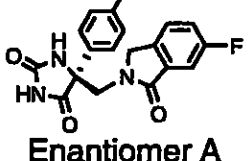
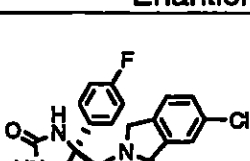
Another embodiment of the invention discloses the following compounds shown in Table A below.

Table A

Structures






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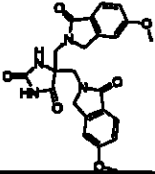
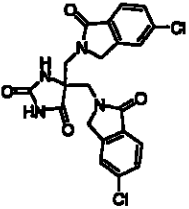
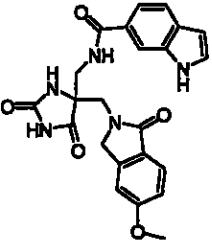
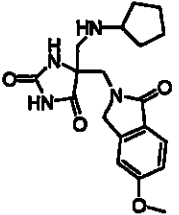
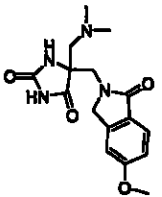
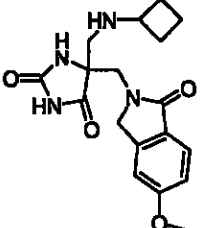
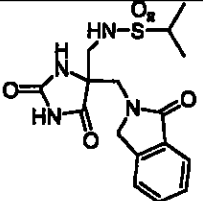














 Enantiomer A
 Enantiomer B
 Enantiomer A
 Enantiomer B
 Enantiomer A

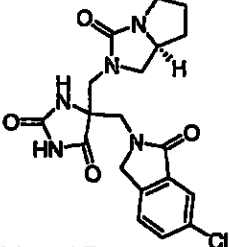
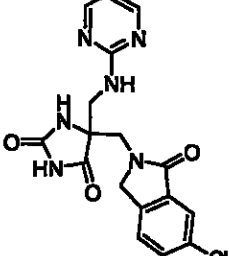
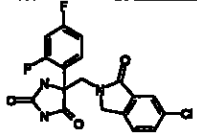
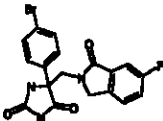
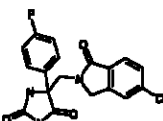
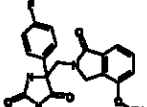
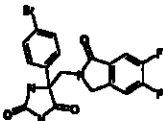
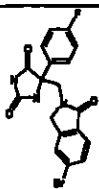
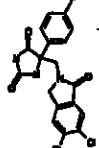
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<chem>O=C1NC(=O)C(C2=CC(=CC=C2C3=CC(=CC=C3)F)C4=CC(=CC=C4)C(=O)N1C5=CC(=CC=C5)Cl)C6=CC(=CC=C6)C(=O)O</chem> Enantiomer B
<chem>COc1ccc2c(c1)c(=O)n(Cc3c[nH]c3-c4ccc(Br)cc4)c2=O</chem>
<chem>COc1ccc2c(c1)c(=O)n(Cc3c[nH]c3-c4ccc(Cc5cc(F)(F)Fcc5)cc4)c2=O</chem>
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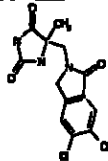
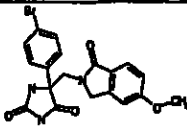
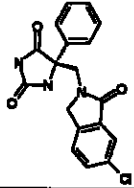
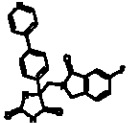
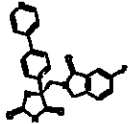
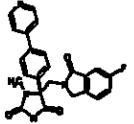
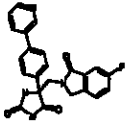
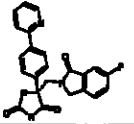
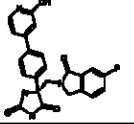
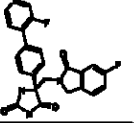
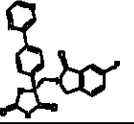
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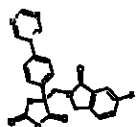
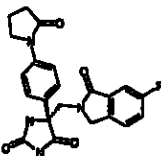
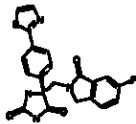
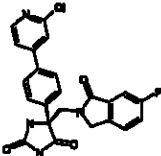
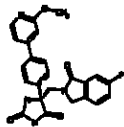
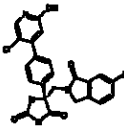
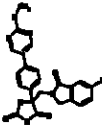
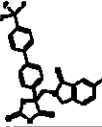
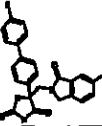
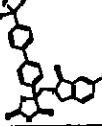








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27 27

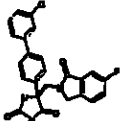
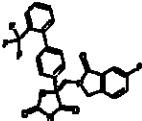
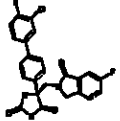
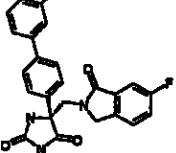
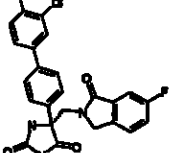
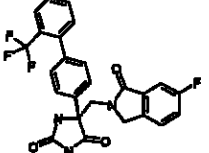
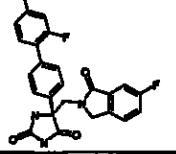
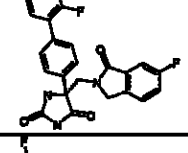
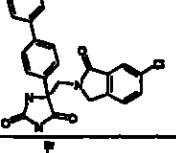
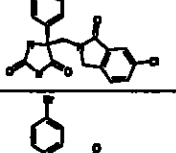
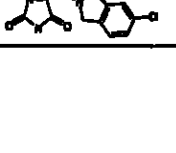












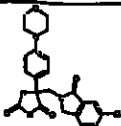
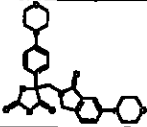
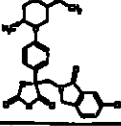
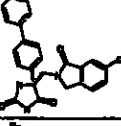
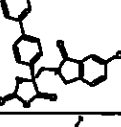
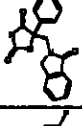
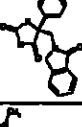
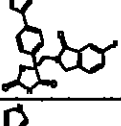
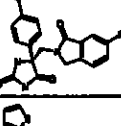
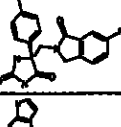
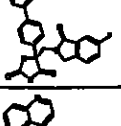
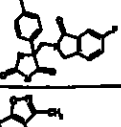
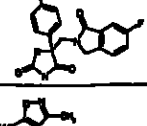
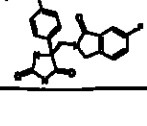











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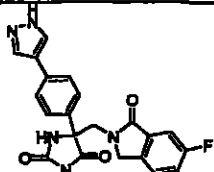
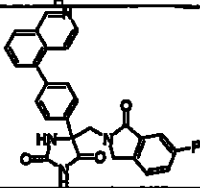
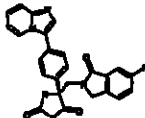
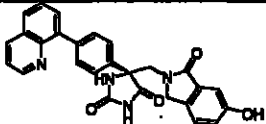
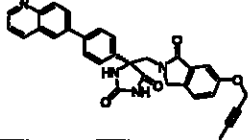
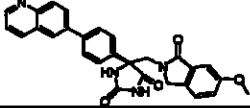
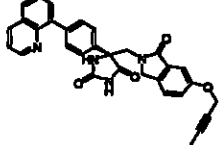
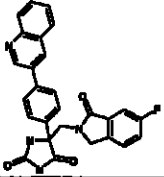
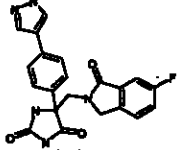
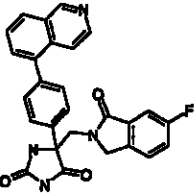
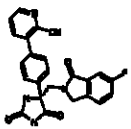
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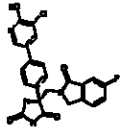
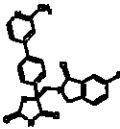
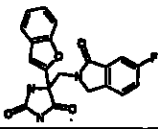
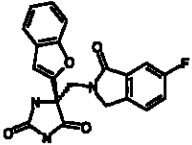
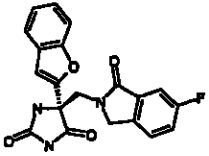
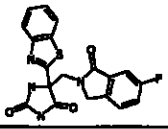
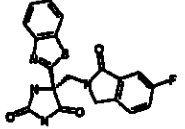
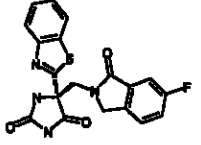















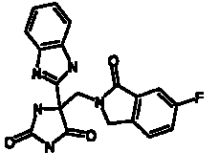
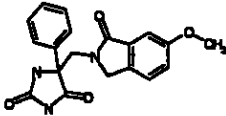
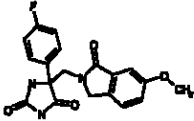
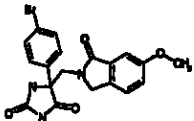
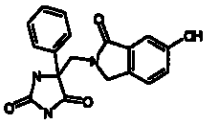
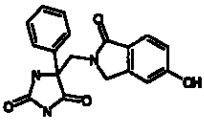
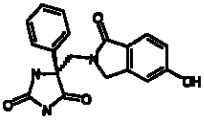
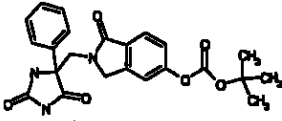
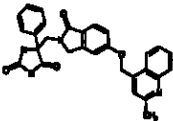
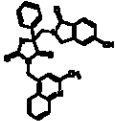
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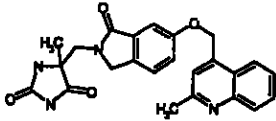
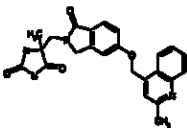
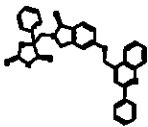
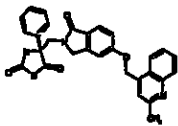
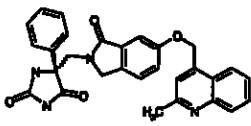
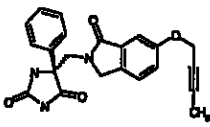
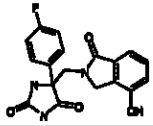
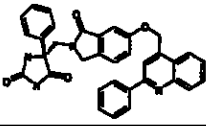
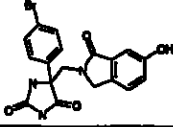
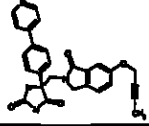












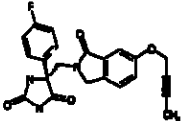
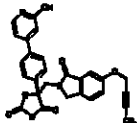
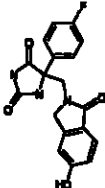
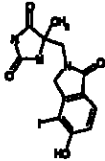
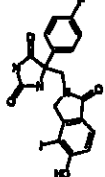
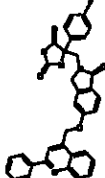
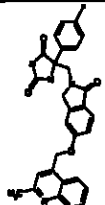
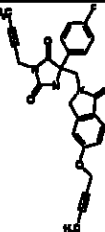
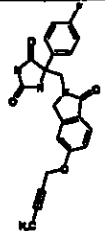
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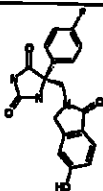
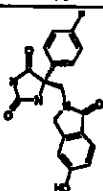
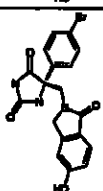
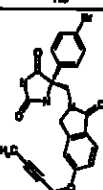
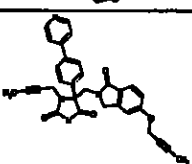
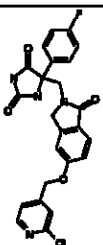
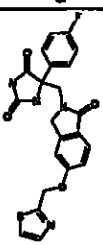
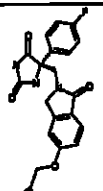
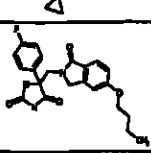











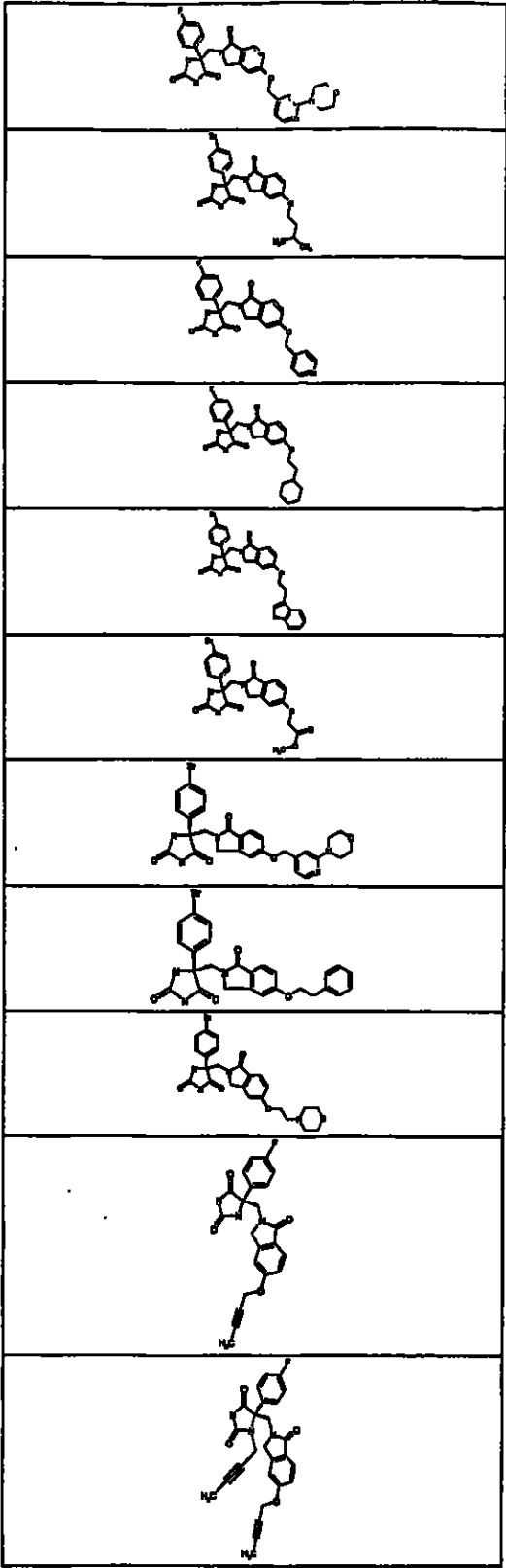
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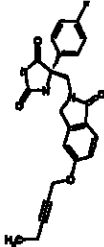
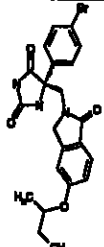
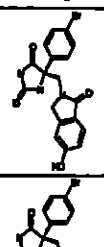
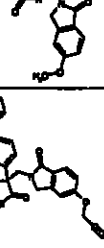
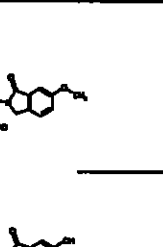
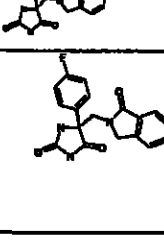
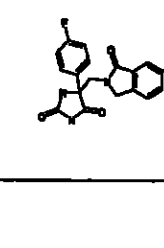
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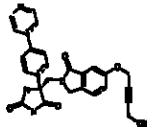
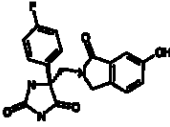
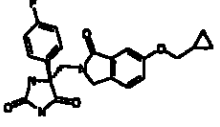
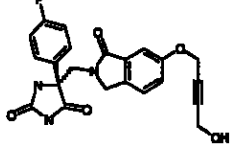
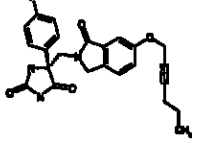
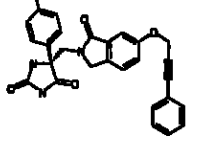
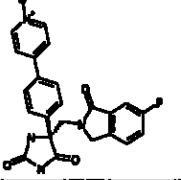
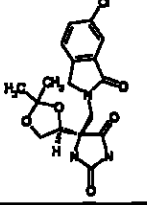










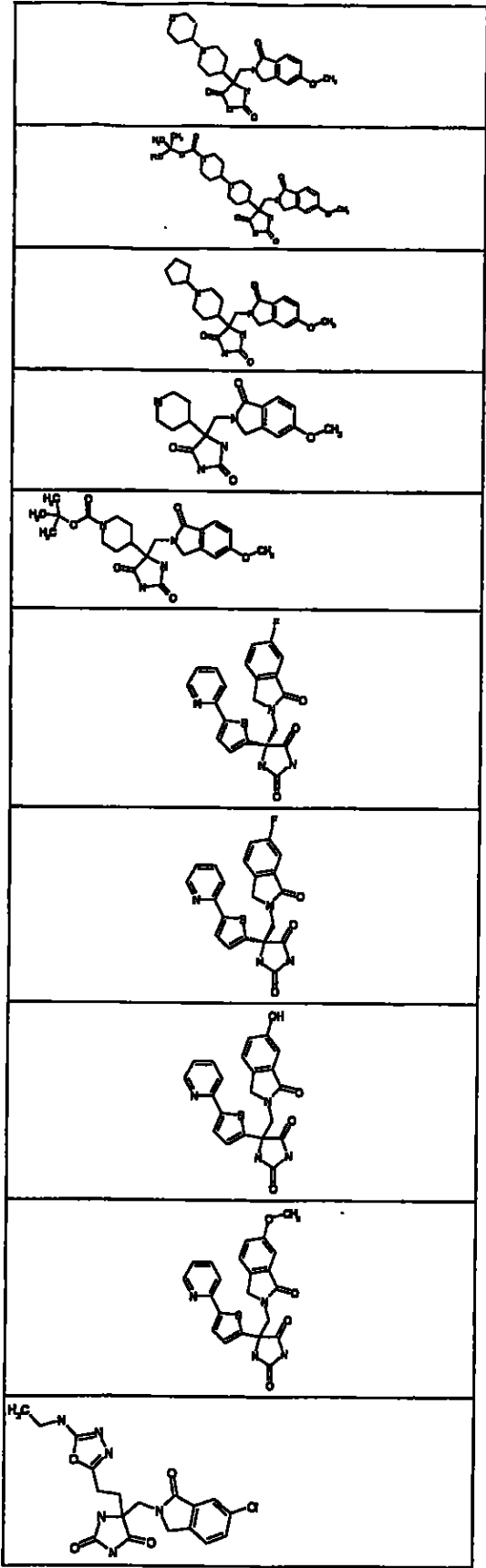


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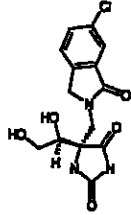
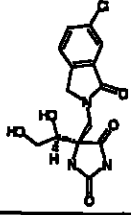
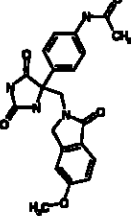
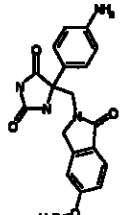
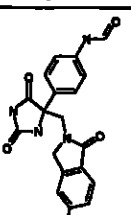
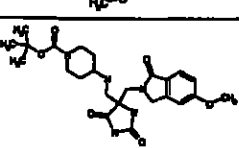
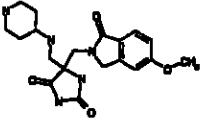
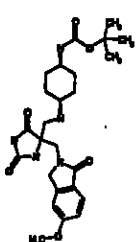
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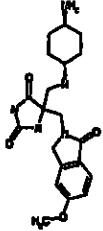
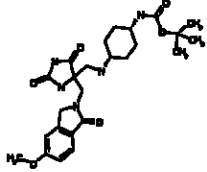
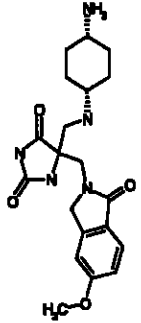
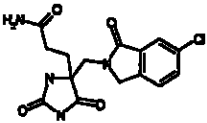
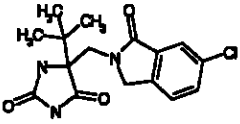
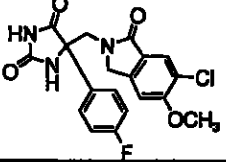
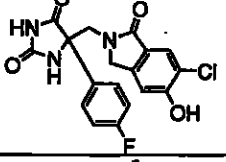
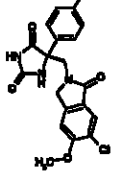











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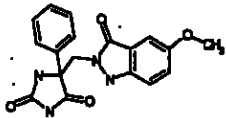
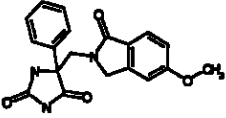
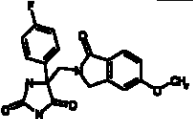
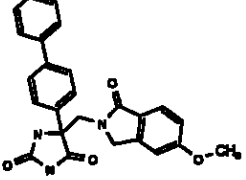
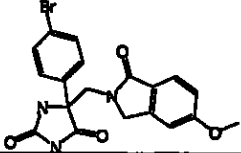
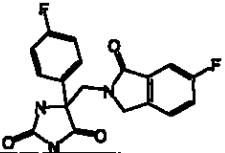
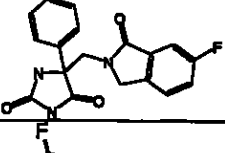
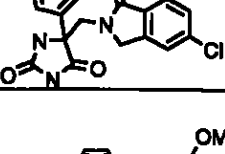
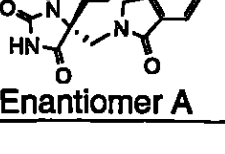
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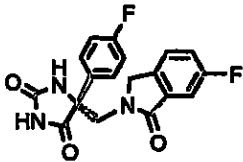
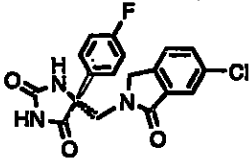
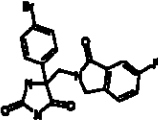
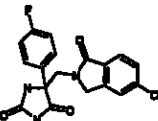
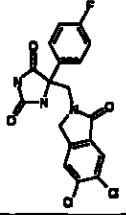
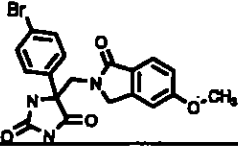
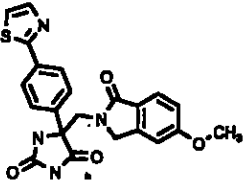
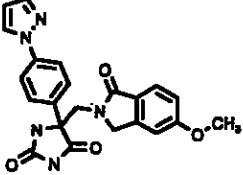









Another embodiment of the invention discloses the preferred compounds shown in Table B below:

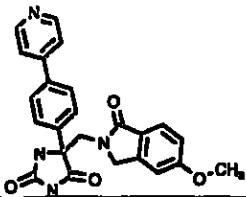
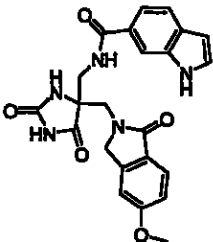
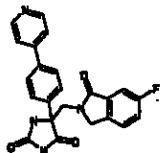
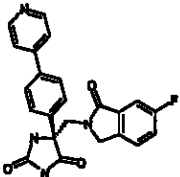
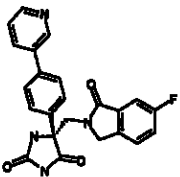
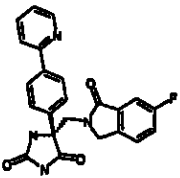
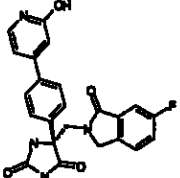
Table B

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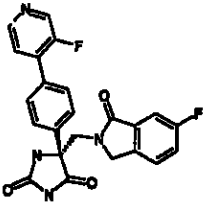
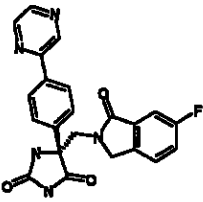
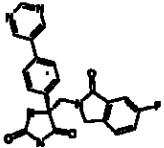
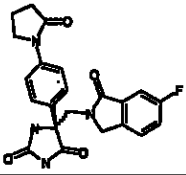
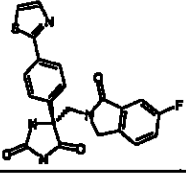
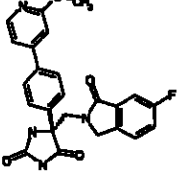
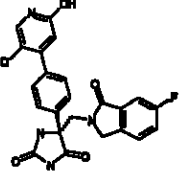
Structure









Enantiomer A

 Enantiomer B
 Enantiomer B







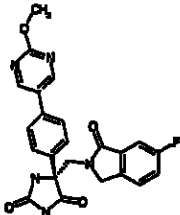
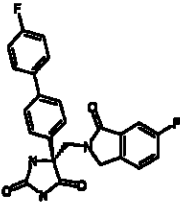
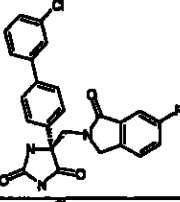
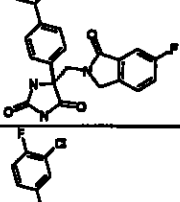
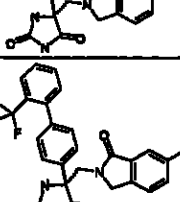
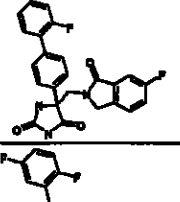
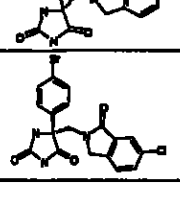
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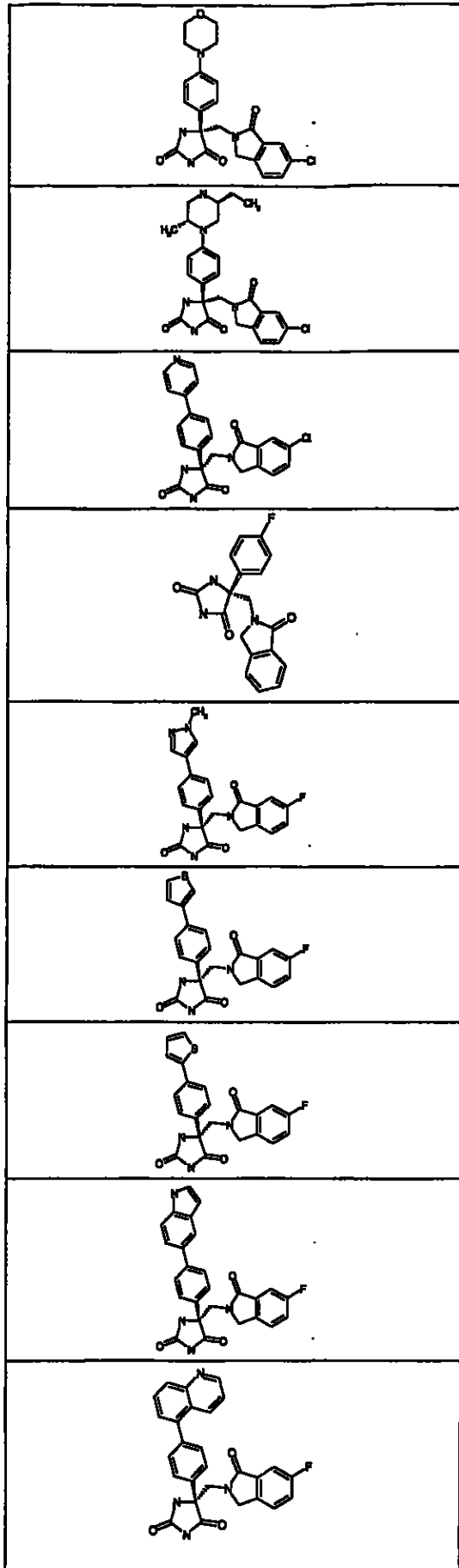








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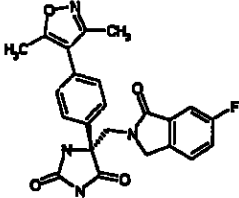
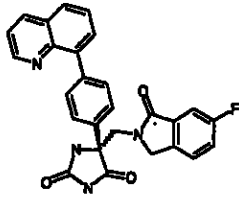
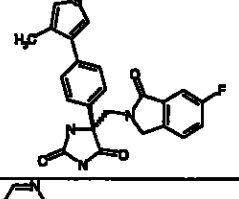
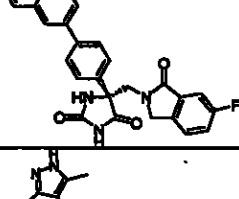
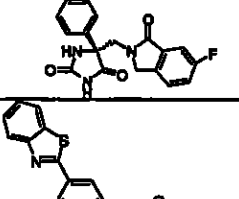
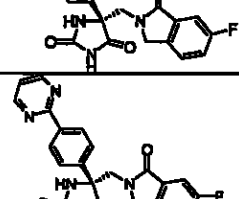
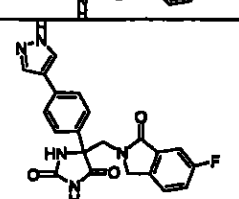
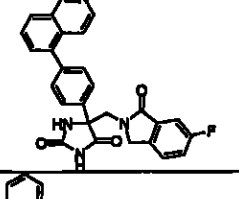
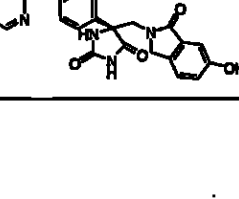










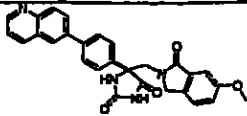
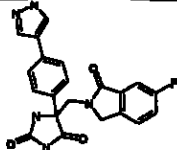
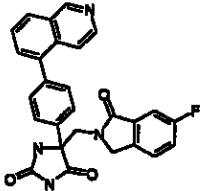
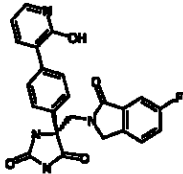
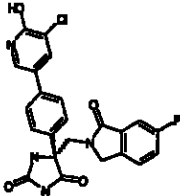
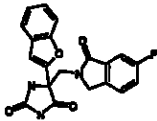
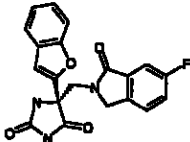
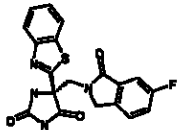
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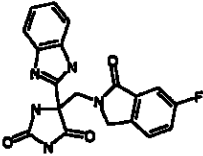
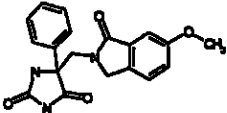
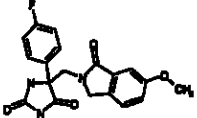
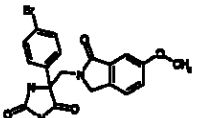
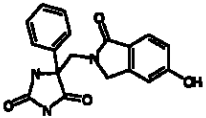
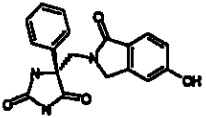
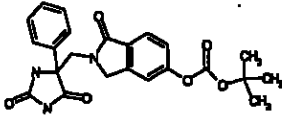
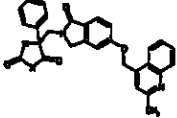
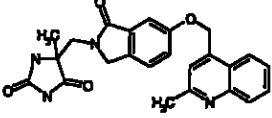
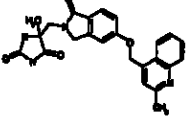
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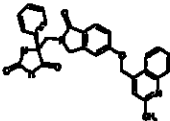
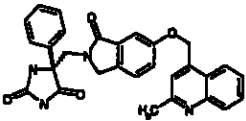
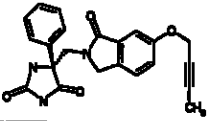
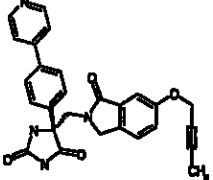
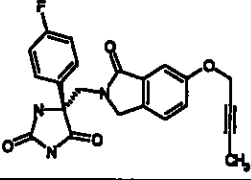
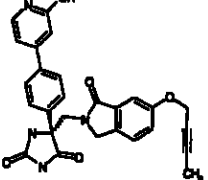
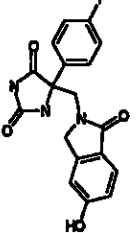
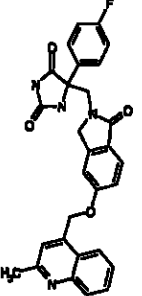
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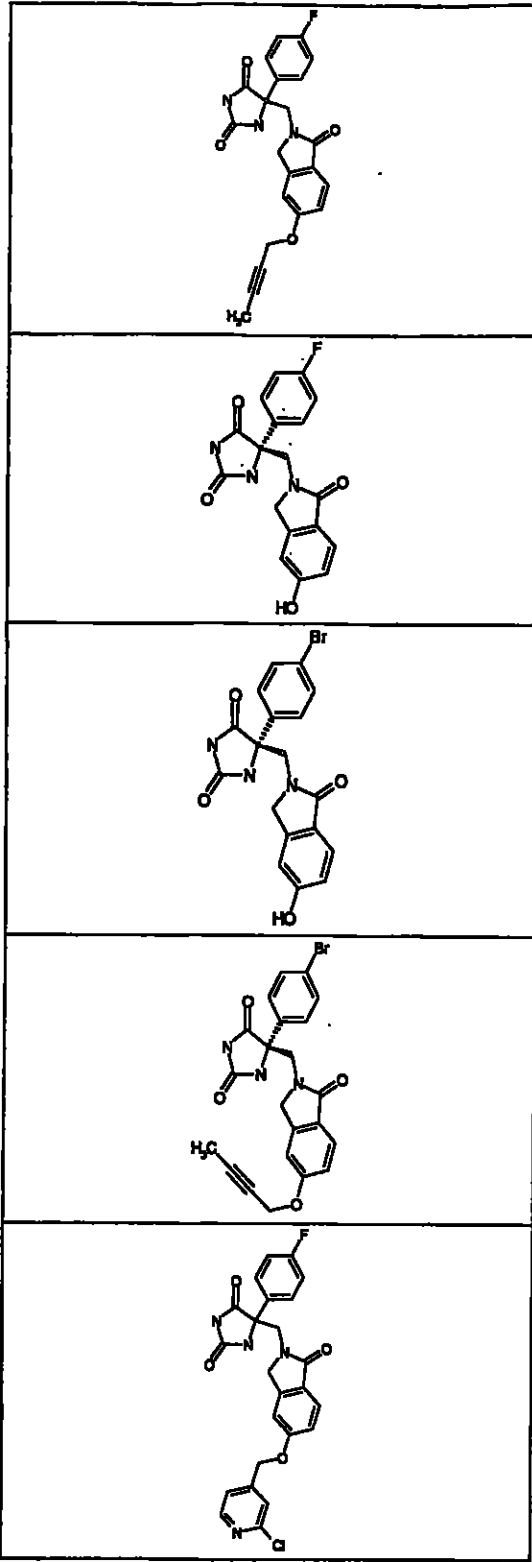
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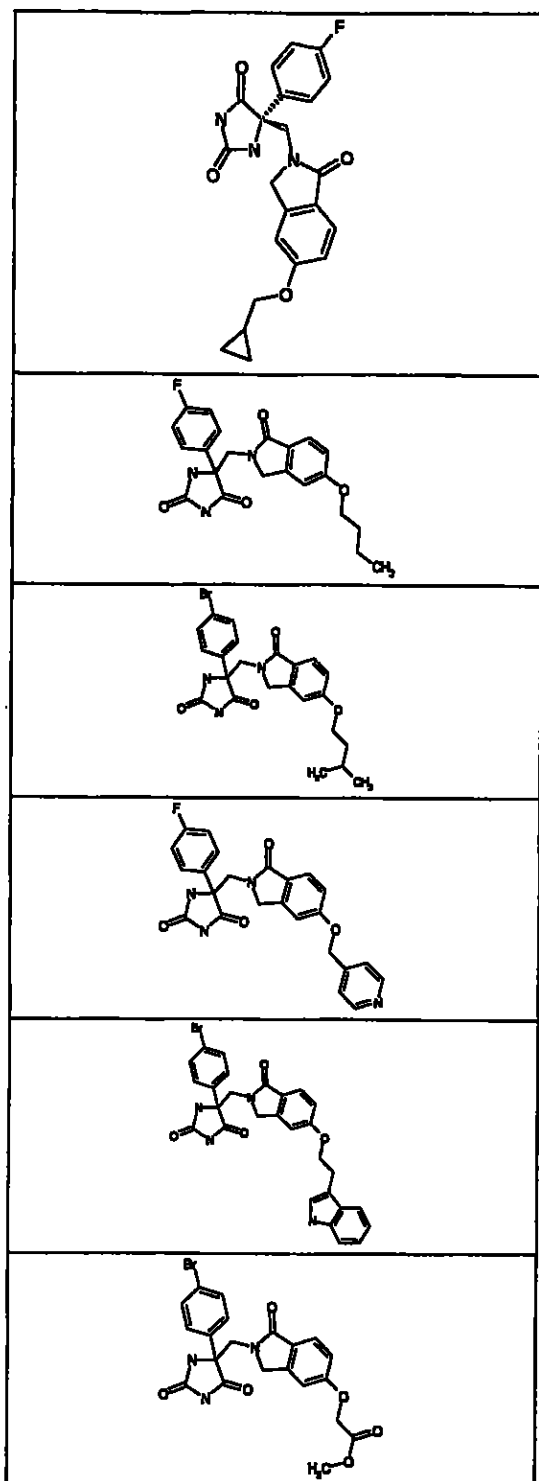
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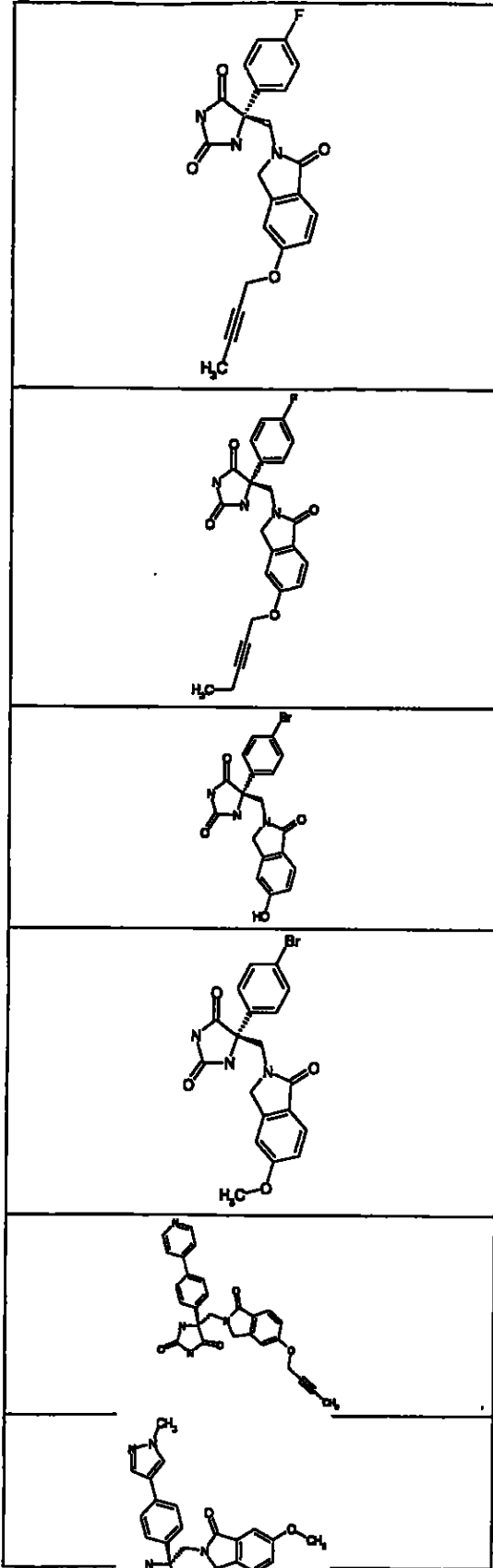
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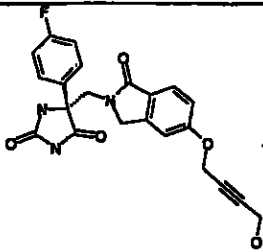
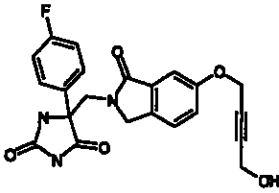
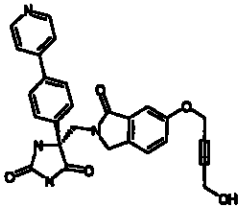
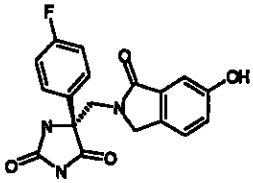
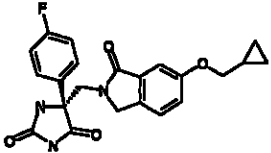
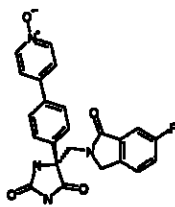
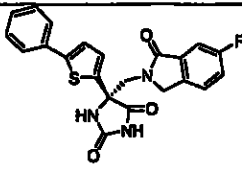
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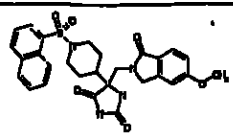
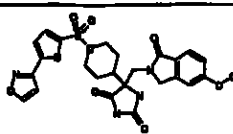
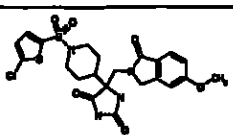
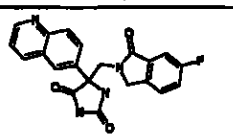
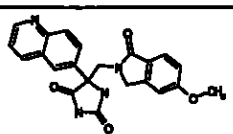
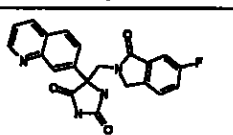
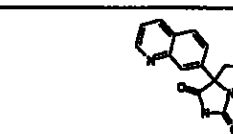
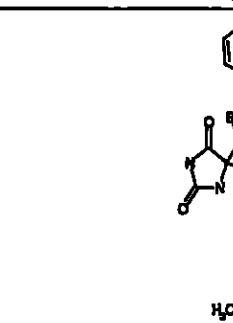
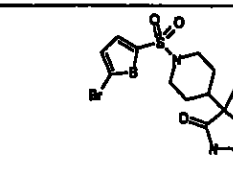
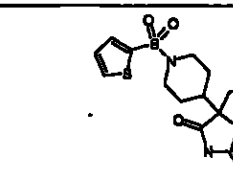
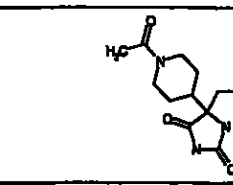
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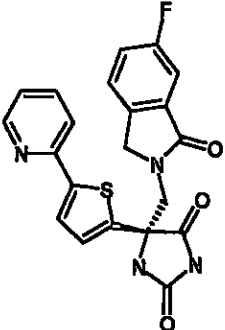
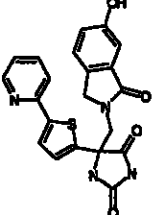
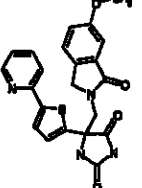
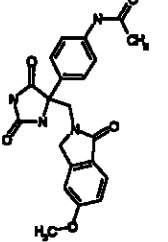
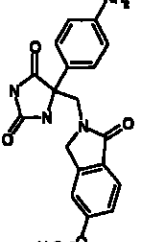
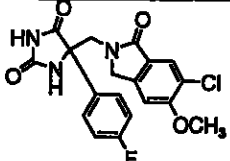
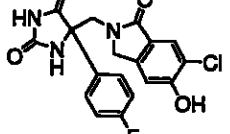
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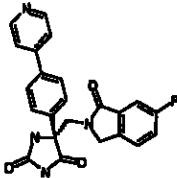
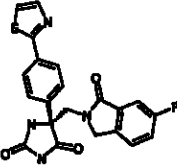
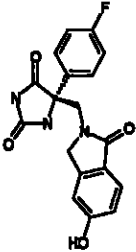
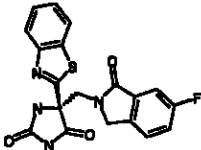
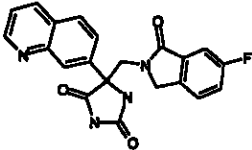
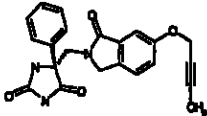
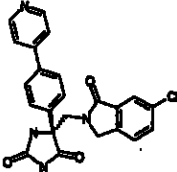
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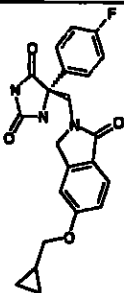
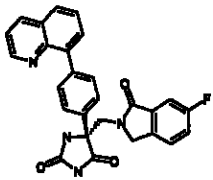
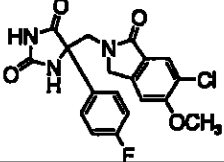
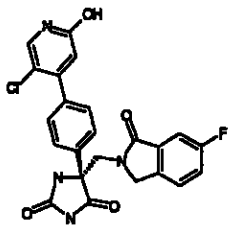
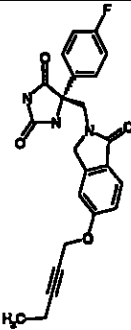
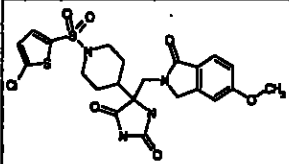
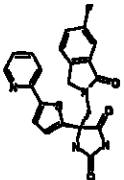
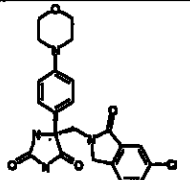
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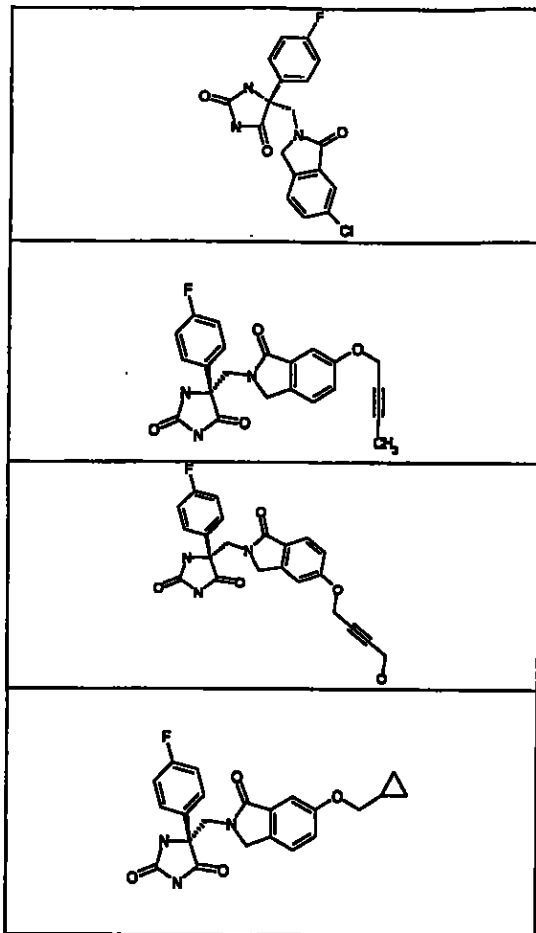








Another embodiment of the invention discloses the more preferred compounds shown in **Table C** below.

Structure








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As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl),

-NH(cycloalkyl), -N(alkyl)₂, carboxy and -C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butyne and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring

atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxaliny, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinoliny, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinoliny, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

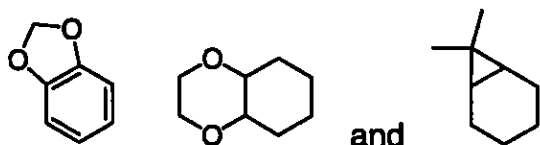
"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include

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cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

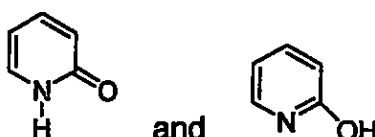
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, G_1G_2N- , $G_1G_2N-alkyl-$, $G_1G_2NC(O)-$, $G_1G_2NSO_2-$ and $-SO_2NG_1G_2$, wherein G_1 and G_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, $-C(CH_3)_2-$ and the like which form moieties such as, for example:



"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to

about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any -NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

It should be noted that tautomeric forms such as, for example, the moieties:



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent

moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

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"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-S(O₂)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O₂)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any carbon as well as heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is

assumed to have the sufficient number of hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R², etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula I or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates,

methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H₂O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting TACE, the production of TNF- α , MMPs, ADAMS or any combination thereof and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula I can form salts which are also within the scope of this invention. Reference to a compound of Formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula I contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula I may be formed, for example, by reacting a compound of Formula I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977)

66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Compounds of Formula I, and salts, solvates and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as

racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula I can be inhibitors of TACE, TNF- α and/or MMP activity.

In one aspect, the invention provides a pharmaceutical composition comprising as an active ingredient at least one compound of formula 1.

In another aspect, the invention provides a pharmaceutical composition of formula 1 additionally comprising at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a method of treating disorders associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of formula 1.

In another aspect, the invention provides a use of a compound of formula 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof.

The compounds of Formula I can have anti-inflammatory activity and/or immunomodulatory activity and can be useful in the treatment of diseases including but not limited to septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, OA and

RA, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behçet's disease, Sjögren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing alveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and/or bronchitis. It is contemplated that a compound of this invention may be useful in treating one or more of the diseases listed.

In another aspect, the invention provides a method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of formula 1 and at least one pharmaceutically acceptable carrier.

In another aspect, the invention provides a compound of formula (I) exhibiting TACE, TNF- α , MMPs, ADAMs or any combination thereof inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed in Table A set forth above.

In another aspect, the invention provides a pharmaceutical composition for treating disorders associated with TACE, TNF- α , MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a compound of formula 1 in purified form.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF- α , aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome,

radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

In another aspect, the invention provides a method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

Additionally, a compound of the present invention may be co-administered or used in combination with disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, azathioprine, leflunomide, pencillinamine, gold salts, mycophenolate mofetil, cyclophosphamide and other similar drugs. They may also be co-administered with or used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) such as

piroxicam, naproxen, indomethacin, ibuprofen and the like; cyclooxygenase-2 selective (COX-2) inhibitors such as Vioxx® and Celebrex®; immunosuppressives such as steroids, cyclosporin, Tacrolimus, rapamycin and the like; biological response modifiers (BRMs) such as Enbrel®, Remicade®, IL-1 antagonists, anti-CD40, anti-CD28, IL-10, anti-adhesion molecules and the like; and other anti-inflammatory agents such as p38 kinase inhibitors, PDE4 inhibitors, other chemically different TACE inhibitors, chemokine receptor antagonists, Thalidomide and other small molecule inhibitors of pro-inflammatory cytokine production.

Also, a compound of the present invention may be co-administered or used in combination with an H1 antagonist for the treatment of seasonal allergic rhinitis and/or asthma. Suitable H1 antagonists may be, for example, Claritin®, Clarinex®, Allegra®, or Zyrtec®.

In another aspect, the invention provides a method of treating a condition or disease mediated by TACE, MMPs, TNF- α , aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of formula 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDS), NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1

inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists:

In another aspect, the invention provides a method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, ureitis, Wegener's granulomatosis, Behçet's disease, Sjögren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof in combination with a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDS, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

In another aspect, the invention provides a method for treating RA comprising administering a compound of the formula I in combination with compound selected from the class consisting of a COX-2 inhibitor e.g.

Celebrex® or Vioxx®; a COX-1 inhibitor e.g. Feldene®; an immunosuppressive e.g. methotrexate or cyclosporin; a steroid e.g. β -methasone; and anti-TNF- α compound, e.g. Enbrel® or Remicade®; a PDE IV inhibitor, or other classes of compounds indicated for the treatment of RA.

In another aspect, the invention provides a method for treating multiple sclerosis comprising administering a compound of the formula I in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

TACE activity is determined by a kinetic assay measuring the rate of increase in fluorescent intensity generated by TACE catalyzed cleavage of an internally quenched peptide substrate (SPDL-3). The purified catalytic domain of recombinant human TACE (rhTACEc, Residue 215 to 477 with two mutation (S266A and N452Q) and a 6xHis tail) is used in the assay. It is purified from the baculovirus/Hi5 cells expression system using affinity chromatography. The substrate SPDL-3 is an internally quenched peptide (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-NH₂), with its sequence derived from the pro-TNF α cleavage site. MCA is (7-Methoxycoumarin-4-yl)acetyl. Dpa is N-3-(2,4-Dinitrophenyl)-L-2,3-diaminopropionyl.

A 50 μ l assay mixture contains 20 mM HEPES, pH 7.3, 5 mM CaCl₂, 100 μ M ZnCl₂, 2 % DMSO, 0.04% Methylcellulose, 30 μ M SPDL-3, 70 pM rhTACEc and a test compound. RhTACEc is pre-incubated with the testing compound for 90 min. at 25 °C. Reaction is started by addition of the substrate. The fluorescent intensity (excitation at 320 nm, emission at 405 nm) was measured every 45 seconds for 30 min. using a fluorospectrometer (GEMINI XS, Molecular Devices). Rate of enzymatic reaction is shown as Units per second. Effect of a test compound is shown as % of TACE activity in the absence of the compound.

Useful compounds for TACE inhibitory activity can exhibit K_i values of less than about 1000 nm, preferably about 0.01 nm to about 1000 nm, more preferably about 0.1 nm to about 100 nm, and most preferably less than about 15 nm. The TACE inhibitory activity (K_i values) of some representative

compounds of the present invention are listed in the "EXAMPLES" section hereinbelow.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the technique described in the U.S. Pat. Nos. 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for controlled release.

The term pharmaceutical composition is also intended to encompass both the bulk composition and individual dosage units comprised of more than one (e.g., two) pharmaceutically active agents such as, for example, a compound of the present invention and an additional agent selected from the lists of the additional agents described herein, along with any pharmaceutically inactive excipients. The bulk composition and each individual dosage unit can contain fixed amounts of the afore-said "more than one pharmaceutically active agents". The bulk composition is material that has not yet been formed into individual dosage units. An illustrative dosage

unit is an oral dosage unit such as tablets, pills and the like. Similarly, the herein-described method of treating a patient by administering a pharmaceutical composition of the present invention is also intended to encompass the administration of the afore-said bulk composition and individual dosage units.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredients is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatin capsules where in the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active material in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example, ethyl or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose, saccharin or aspartame.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example, arachis oil, olive oil, sesame oil or coconut oil, or in mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example, beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring

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agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of an oil-in-water emulsion. The oily phase may be a vegetable oil, e.g., olive oil or arachis oil, or a mineral oil, e.g., liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring phosphatides, e.g., soy beans, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example, sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, e.g., polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, e.g., as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be

employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. The compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds for the present invention can be administered in the intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen. Compounds of the present invention may also be delivered as a suppository employing bases such as cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, mixtures of polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

The dosage regimen utilizing the compounds of the present invention is selected in accordance with a variety of factors including type, species, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound thereof employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter, arrest or reverse the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug. Preferably, doses of the compound of Formula I useful in the method of the

present invention range from 0.01 to 1000 mg per day. More preferably, dosages range from 0.1 to 1000 mg/day. Most preferably, dosages range from 0.1 to 500 mg/day. For oral administration, the compositions are preferably provided in the form of tablets containing 0.01 to 1000 milligrams of the active ingredient, particularly 0.01, 0.05, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 15.0, 25.0, 50.0, 100 and 500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. An effective amount of the drug is ordinarily supplied at a dosage level of from about 0.0002 mg/kg to about 50 mg/kg of body weight per day. The range is more particularly from about 0.001 mg/kg to 1 mg/kg of body weight per day.

Advantageously, the active agent of the present invention may be administered in a single daily dose, or the total daily dosage may be administered in dividend doses of two, three or four time daily.

The amount of active ingredient that may be combined with the carrier materials to produce single dosage form will vary depending upon the host treated and the particular mode of administration.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route or administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

The compounds of the invention may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below.

EXAMPLES

The following abbreviations are used in the procedures and schemes:

ACN	Acetonitrile
AcOH	Acetic acid
Aq	Aqueous
BOC	tert-Butoxycarbonyl
BOC-ON	[2-(tert-butoxycarbonyloxyimino)-2-phenylacetonitril]
BOC ₂ O	BOC Anhydride

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C	degrees Celsius
CBZCl	Benzyl chloroformate
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
(DHQ)2PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIAD	Diisopropylazodicarboxylate
DIPEA	Diisopropylethylamine
DMA	N,N-Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	N,N-Dimethylformamide dimethylacetal
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1h)-pyrimidinone
DMSO	Dimethyl sulfoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron ionization
Eq	Equivalents
EtOAc	Ethyl acetate
EtOH	Ethanol
g	grams
h.	hours
¹ H	proton
HATU	N,N,N',N'-Tetramethyl-O-(7-Azabenzotriazol-1-yl)Uronium hexafluorophosphate
Hex	hexanes
HOBT	1-Hydroxybenzotriazole
HPLC	High pressure liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
M	Molar
mmol	millimolar
mCPBA	<i>meta</i> -Chloroperoxybenzoic acid



Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
mg	Milligrams
MHZ	Megahertz
mL	Milliliter
MPLC	Medium Pressure Liquid Chromatography
NMR	Nuclear Magnetic Resonance
MS	Mass Spectroscopy
NBS	N-Bromosuccinimide
NMM	N-Methylmorpholine
NMP	1-methyl-2-pyrrolidone
ON	Overnight
PCC	Pyridinium Chlorochromate
PTLC	Preparative thin layer chromatography
PyBrOP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
Pyr	Pyridine
RT	Room temperature
sgc	Silica gel 60 chromatography
tBOC	tert-Butoxycarbonyl
TACE	TNF-alpha converting enzyme
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography



NMR spectra were acquired on the following instruments: 400 MHZ NMR (Bruker), 500 MHZ NMR (Bruker), 400 MHz NMR (Varian), 300 MHZ NMR (Varian) using CD₃OD, CDCl₃ or DMSO-d₆ as solvents. LC-MS data were obtained using a PEsCiex API 150EX quadropole mass spectrometer using electrospray ionization.

Purification via reverse phase chromatography (Gilson) was accomplished using a C18 reverse phase column with a gradient of (0.1 %

formic acid) 5:95 to 90:10 acetonitrile:water, at a flow rate of 14 mL/min.

Samples were collected using UV detection. Alternatively an ISCO Companion with (0.1% formic acid) 5:95 to 95:5 acetonitrile:water, at a flow rate = 10 - 55 mL/min.

Normal phase silica gel chromatography was either accomplished on a Biotage instrument using a 60 Å 12/M, 25/M, or 40/M flash cartridges, or on a Jones Flash Master Personal instrument using Isolute flash SI 5g, 10g, 20g, 50g, or 70 g cartridges.

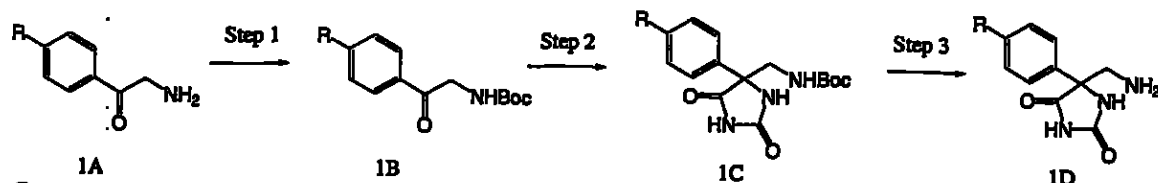
The compounds of formula (I) may be produced by processes known to those skilled in the art and as shown in the following reaction schemes and in the preparations and examples described below. These preparations and examples should not be construed to limit the scope of the disclosure.

Alternate mechanistic pathways and analogous structures may be apparent to those skilled in the art. Some of the compounds made by these processes are listed in the tables below. All kinds of isomeric forms of the compounds are considered to be within the scope of this invention.

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SYNTHETIC ROUTES AND EXAMPLES

Example 1



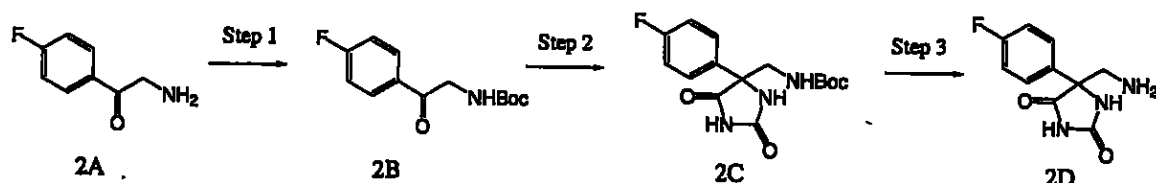
General procedures for Example 1:

In step 1, Compound 1A (either commercially available, or prepared by a procedure similar to that described by Abdalla, G. M. and Sowell, J. W. *Journal of Heterocyclic Chemistry*, 1987, 24(2), 297-301) was treated with one equivalent of Di-tert-butyl dicarbonate in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and compound 1B could be used without further purification or purified by silica gel chromatography.

In step 2, compound 1B was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to 90 °C, for 5 hours to 48 hours. After cooling down, water was added and compound 1C could be collected by filtration.

In step 3, compound 1C was stirred with 2 to 20. equivalents of hydrogen chloride in methanol for 5 to 48 hours. After ethyl ether was added, compound 1D could be collected by filtration.

Example 2



Step 1

Compound 2A (Abdalla, G. M. and Sowell, J. W. *Journal of Heterocyclic Chemistry*, 1987, 24(2), 297-301) (Hydrochloride salt, 8.60g, 45.4 mmol), triethyl amine (19.0 mL, 136 mmol), and di-tert-butyl dicarbonate (11.9g, 54.4 mmol) were stirred in methylene chloride (100 mL) at 25 °C for 16 hours.

Saturated aqueous NaHCO_3 (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (100 mL) twice. The organic phase was washed with brine (100 mL) and dried over Na_2SO_4 . The solvent was removed by rotary evaporator to give compound **2B** which was used without further purification.

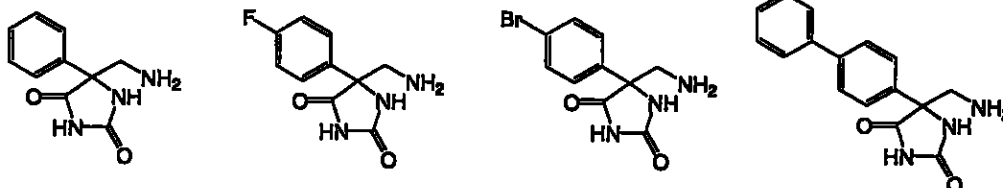
Step 2

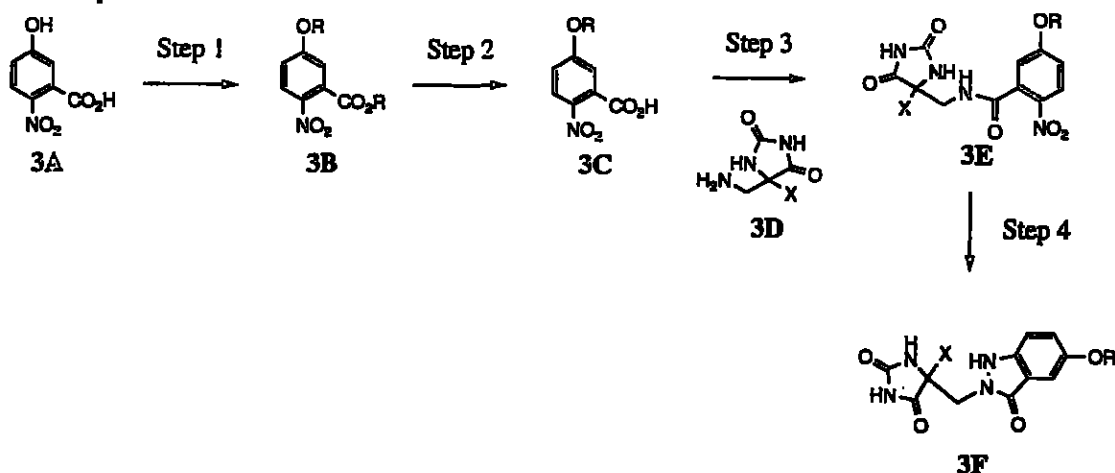
Compound **2B** (9.06g, 35.8 mmol), KCN (3.49g, 53.7 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (12.0 g, 125.2 mmol) were suspended in a mixture of EtOH (35 mL) and water (35 mL). The solution was stirred at 70 °C for three days. After cooling down, water (35 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum at 40 °C for 16 hours to give compound **2C** (7.9 g, 68%).

Step 3

Compound **2C** (4.0 g) was suspended in methanol (50 mL) and HCl (4M in dioxane, 20 mL) was added. The solution was stirred at 25 °C for 3 hours. Ethyl ether (50 ml) was added. The solid was filtered, washed with ethyl ether twice, and dried under vacuum for 12 hours to give compound **2D** (2.7 g, 84%).

The following intermediates were prepared as described in Examples 1 and 2.



Example 3**General procedures for Example 3**

In step 1, 5-Hydroxy-2-nitro-benzoic acid (compound 3A) was dissolved in a suitable solvent, such as DMF, and reacted with an alkyl chloride or alkyl bromide in the presence of cesium carbonate at room temperature for 2 to 16 hours. Water and EtOAc were added. The organic phase was washed by water 1 to 5 times to remove DMF. The organic phase was washed with brine, dried, concentrated to give the crude product (compound 3B) which was used without further purification.

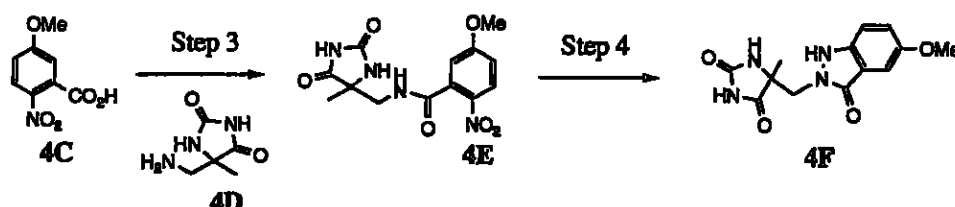
In step 2, compound 3B was dissolved in dioxane/water (3:1) and treated with lithium hydroxide at room temperature for 3 to 6 hours. The solution was made acidic by addition of 1N HCl solution and extracted with EtOAc. The products (compound 3C) were either used without further purification or purified by chromatography depending on the boiling point of the alcohol side products.

In step 3, compound 3C was dissolved in a suitable solvent, such as DMF, and coupled with compound 3D using EDCI and HOBT at room temperature overnight. After an aqueous/EtOAc work up, the product (compound 3E) was isolated by chromatography.

In step 4, compound 3E was suspended in MeOH/water (1:1) under N₂ atmosphere. NaOH and Zinc powder were added and the reaction mixture

was stirred at 70 °C to 80 °C for 8 to 24 hours. After cooling to room temperature, the solution was adjusted to pH=6~7 with 1N HCl solution. The product (compound 3F) was extracted with EtOAc and purified by reverse phase HPLC.

Example 4

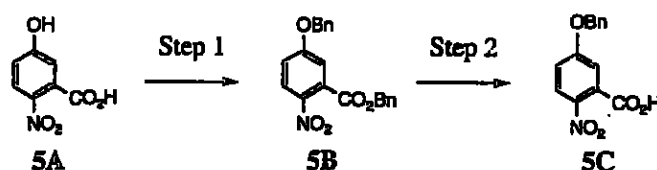


Step 3

A 25 mL flask was charged with compound 4C (331 mg, 1.68 mmol), compound 4D (Stratford, E. S. and Curley, R. W. Jr, *J. Med. Chem.* 1983, 26, 1463-1469) (200 mg, 1.4 mmol), EDCI (403 mg, 2.1 mmol), HOBT (227 mg, 1.68 mmol), NMM (0.46 mL, 4.2 mmol), and DMF (7 mL). The solution was stirred at room temperature overnight. Saturated aqueous NaHCO₃ (30 mL) and EtOAc (50 mL) were added. The organic phase was separated and washed with water (20 mL) and brine (20 mL), then dried over Na₂SO₄. The solvent was evaporated and the crude product was isolated by silica gel chromatography (CH₂Cl₂/MeOH/NH₄OH 20:1:0.1 to 10:1:0.1) to give compound 4E (201 mg, 45%).

Step 4

To a 10 mL flask was added compound 4E (50 mg, 0.155 mmol), NaOH (25 mg, 0.62 mmol), Zinc powder (62 mg, 0.47 mmol), MeOH (0.5 mL), and water (0.5 mL). The solution was stirred at 75 °C for 16 hours. After cooling to room temperature, solid was removed by filtration. The filtrate was adjusted to pH=5 by adding 2N HCl. The aqueous phase was extracted by EtOAc (10 mL). The organic solution was dried over Na₂SO₄ and concentrated. The product was isolated by silica gel chromatography (CH₂Cl₂/MeOH/NH₄OH, 40:1:0.1 to 20:1:0.1 to 10:1:0.1) to give compound 4F 6.5 mg (14%).

Example 5**Step 1**

Compound 5A (1.33 g, 7.26 mmol), benzyl bromide (2.73 g, 16.0 mmol), and Cs_2CO_3 (7.1 g, 22.0 mmol) were mixed in DMF (30 mL) and stirred at room temperature overnight. Saturated aqueous NaHCO_3 (100 mL) was added and the aqueous phase was extracted with EtOAc (100 mL) twice. The combined organic phases were washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated by rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc: 10:1 to 5:1) to give compound 5B (2.25 g, 89%).

Step 2

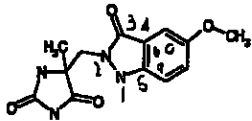
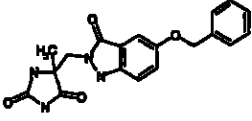
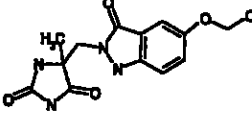
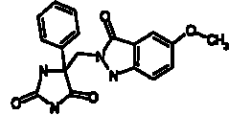
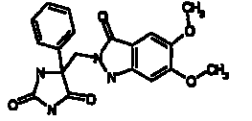
Compound 5B (2.25 g, 6.44 mmol) was dissolved in dioxane/water (3:1, 35 mL) and LiOH (810 mg, 19.3 mmol) was added. The solution was stirred at room temperature for 3 hours. Water (30 mL) was added followed by addition of 2N HCl (30 mL). The aqueous phase was extracted with EtOAc (50 mL) three times. The organic phase was washed with brine, dried over Na_2SO_4 , filtered, and concentrated by rotary evaporator. The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{HCO}_2\text{H}$: 40:1:0.1 to 20:1:0.1) to give compound 5C (1.6 g, 91%).

The following compounds were prepared as described in Examples 3-5.

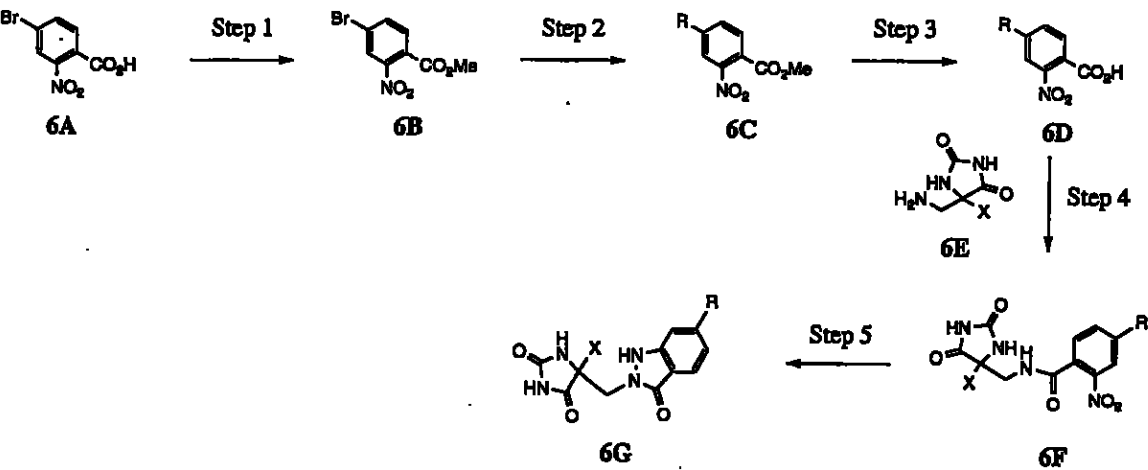
In each of the tables below, those compounds having a KI value of less than 10 nM (<10 nM) are designated with letter "A"; those with a KI value of from 10 to less than 100 nM (10 - <100 nM) are designated with letter "B"; those with a KI value of from 100 to 1000 nM are designated with letter "C"; and those with a KI value of more than 1000 nM (>1000 nM) are designated with letter "D".

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Table 1

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
1		290.27	291.1 [M+H] ⁺	B
2	 <i>4,5-Dioximidazole benzo 3,5-dio methyl</i> <i>benzo[4,5-b]imidazole</i>	366.13	367.1 [M+H] ⁺	C
3		304.12	305.0 [M+H] ⁺	C
4		352.12	353.1 [M+H] ⁺	A
5		382.13	383.1 [M+H] ⁺	B

Example 6



General procedures for Example 6

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In step 1, 4-Bromo-2-nitro-benzoic acid (compound 6A) was dissolved in a suitable solvent, such as DMF, and reacted with methyl iodide in the presence of cesium carbonate at room temperature for 2-16 hours. Water and EtOAc were added and the organic phase was washed by water 1-5 times to remove DMF. The organic phase was washed with brine, dried, concentrated, and dried to give the crude product (compound 6B) which used without further purification.

In step 2, the methyl ester (compound 6B) was mixed with Pd(OAc)₂, Cs₂CO₃, and an appropriate ligand, such as racemic-2-(Di-*t*-butylphosphino)-1,1'-binaphthyl. The mixture was placed under vacuum for 1 to 10 minutes to remove oxygen, and refilled with N₂. An alcohol and toluene were added and the solution was stirred at 50 °C to reflux temperature for 12 to 72 hours. After cooling to room temperature, the solid was removed by filtration and the solvent was removed. The product could be purified by chromatography. During this reaction, the methyl ester may be partially converted to the ester of the alcohol used. This side product was also collected and hydrolyzed in the next step.

In step 3, compound 6C was dissolved in Dioxane/water (3:1) and treated with lithium hydroxide at room temperature for 3-6 hours. The solution was made acidic by addition of 1N HCl solution and subjected to aqueous/EtOAc work up. The products (compound 6D) were either used without further purification or purified by chromatography depending on the boiling point of the alcohol side products.

In step 4, compound 6D was dissolved in a suitable solvent, such as DMF, and coupled with compound 6E under EDCI and HOBt conditions at room temperature overnight. After an aqueous/EtOAc work up, the product (compound 6F) could be isolated by chromatography.

In step 5, compound 6F was suspended in MeOH/water (1:1) under N₂ atmosphere. NaOH and zinc powder were added and the reaction mixture was stirred at 70 °C to 80 °C for 8 to 24 hours. After cooling to room temperature, the solution was adjusted to pH=6~7 with 1N HCl solution. Compound 6G was extracted with EtOAc and isolated by reverse phase HPLC.

Example 7



Step 1

Compound 7A (10.0 g, 40.7 mmol) was dissolved in DMF (100 mL). Cs₂CO₃ (27.0g, 81.3 mmol) and methyl iodide (7.60 mL, 122.0 mmol) were added. The solution was stirred at room temperature overnight. EtOAc (250 mL) and water (100 mL) were added. The organic phase was separated and washed with water (100 mL) three times and brine (50 mL), then dried over Na₂SO₄, filtered, and concentrated using a rotary evaporator. The product was dried under vacuum to give compound 7B (10.3 g, 97%).

Step 2

Pd(OAc)₂ (43 mg, 0.19 mmol), racemic-2-(di-*t*-butylphosphino)-1,1'-binaphthyl (92 mg, 0.23 mmol), and Cs₂CO₃ (1.88 g, 5.76 mmol) were placed in a 50 mL flask. The flask was placed under vacuum for 2 minutes and refilled with N₂. Compound 7B (1.00 g, 3.84 mmol) and MeOH (0.311 mL, 7.69 mmol) were dissolved in toluene (10 mL). The resulting solution was added to the above flask by pipette. The reaction mixture was stirred at 70 °C oil bath for 48 hours. After cooling to room temperature, the solid was filtered and the solvent was removed using a rotary evaporator. The product was isolated by silica gel chromatography (Hexane/EtOAc 20:1 to 10:1) to give compound 7C (380 mg, 47%).

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Step 3

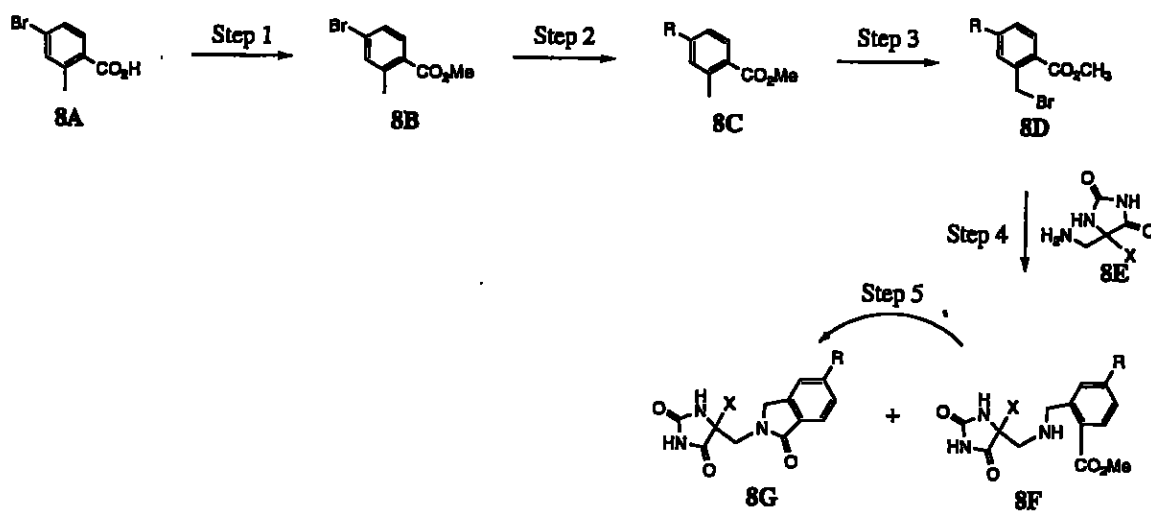
Compound 7C (380 mg, 1.80 mmol) was dissolved in dioxane/water (3:1, 8 mL) and LiOH (378 mg, 9.0 mmol) was added. The solution was stirred at room temperature for 3 hours. Water (5 mL) was added followed by addition of 2N HCl to adjust the pH = 2-4. The aqueous phase was extracted with EtOAc (10 mL) three times. The organic phase was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was dried under vacuum to give compound 7D which was used without further purification.

The following compounds were prepared as described in Examples 6-7

Table 2

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
6		289.11	291.1 [M+H] ⁺	B
7		366.13	367.1 [M+H] ⁺	C

Example 8



General procedure for Example 8

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In step 1, Compound 8A was dissolved in a suitable solvent, such as DMF, and reacted with methyl iodide in the presence of cesium carbonate at room temperature for 2-16 hours. Water and EtOAc were added and the organic phase was washed by water 1-5 times to remove DMF. The organic phase was washed with brine, dried, concentrated, and dried to give the crude product (compound 8B) which was used without further purification.

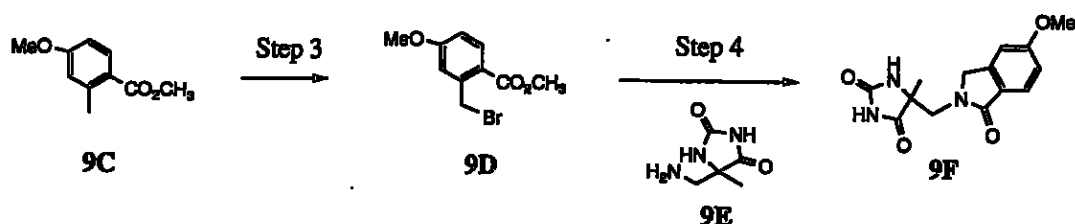
In step 2, when alcohol was used, the reaction was operated in a similar manner as step 2 in example 6. When an aromatic or heterocyclic stannane was used, the reaction was operated in the following manner. The aromatic or heterocyclic stannane was added into a dry flask, followed by addition of the 4-Bromo-2-methyl-benzoic acid methyl ester (compound 8B), a base, such as Cs_2CO_3 , K_3PO_4 , and a palladium catalyst, such as $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. The flask was placed under vacuum for 1 to 10 minutes to remove oxygen and was refilled with N_2 . An appropriate solvent, such as dry CH_3CN , was added and the solution was stirred at 60 °C to reflux temperature overnight to 3 days. The solid was removed by filtration and the solvent was removed. Compound 8C was isolated by chromatography.

In step 3, compound 8C was dissolved in a suitable inert solvent, such as benzene, CCl_4 or α,α,α -Trifluorotoluene. NBS and benzoyl peroxide were added and the solution was stirred at 50 °C to 90 °C for 1 to 24 hours. The solid was filtered and the solvent was removed. The residue was dissolved in ether and washed by water. The ether was removed to afford the compound 8D which was used without further purification.

In step 4, the benzyl bromide (compound 8D) was mixed with hydantoin methyl amine 8E, K_2CO_3 , and DMF. The solution was stirred at room temperature for 12 to 24 hours. Then the solid was removed by filtration. The product could be purified by reverse phase HPLC. Compounds 8F and 8G could be obtained in a variable ratio.

Step 5 is used when the compound 8F was isolated in step 4. Compound 8F was dissolved in an appropriate solvent, such as MeOH, and stirred at 50 °C to reflux temperature for 1 to 12 hours. The product could be obtained by removing the solvent by rotary evaporator or purifying via reverse phase chromatography.

Example 9



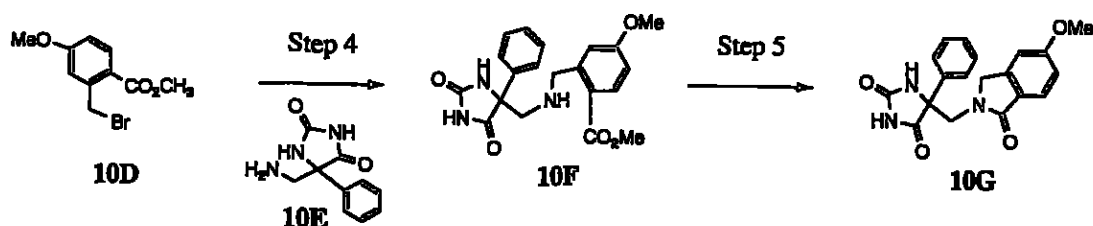
Step 3

Compound 9C (prepared according to the procedure described by Wyrick, S. D. et al. *Journal of Medicinal Chemistry*, 1987, 30(10), 1798-806) (3.33 g, 18.5 mmol) was dissolved in dry benzene (40 mL). NBS (3.45 g, 19.4 mmol) and benzoyl peroxide (134 mg, 0.55 mmol) were added. The solution was stirred in a 75 °C oil bath for about 2 hours. After cooling down, the solid was filtered and washed with Et₂O (150 mL). The organic solution was then washed with water (50 mL) twice, dried over Na₂SO₄ or MgSO₄, filtered, and concentrated by rotary evaporator. The crude product was dried under vacuum to give compound 9D which was used without further purification. ¹H-NMR appeared to indicate that approximately 75% of this material was compound 9D.

Step 4

Compound 9D (4.62 mmol), Compound 9E (824 mg, 4.62 mmol), and K₂CO₃ (1.28 g, 9.24 mmol) were mixed in DMF (30 mL). The solution was stirred at room temperature for 20 hours. DMF (15 mL) was added and the solid was filtered and washed with DMF. All the DMF solution was combined and concentrated to 25 mL. The resulting solution was applied to reverse phase MPLC (CH₃CN/water, 5% to 90%, containing 0.1% HCO₂H) to give compound 9F (198 mg, 15%).

Example 10



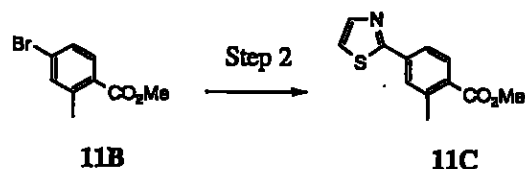
Step 4

Compound **10D** (prepared in example 9) (902 mg, 2.07 mmol, factor = 0.75), Compound **10E** (prepared as described in Example 1, 500 mg, 2.07 mmol), and K₂CO₃ (629 mg, 4.56 mmol) were mixed in DMF (15 mL). The solution was stirred at room temperature for 20 hours. DMF (15 mL) was added and the solid was filtered and washed with DMF. All the DMF solution was combined and concentrated to 20 mL. It was applied to reverse phase MPLC (CH₃CN/water: 5% to 90%, containing 0.1% HCO₂H) to give compound **10F**.

Step 5

Compound 10F (prepared in step 4) was dissolved in MeOH (5 mL), stirred at 65 °C for 5 hours, then concentrated to dryness. The compound was suspended in water and dried with lyophilizer to give compound 10G (68.3 mg, 9.4%).

Example 11



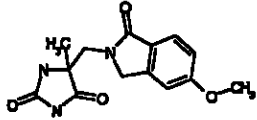
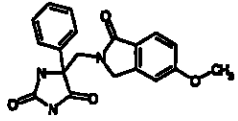
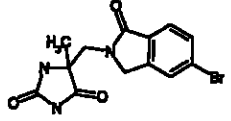
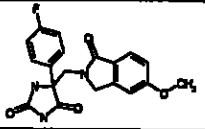
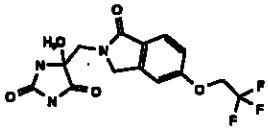
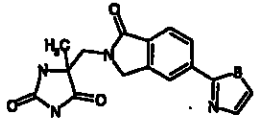
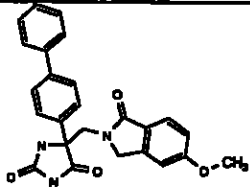
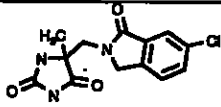
Step 2

Compound **11B** (500 mg, 2.18 mmol), 2-tributylstannylthiazole (0.97 mL, 2.84 mmol), Pd(PPh₃)₂Cl₂, and dry CH₃CN were stirred under nitrogen at reflux temperature overnight. After cooling to room temperature, the solid was filtered. The product was isolated by silica gel chromatography (Hexane/EtOAc: 20:1 to 10:1 to 5:1) to give compound **11C** (480 mg, 94%).

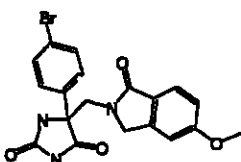
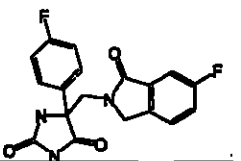
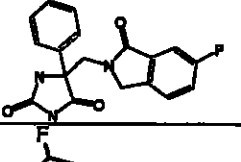
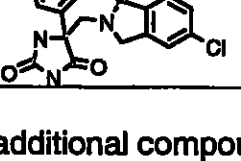
The following compounds were prepared as described in Examples 8-11.

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Table 3

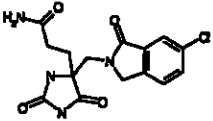
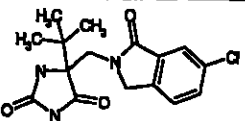
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
8		289.11	290.1 [M+H] ⁺	B
9		351.12	352.1 [M+H] ⁺	A
10		337.01	338 [M+H] ⁺ 340.1	C
11		369.11	370.1 [M+H] ⁺	A
12		357.09	358.1 [M+H] ⁺	B
13		342.08	343.1 [M+H] ⁺	C
14		427.2	428.2 [M+H] ⁺	A
15		293.06	294.1 [M+H] ⁺	B

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16		431.0	432.1 [M+H] ⁺	A
17		357.1	358.1 [M+H] ⁺	A
18		417.0	418.1 [M+H] ⁺	A
19		373.1	374.2 [M+H] ⁺	A

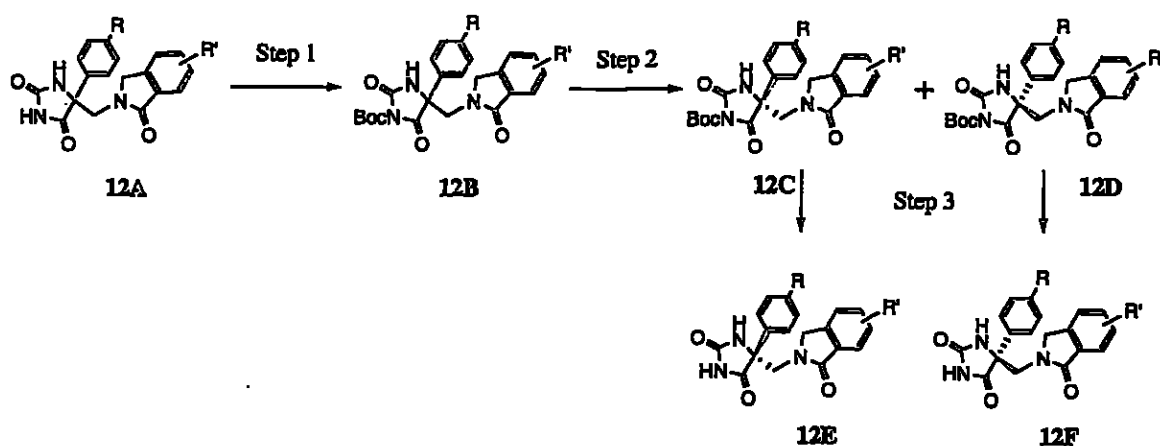
The following additional compounds were prepared as described in Examples 8 to 11.

Table 4

Compound #	Structures	Exact Mass	Mass Obsvd	Ki (nM)
294		350.08	351.1[M+H] ⁺	B
295		335.10	336.1[M+H] ⁺	B

Example 12

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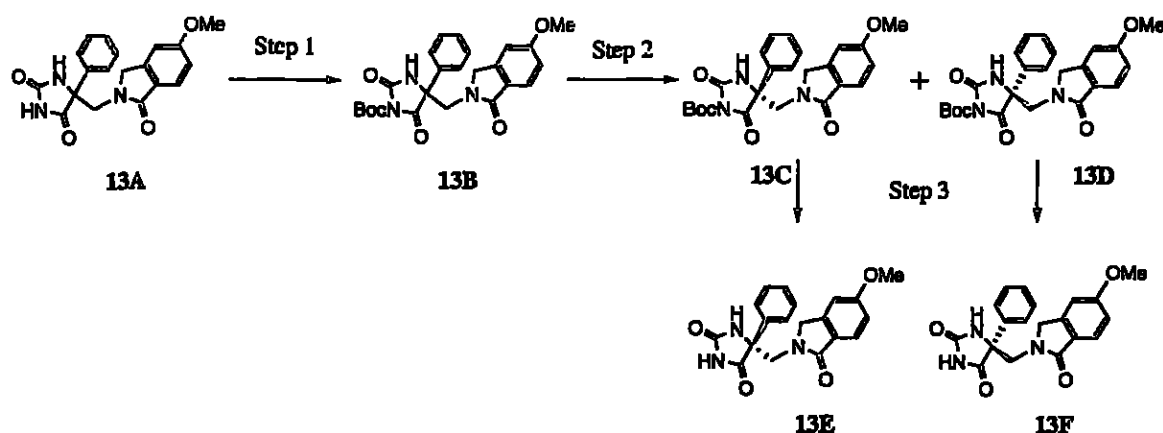


General procedures for Example 12:

In step 1, racemic compound 12A was treated with one equivalent of di-tert-butyl dicarbonate and 4-N,N-dimethylaminopyridine in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and the product (compound 12B) was isolated by silica gel (pretreated with 1% triethylamine in Hexane) chromatography.

In step 2, compound 12B was dissolved in proper solvents allowed by HPLC column, and resolved by HPLC using a preparative Chiralpak AD or Chiralcel OD column to give compound 12C and 12D.

In step 3, compound 12C and 12D were treated with excess HCl in methanol at 25 °C to 60 °C for one hour to 12 hours. The solvent was concentrated to give compound 12E and 12F.

Example 13**Step 1**

Compound **13A** (810 mg, 2.07 mmol), di-tert-butyl dicarbonate (429 mg, 1.97 mmol), and 4-dimethylaminopyridine (20 mg) were dissolved in a mixture of DMF (10 mL) and THF (20 mL). The solution was stirred at 25 °C overnight. Solvents were removed by rotary evaporator. The product was isolated by C18 chromatography (CH₃CN/water: 5% to 90%) to give product **13B** (650 mg, 70%).

Step 2

Compound **13B** (600 mg) was dissolved in a mixture of iso-propanol (6 mL) and CHCl₃ (4 mL). 2.5 mL was separated via HPLC with preparative chiralcel OD column (Mobile phase: iso-propanol/Hexane: 1:4). Fractions for each peak were collected and concentrated by rotary evaporator to give compound **13C** (First peak, 197 mg) and compound **13D** (second peak, 178 mg).

Step 3

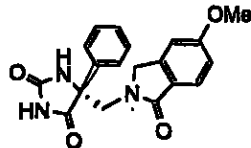
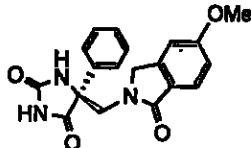
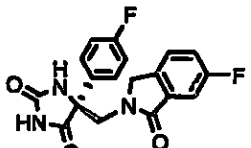
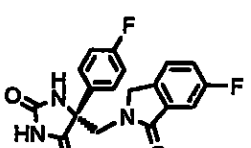
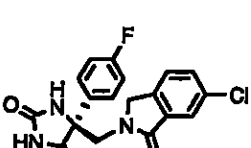
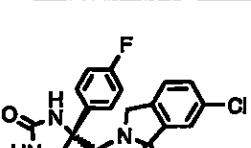
Compound **13C** (197 mg) was dissolved in methanol (3 mL). HCl (4M in Dioxane, 0.5 mL) was added. The solution was stirred in a 60 °C oil bath for three hours. Methanol was removed by rotary evaporator to give compound **13E**.

Compound **13F** was prepared in the same way as compound **13D** (178 mg).

The following compounds were prepared as described in **Examples 12-13**

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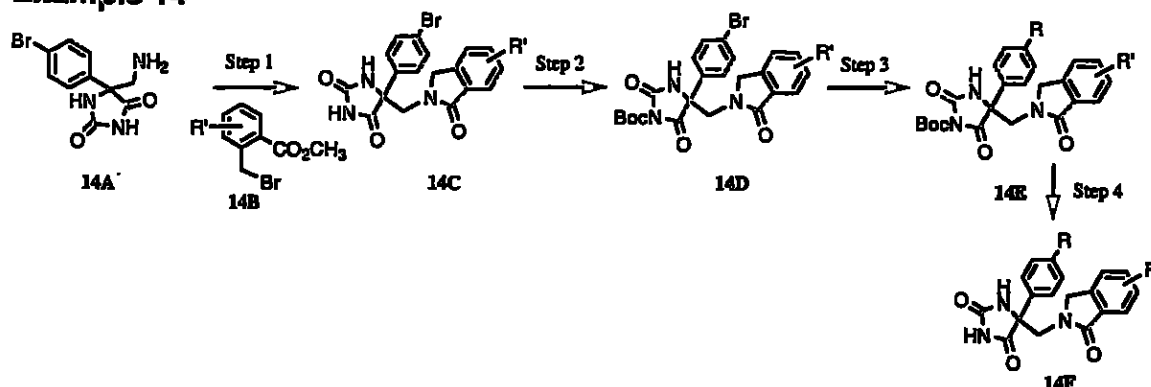
Table 5

Compound #	Structures	Exact Mass	Mass Obsvd	Ki (nM)
20	 Enantiomer A	351.1	352.2 [M+H] ⁺	A
21	 Enantiomer B	351.1	352.2 [M+H] ⁺	C
22	 Enantiomer A	357.1	358.1 [M+H] ⁺	C
23	 Enantiomer B	357.1	358.1 [M+H] ⁺	A
24	 Enantiomer A	373.06	374.2 [M+H]	C
25	 Enantiomer B	373.06	374.2 [M+H]	A

Proton NMR Spectral Data for Selected Compounds in Table 5.

Compound 25. ¹H NMR (500 Hz, DMSO-d₆) δ 4.06 (d, J = 14Hz, 1H), 4.20 (d, J = 14 Hz, 1H), 4.32 (d, J = 18 Hz, 1H), 4.38 (d, J = 18 Hz, 1H), 7.19-7.39 (m, 2H), 7.55-7.80 (m, 5H), 8.93 (s, 1H), 10.96 (s, 1H).

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Example 14**General procedure for Example 14**

In step 1, compound 14A (prepared as described in **Example 1**) was treated with a benzyl bromide (Compound 14B) and DIPEA base in DMF at 25 °C to 60 °C for 12 to 24 hours. The reaction solution was purified via C18 reverse phase chromatography to give compound 14C.

In step 2, compound 14C was treated with one equivalent di-tert-butyl dicarbonate in polar solvent, such as DMF, for 30 minutes to 12 hours. The solvent was removed and the product (compound 14D) was isolated by silica gel (pretreated with 1% triethylamine in Hexane) chromatography.

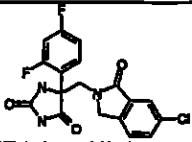
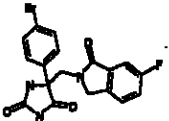
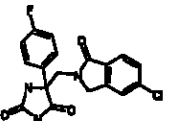
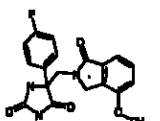
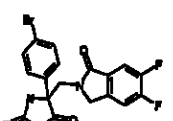
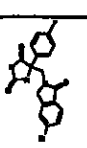
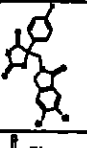
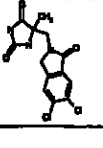
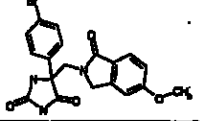
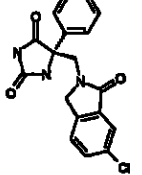
In step 3, compound 14D was subjected to either a Pd catalyzed reaction with a heterocyclic boronic acid or a heterocyclic stannane, or a copper catalyzed reaction with a heterocyclic amine. The reaction were heated in appropriate solvents, such as DMF and acetonitrile, at 60 °C to 150 °C, for 5 minutes to 12 hours. In some cases, a microwave reactor was used. The product was purified by silica gel chromatography to give compound 14E or compound 14F.

In step 4, compound 14E was dissolved in methanol and was stirred with HCl for 1 hour to 12 hours at 25 °C to 60 °C. The solvent was removed to give compound 14F.

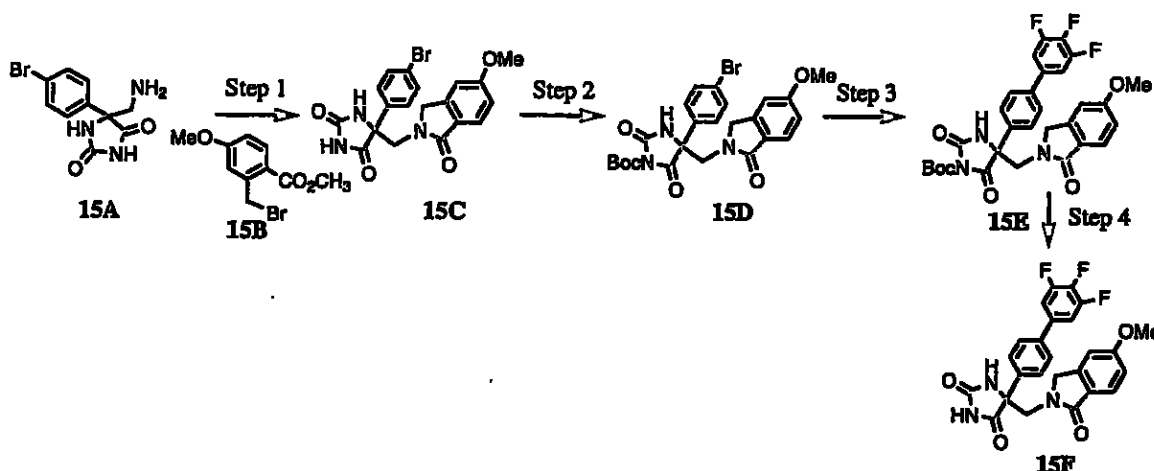
The following compounds were prepared as described in step 1 of **Example 14** above.

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Table 6

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
100		391.05	392.07 [M+H] ⁺	n/a
101		417.01	418.1 [M+H] ⁺	A
102		373.06	374.2 [M+H] ⁺	A
103		369.11	370.1 [M+H] ⁺	D
104		435.00	436.1 [M+H] ⁺	B
105		417.01	418.420 [M+H] ⁺	B
106		407.0	408 [M+H] ⁺	A
107		327.0	328 [M+H] ⁺	B
108		429.03	430.432 [M+H] ⁺	B
109		355.07	378.2 [M+Na] ⁺	B

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Example 15**Step 1**

Compound 15A (prepared as described in Example 1, 1.0 g, 3.12 mmol), Compound 15B (prepared in Example 9, 1.06 g, 3.12 mmol, factor = 0.76), and DIPEA base (1.14 mL, 6.55 mmol) were mixed in DMF (22 mL). The solution was stirred at 55 °C for 20 hours. The reaction solution was purified via C18 reverse phase MPLC (130g column, CH₃CN/water/0.1% HCO₂H, 5% to 90%, two separations) to give compound 15C (900 mg, 67%).

Step 2

Compound 15C (2.7 g, 6.28 mmol) was suspended in a mixture of DMF (20 mL) and THF (40 mL). Di-tert-butyl dicarbonate (1.51 g, 6.91 mmol) and 4-dimethylaminopyridine (38 mg, 0.31 mmol) were added. The solution was stirred at 25 °C for 16 hours. The solvents were removed by rotary evaporator. The residue was subjected to silica gel chromatography (Hexane/EtOAc: 2:1 to 1:1) to give compound 15D (2.36 g, 71%).

Step 3

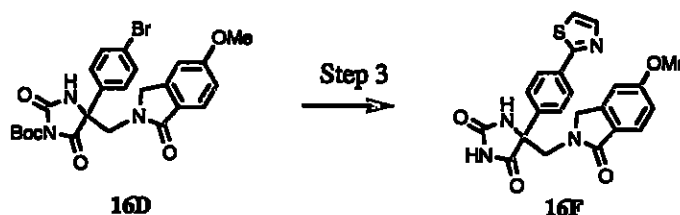
Compound 15D (100 mg, 0.19 mmol), 3,4,5-trifluorophenyl boronic acid (40 mg, 0.23 mmol), 1,1'-bis(triphenylphosphino)ferrocene palladium (II) chloride (15 mg, 0.02 mmol), potassium carbonate (1M in water, 1 mL) and acetonitrile (1 mL) were added to a microwave reactor tube. The tube was sealed and reacted in the microwave reactor at 150 °C for 10 minutes. After cooling down, the aqueous layer was removed and the organic layer was

concentrated. The crude product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$: 40:1:0.1) to give compound **15E**.

Step 4

Compound **15E** obtained from step 3 was suspended in MeOH. HCl (2M in ethyl ether, 0.5 mL) was added. The reaction mixture was stirred at 50 °C for five hours. The solvent was removed. The product was purified via C18 reverse phase chromatography ($\text{CH}_3\text{CN}/\text{water}/0.1\% \text{HCO}_2\text{H}$, 5% to 90%) to give compound **15F** (8 mg, 8.8% from compound **15D**).

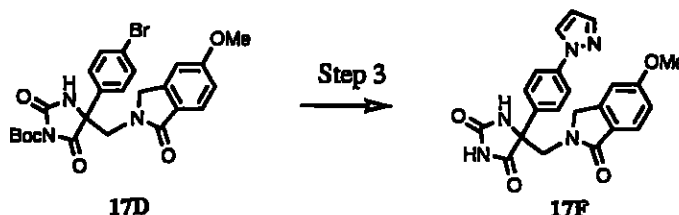
Example 16



Step 3

Compound **16D** (50 mg, 0.094 mmol, prepared in example 13), 2-tributylstannylthiazole (53 mg, 0.14 mmol), dichlorobis(triphenylphosphine) palladium (II) (7 mg, 0.01 mmol), and acetonitrile (1 mL) were added to a microwave reactor tube. The tube was sealed and reacted in a microwave reactor at 150 °C for 10 minutes. The solvent was evaporated and the product was purified by silica gel chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$: 40:1:0.1 to 20:1:0.1) to give compound **16F** (15 mg, 37%).

Example 17



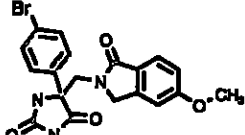
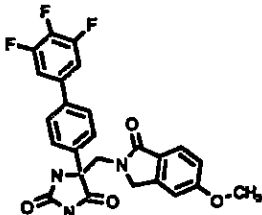
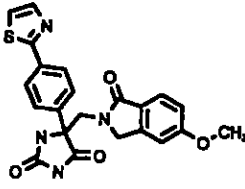
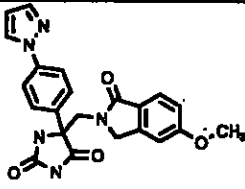
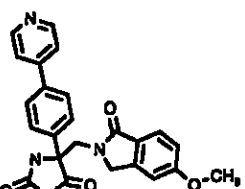
Step 3

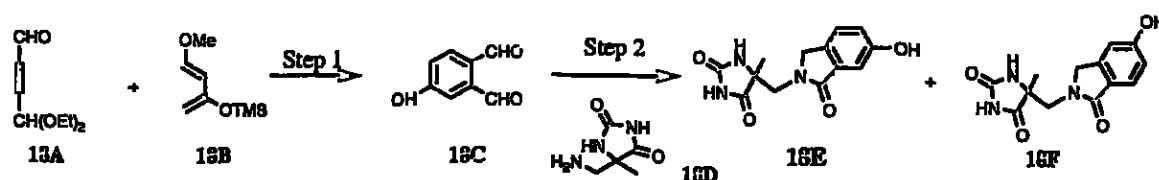
Compound **17D** (100 mg, 0.19 mmol, prepared in example 13), pyrazole (15.4 mg, 0.23 mmol), cesium carbonate (124 mg, 0.38 mmol), copper iodide (7.2 mg, 0.038 mmol), 1,10-phenanthroline (14 mg, 0.076 mmol), and N,N-dimethylacetamide (0.5 mL) were added to a dry reaction tube and filled with

nitrogen. The reaction tube was sealed and heated in a 120 °C oil bath for two days. After cooling down, the reaction solution was purified by C18 chromatography (CH₃CN/water/0.1% HCO₂H, 5% to 90%) to give compound 17F (5 mg, 6.4%).

The following compounds were prepared as described in Examples 14-17

Table 7.

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
26		429.0	430.1 [M+H] ⁺	A
27		481.1	482.3 [M+H] ⁺	B
28		434.1	435.1 [M+H] ⁺	A
29		417.1	418.2 [M+H] ⁺	A
30		428.2	429.1 [M+H] ⁺	A

Example 18**Step 1:**

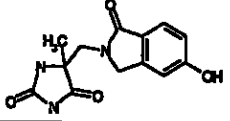
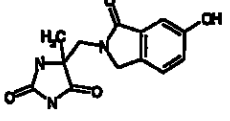
Compound **18A** (1.0 g, 6.4 mmol) and compound **18B** (1.324 g, 7.68 mmol) were dissolved in toluene (4 mL) and stirred at 80 °C for 24 hours. After cooling to room temperature, the solvent was removed by rotary evaporator. Half of the crude product was dissolved in THF/1N HCl (1:1, 14 mL) and stirred at room temperature for 2 hours. EtOAc (15 mL) and water (5 mL) were added. The organic phase was separated and the aqueous phase was extracted with EtOAc (15 mL) twice. The combined organic phase was dried over Na₂SO₄ and concentrated by rotary evaporator to give compound **18C** which was used without further purification.

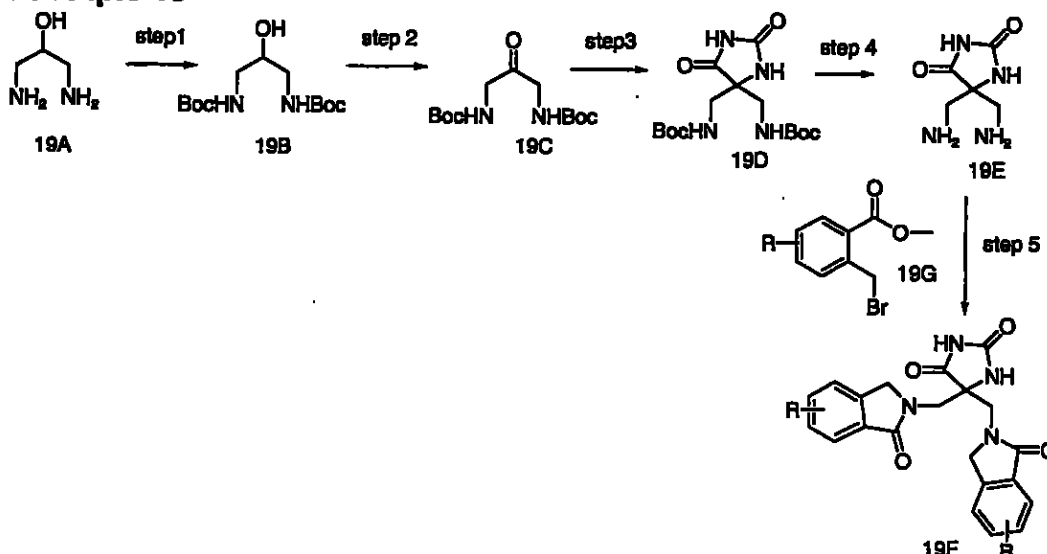
Step 2

Compound **18C** (prepared in step 1) was dissolved in DMF (15 mL) and was cooled to 0 °C in an ice-water bath. Compound **18D** (571 mg, 3.2 mmol) was added in one portion. The solution was allowed to warm up to room temperature over 2 hours, and stirred at room temperature for 3 days. A 2N HCl solution (20 mL) was added and the aqueous phase was extracted with EtOAc (50 mL) three times. The organic phases were combined, dried over Na₂SO₄, and concentrated to dryness. The product was isolated by reverse phase LC (CH₃CN/water/0.1% HCO₂H: 5% to 90%) to give compound **18E** (65 mg, 7.4% from step 1) and Compound **18F** (16 mg, 1.8% from step 1).

The following compounds were prepared as described in **Example 18**

Table 8

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
31		275.09	276.0 [M+H] ⁺	B
32		275.09	276.0 [M+H] ⁺	C

Example 19**General procedures for Example 19:**

In step1, compound **19A** was treated with two equivalent of Boc₂O in a suitable solvent, such as dichloromethane, for 30 min. to 12 h. The solvent was removed and the compound **19B** could be used without further purification or purified by silica gel chromatography.

In step 2, compound **19B** was treated with PCC and celite in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound **19C** was purified by silica gel chromatography.

In step 3, compound **19C** was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to

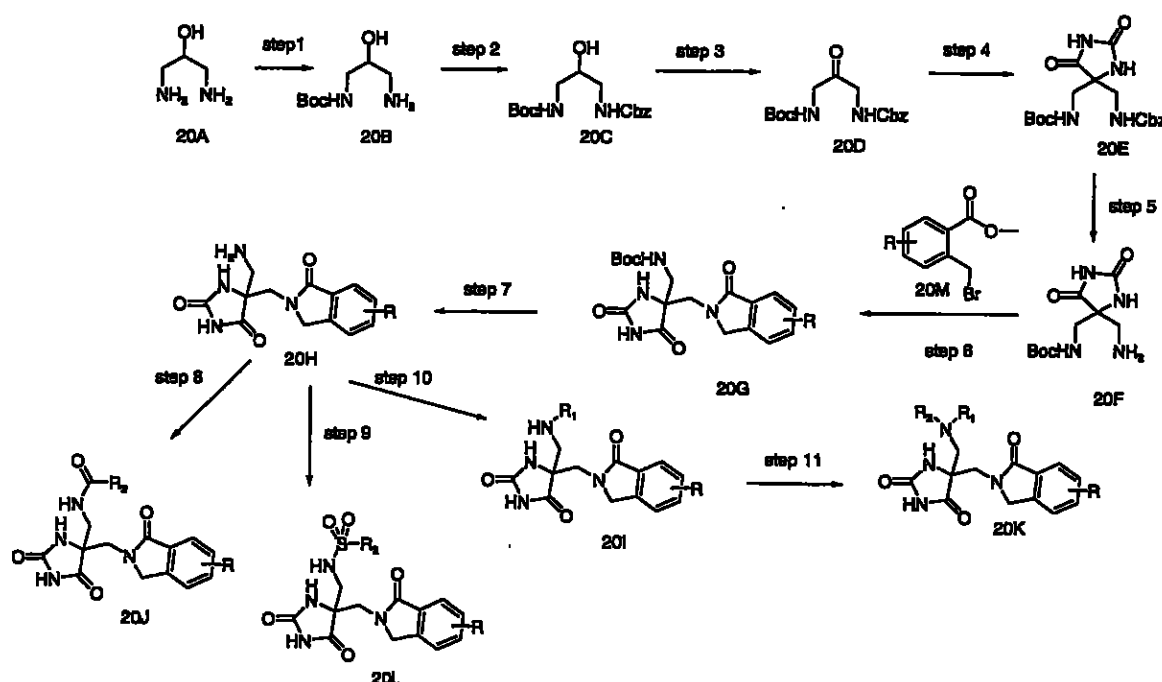
90 °C, for 5 hours to 48 hours. After cooling down, water was added and compound **19D** could be collected by filtration.

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In step 4, compound **19D** was stirred with 2 to 20 equivalents of hydrogen chloride in methanol for 5 to 48 hours. The solvent was removed and the compound **19E** could be used without further purification.

In step 5, the benzyl bromide (compound **19G**) was mixed with hydantoin methyl amine **19E**, DIPEA, and DMF. The solution was stirred at room temperature for 12 to 24 hours. The product (**19F**) was either removed by filtration or purified by silica gel chromatography.

Example 20.



General procedures for Example 20:

In step 1, Compound **20A** was treated with BOC-ON in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound **20B** was purified by silica gel chromatography.

In step 2, Compound **20B** was treated with CbzCl and a base such as DIPEA, in a suitable solvent, such as dichloromethane, for 2 hr to 12 hr. Compound **20C** was purified by silica gel chromatography.

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In step 3, compound **20C** was treated with PCC and celite in a suitable solvent such as dichloromethane, for 2 hr to 12 hr. Compound **20D** was purified by silica gel chromatography.

In step 4, compound **20D** was reacted with potassium cyanide and ammonium carbonate in appropriated alcohol and water solution, at 50 °C to 90 °C, for 1 hour to 48 hours. After cooling down, water was added and compound **20E** could be collected by filtration.

In step 5, Compound **20E** was treated with Pd/C in a suitable solvent such as methanol, in a par shaker under H₂ atmosphere. After filtering off the catalyst and concentration of solvent, the product was used without further purification.

In step 6, the benzyl bromide (compound **20M**) was mixed with hydantoin methyl amine **20F**, DIPEA, and DMF. The solution was stirred at at room temperature to 80 °C for 12 to 24 hours. The product was either removed by filtration or purified by silica gel chromatography.

In step 7, compound **20G** was stirred with 2 to 20 equivalents of hydrogen chloride in dioxane for 1 to 12 hours. The solvent was removed and the compound **20H** was used without further purification.

In step 8, Compound **20H** was coupling with carboxylic acid to give compound **20J** which was purified by silica gel chromatography.

In step 9, Compound **20H** was coupling with sulphonyl chloride compound to give compound **20L** which was purified by silica gel chromatography.

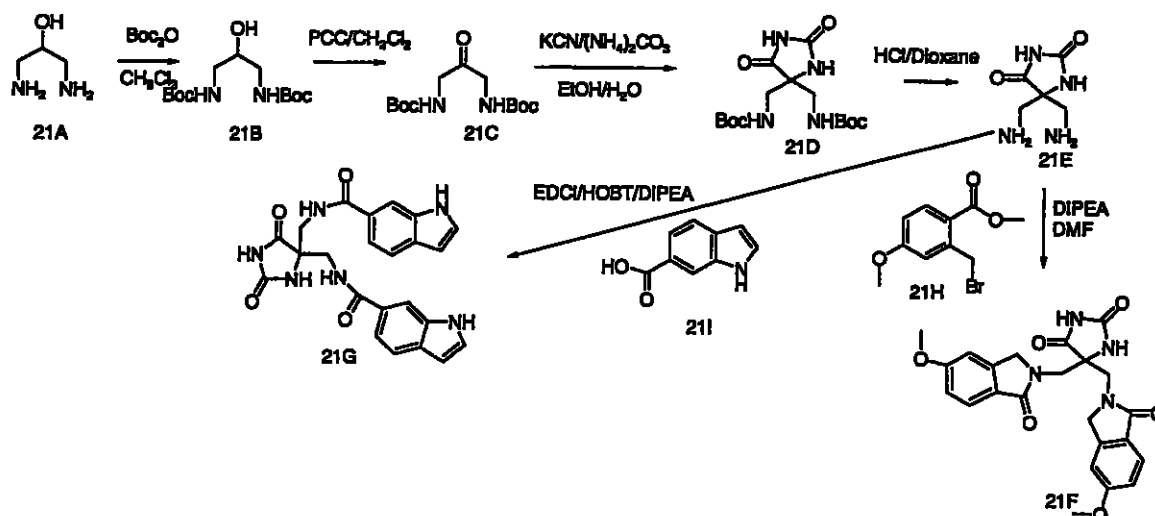
In step 10, Compound **20H** was reacted with carbonyl compound under reductive amination condition to give compound **20I**. Alternatively, compound

20H was treated with a suitable electrophile and a base to give the product 20I, which was purified by silica gel chromatography.

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In step 11, compound 20I was reacted with carbonyl compound under reductive amination condition to give product 20K. Alternatively, compound 20I was treated with a suitable electrophile and a base to give the product 20K, which was purified by silica gel chromatography.

Example 21:



Compound 21B: Compound 21A (7 g, 77.7 mmol), and di-tert-butyl dicarbonate (35.6 g, 163 mmol) were stirred in methylene chloride (100 mL) at 25 °C for 2 hr. Saturated aqueous NaCl (150 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (100 mL) twice. The organic phase was washed with brine (100 mL), dried over Na_2SO_4 . The solvent was removed by rotary evaporator to give compound 21B (17g, 76%) which was used without further purification.

Compound 21C: compound 21B (17 g, 58.6 mmol) was dissolved in methylene chloride (100 mL). PCC (25.2 g, 117 mmol) and celite (15 g) were added and the reaction mixture was stirred at 25 °C overnight. The solid was filtered off and the resulting solution was concentrated and purified via sgc (40% EtOAc/Hexanes) to give 3.62 g (22%) of compound 21C.

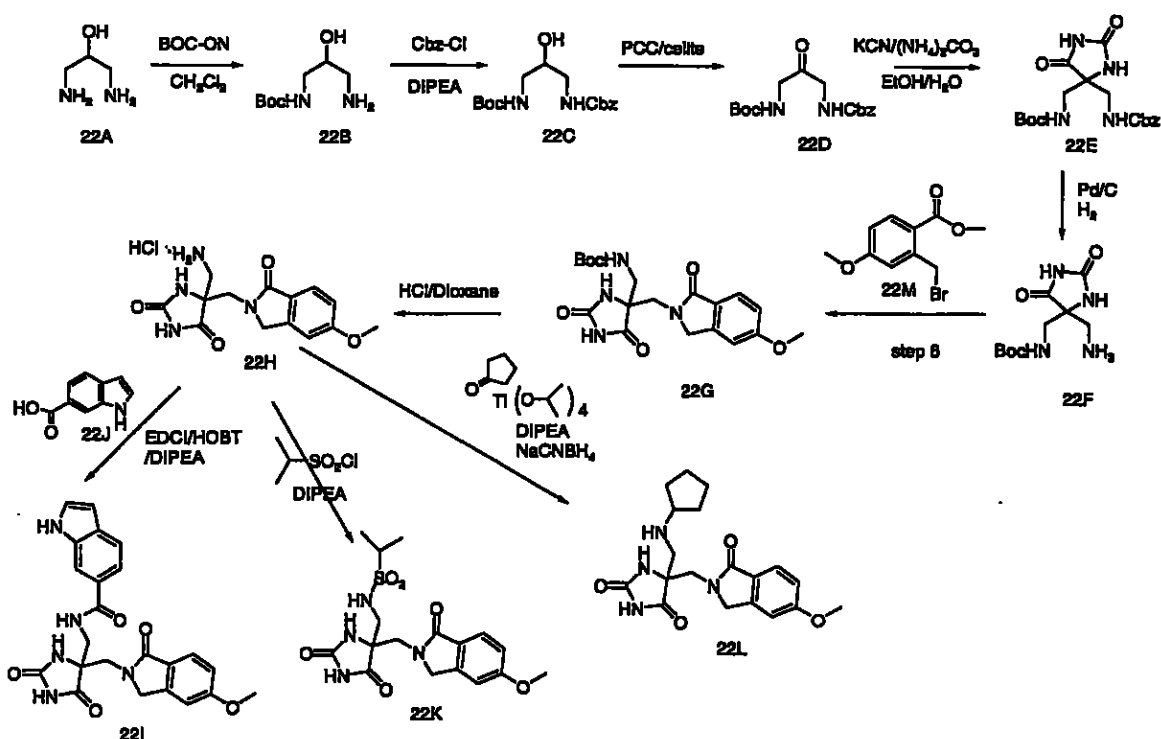
117

Compound 21D: Compound 21C (3.62, 12.6 mmol), KCN (1.23g, 18.9 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (3.62 g, 37.7 mmol) were suspended in a mixture of EtOH (30 mL) and water (30 mL). The solution was stirred at 80 °C overnight. After cooling down, water (35 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound 21D (3 g, 67%).

Compound 21E: Compound 21D (3.0 g) was suspended in methanol (50 mL) and HCl (4M in dioxane, 20 mL) was added. The solution was stirred at 25 °C for 3 hours. Ethyl ether (50 mL) was added. The solid was filtered, washed by ethyl ether twice, and dried under vacuum compound 21E (1.34 g, 70%).

Compound 21F: Compound 21E (130 mg, 0.82 mmol), compound 21H (0.27 g, 1 mmol) and DIPEA (0.55 mL, 2 mmol) were mixed in DMF (5 mL). The solution was stirred at room temperature overnight. Solvent was removed and the crude material was and purified via sgc (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 129 mg (35%) of compound 21E.

Example 22:



Compound **22B**: Compound **22A** (7.3 g, 81 mmol) was treated with BOC-ON (21.9 g, 89 mmol) in dichloromethane for 3 hr. Solvent was removed and the crude material was purified via sgc (10% $\text{NH}_3/\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 6.5 (42%) of compound **22B**.

Compound **22C**: Compound **22B** (1.5g, 7.9 mmol) was dissolved in dichloromethane (50 mL) at 0 °C. CbzCl (1.24 ml, 8.7 mmol) and DIPEA (1.52 ml, 8.7 mmol) were added and the reaction was stirred at 0 °C for 30 min. The reaction mixture was washed by HCl (1N, 50 mL) and brine (50 mL). The organic layer was dried and concentrated to give crude compound **22C** (2.6 g, 99%) which was used without further purification.

Compound **22D**: Compound **22C** (2.78g, 8.57 mmol) was dissolved in methylene chloride (100 mL). PCC (4.62 g, 21.4 mmol) and celite (4.6 g) were added and the reaction mixture was stirred at 25 °C overnight. Another 0.5 eq. of PCC (923 mg, 4.3 mmol) was added and it was stirred for 3 hr at room temperature. The solid was filtered off and the resulting solution was concentrated and purified via sgc (50% EtOAc/Hexanes) to give 1.86 g (73%) of compound **22D**.

Compound **22E**: Compound **22D** (1.86, 5.8 mmol), KCN (0.56 g, 8.65 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (1.66 g, 17.3 mmol) were suspended in a mixture of EtOH (20 mL) and water (20 mL). The solution was stirred at 80 °C overnight. After cooling down, EtOH was removed. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound **22E** (1.45 g, 64%).

Compound **22F**: Compound **22E** (1.45 g, 3.68 mmol) was treated with Pd/C in methanol in a par shaker under H_2 atmosphere of 50 psi for 60 hr. After filtering off the catalyst and concentration of solvent, Compound **22E** (0.95 g, 99%) was used without further purification.

Compound **22G**: Compound **22F** (150 mg, 0.58 mmol), compound **22M** (170 mg, 0.64 mmol) and DIPEA (0.22 mL, 1.28 mmol) were mixed in DMF (5 mL). The solution was stirred at 70 °C overnight. Solvent was removed and the crude material was and purified via sgc (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 166 mg (71%) of compound **22G**.

Compound **22H**: Compound **22G** (166 mg) was suspended in methanol (10 mL) and HCl (4M in dioxane, 4 mL) was added. The solution was stirred at 25 °C for 2 hours. Ethyl ether (50 ml) was added. Solvent was removed and give compound **22H** (0.14 g, 99%).

Compound **22I**: Compound **22H** (42 mg, 0.12 mmol) and compound **22J** (26 mg, 0.16 mmol) were dissolved in DMF (20 mL). EDCI (30 mg, 0.16 mmol), HOBT (21 mg, 0.16 mmol) and DIPEA (0.05 mL, 0.28 mmol) were added and the reaction mixture was stirred at room temperature for 2 hr. Solvent was removed and the crude material was and purified via sgc (10% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 7 mg (13%) of compound **22I**.

Compound **22L**: Compound **22H** (25 mg, 0.073 mmol) and cyclopentanone (7.5 mg, 0.088 mmol) were stirred in methylene chloride (5 mL). Titanium tetraisopropoxide (0.043 mL, 0.15 mmol) was added followed by addition of DIPEA (0.015 mL, 0.088 mmol). The reaction mixture was stirred at room temperature for 2h. Then, $\text{Na}(\text{OAc})_3\text{BH}$ (31 mg, 0.15 mmol) was added and the mixture was stirred at rt overnight. Saturated K_2CO_3 aq. (20 mL) was added, and the mixture was stirred at rt briefly. The solid was filtered off through a celite pad. The filtrate was diluted with methylene chloride (30 mL), and it was extracted with brine. The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (10% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 7 mg (26%) of compound **22L**.

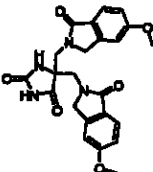
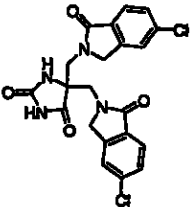
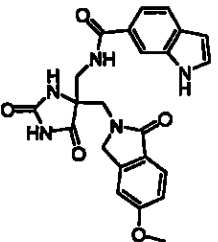
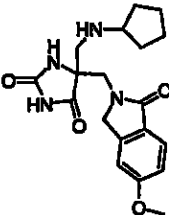
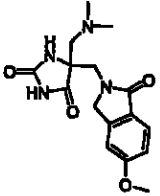
Compound **22K**: Compound **22H** (20 mg, 0.06 mmol) and isopropyl sulphonyl (27 mg, 0.18 mmol) were dissolved in methylene chloride (10 mL). DIPEA (0.04 mL, 0.26 mmol) were added and the reaction mixture was stirred at

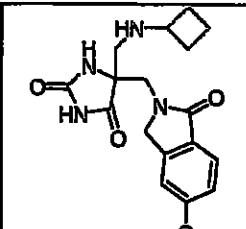
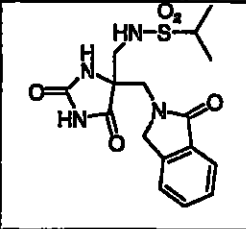
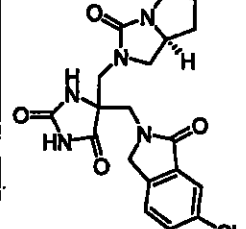
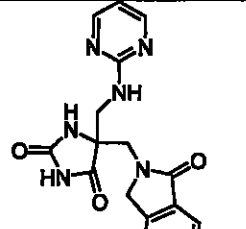
room temperature for 48 hr. Solvent was removed and the crude material was and purified via sgc (10% NH₃•MeOH/CH₂Cl₂) to give 2 mg (8%) of compound 22K.

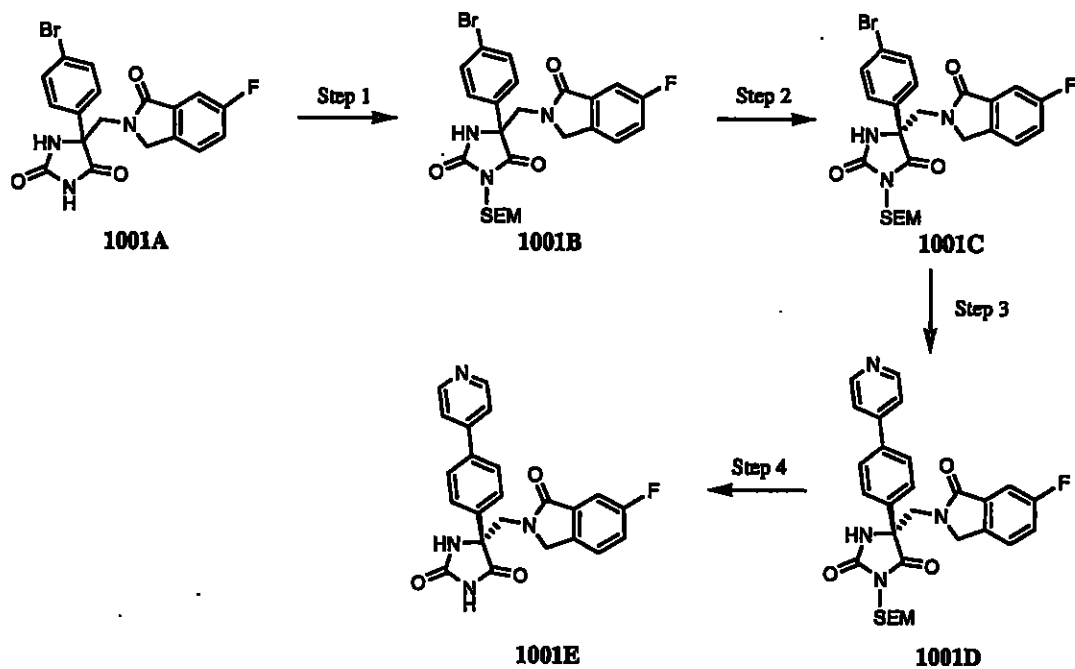
120

The following compounds were prepared as described in Examples 19-22.

Table 9

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
33		450.15	451.1 [M+H] ⁺	B
34		458.05	459.3 [M+H] ⁺	B
35		447.15	448.2 [M+H] ⁺	A
36		372.18	373.2 [M+H] ⁺	B
37		332.15	333.1 [M+H] ⁺	C

38		358.16	359.2 [M+H] ⁺	B
39		380.12	381.2 [M+H] ⁺	C
40		417.12	418.1 [M+H] ⁺	D
41		386.09	387.2 [M+H] ⁺	C

Example 1001:

Step 1

To a solution of compound **1001A** (1.65 g, 3.95 mmol) in anhydrous DMF (35 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl, 0.93 mL, 4.73 mmol) and DIPEA (0.9 mL, 5.14 mmol). The solution was stirred at 25 °C for overnight. DMF was removed under vacuum. The product **1001B** was purified by SGC (Hexane/EtOAc, 2:1, yield: 1.6 g, 74%).

Step 2

Compound **1001B** was resolved by Chiralcel OD column (Mobile phase: Hexane/2-propanol 3:1). The first peak was collected and concentrated to give compound **1001C**.

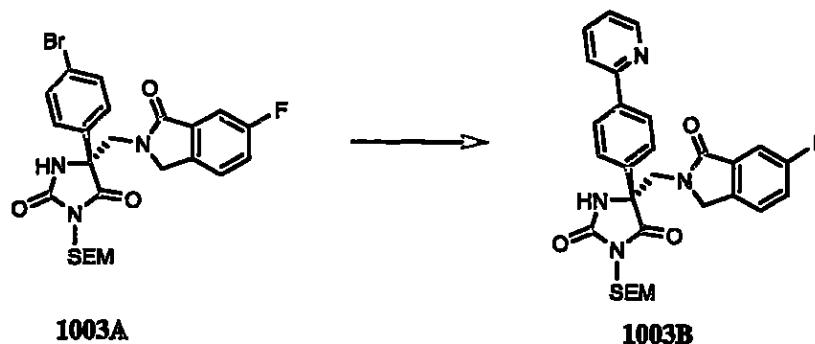
Step 3

To a dry flask was added compound **1001C** (1.5 g, 2.73 mmol) and 4-pyridyl boronic acid (670 mg, 5.50 mmol). The flask was vacuumed and refilled with nitrogen three times. Pd(dppf)Cl₂ (220 mg, 0.30 mmol) was added and followed by addition of CH₃CN (20 mL) and aq. K₂CO₃ (1 M, 15 mL). The solution was stirred at 80 °C (oil bath) for 16 hours. After cooling down, CH₃CN (100 mL) was added and the solid was removed by filtration. The aqueous layer was separated and extracted with EtOAc (20 mL) once. The organic solution was combined and concentrated. The product was purified by SGC (CH₂Cl₂/MeOH/NH₄OH: 20:1:0.1) to give compound **1001D**.

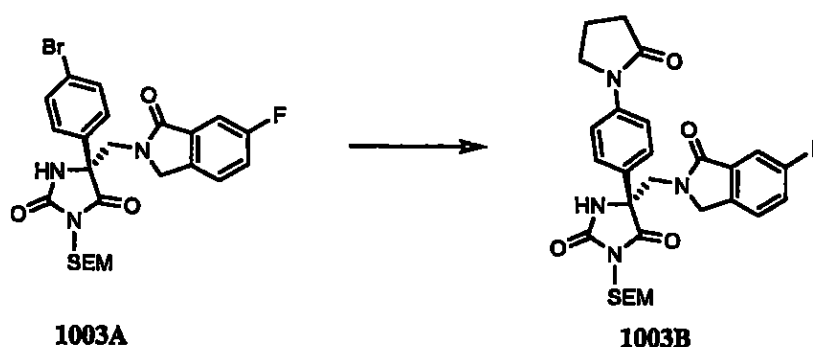
Step 4

Compound **1001D** was dissolved in a mixture of methanol and HCl (4M in dioxane) (2:1, 30 mL) and was stirred overnight in a sealed pressure flask at 90 °C (oil bath). After the solution was cooled, the solution was transferred into a 250 mL round bottom flask. It was concentrated and dried under vacuum. The crude mixture was dissolved in methanol (50 mL) and Et₃N (0.5 mL) was added and stirred overnight at 25 °C. The solvent was then removed and the product was purified by C18 reverse phase chromatography (CH₃CN/water 5% to 90%, with addition of 0.1% HCO₂H) to give compound **1001E** (815g, 71% from compound **1001C**).

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Example 1002

To a flamed dried flask was added compound **1003A** (100 mg, 0.182 mmol), [1,4-bis(diphenylphosphino)butane] palladium(II) dichloride [Pd(dppb)Cl₂, 12 mg, 0.02 mmol], and copper (II) oxide (15 mg, 0.18 mmol). The flask was vacuumed and refilled with nitrogen. 2-Tri-n-butylstannylpyridine (0.076 mL, 0.237 mmol) and DMF (1 mL) were added. The solution was stirred at 100 °C oil bath for 5 hours. After cooling, the DMF was removed by rotary evaporator. The product was purified by SGC (Hexane/EtOAc 2:1) to give **1003B** (84 mg, 84%).

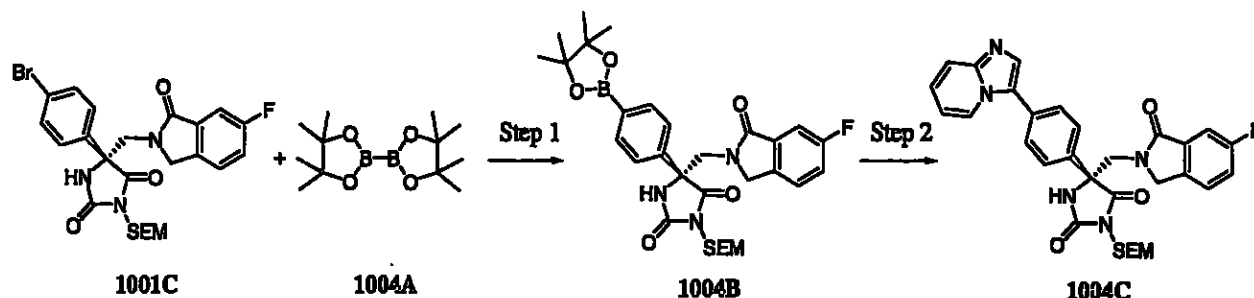
Example 1003

To a dry pressure tube was added compound **1003A** (50 mg, 0.091 mmol), bis(dibenzylideneacetone) palladium [Pd(dba)₂, 1.6 mg, 0.0018 mmol], 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (Xantphos, 3.0 mg, 0.0055 mmol), and Cs₂CO₃ (60 mg, 0.182 mmol). The pressure tube was vacuumed and refilled with nitrogen. Pyrrolidinone (14 mg, 0.16 mmol) and dioxane (0.5 mL) were added. The tube was sealed and stirred overnight at 100 °C (oil bath). After cooling, dioxane (2 mL) was added and the solid was removed by

filtration. The solution was concentrated and purified by SGC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 40:1) to give compound **1003B** (27 mg).

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Example 1004:



Step 1

Compound **1001C** was prepared as described in Example 1001.

A mixture of compound **1001C** (0.3 g, 0.55 mmol), bis(pinacolato)diboron (**1004A**; 170 mg, 0.65 mmol), potassium acetate (170 mg, 1.70 mmol), and $[\text{PdCl}_2(\text{dppf})]\text{CH}_2\text{Cl}_2$ (50 mg, 0.05 mmol) in 1,4-dioxane (10 mL) was vacuumed and refilled with argon three times. The reaction mixture was stirred at 100 °C (oil bath) for 1.5 hours. After cooling down, the mixture was diluted in EtOAc (50 mL) and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residual material was purified by silica gel column chromatography (2% MeOH in CH_2Cl_2) to afford compound **1004B** (300 mg, 91% yield).

Step 2

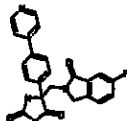
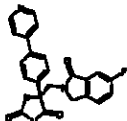
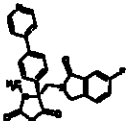
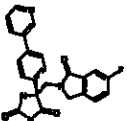
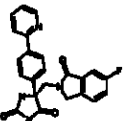
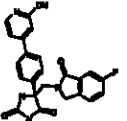
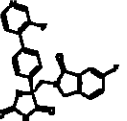
A solution of compound **1004B** (60 mg, 0.10 mmol), 3-bromoimidazo[1,2-a]pyridine (30 mg, 0.15 mmol), and $[\text{PdCl}_2(\text{dppf})]\text{CH}_2\text{Cl}_2$ (8.2 mg, 0.01 mmol) in CH_3CN (3 mL) was treated with potassium carbonate (0.6 mL, 0.6 mmol, 1M in H_2O). The mixture was vacuumed and refilled with argon three times. The reaction mixture was stirred at 90 °C (oil bath) for 17 hours. After cooling, the mixture was diluted in EtOAc (20 mL) and filtered through a Celite pad. The filtrate was concentrated in vacuo and the residual material was purified

by preparative TLC (10% MeOH in CH₂Cl₂) to afford compound **1004C** (42 mg, 71% yield).

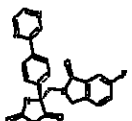
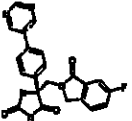
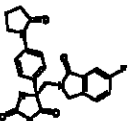
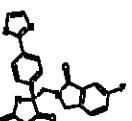
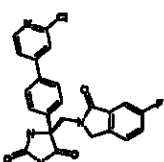
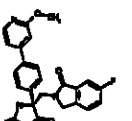
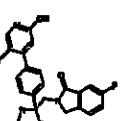
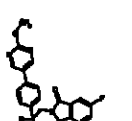
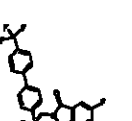
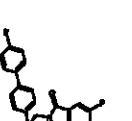
125

The following compounds were prepared as described in Examples 1001, 1002, 1003, or 1004.

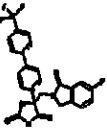
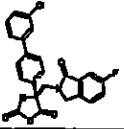
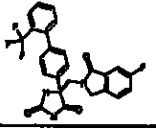
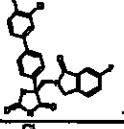
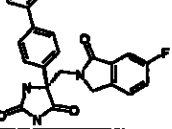
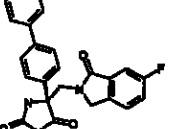
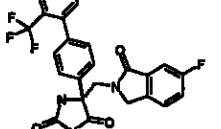
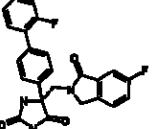
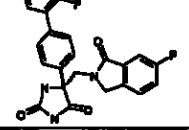
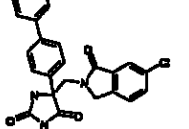
Table 1000

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nm)
110		416.13	417.1 [M+H] ⁺	A
111		416.13	417.1 [M+H] ⁺	A
112		430.14	431.1 [M+H] ⁺	B
113		416.13	417.1 [M+H] ⁺	A
114		416.13	417.1 [M+H] ⁺	A
115		432.12	433.2 [M+H] ⁺	A
116		434.12	435.2 [M+H] ⁺	A

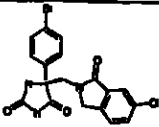
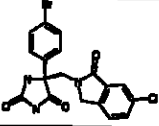
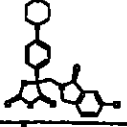
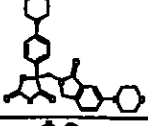
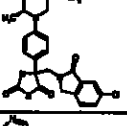
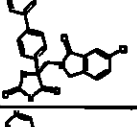
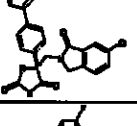
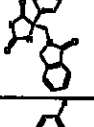
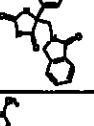
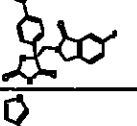
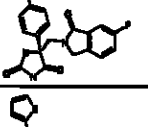
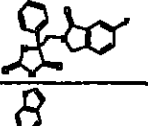
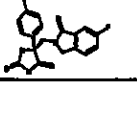
126

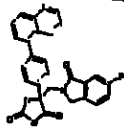
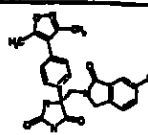
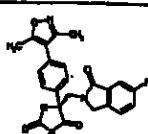
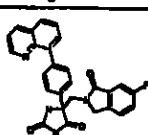
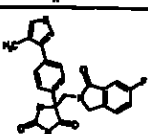
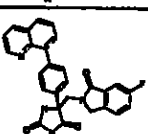
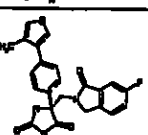
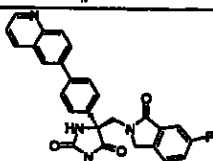
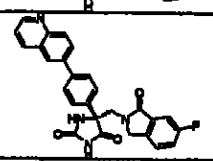
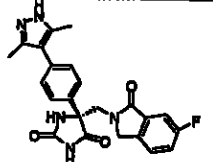
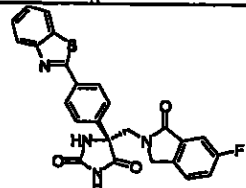
117		417.12	418.1 [M+H] ⁺	A
118		417.12	418.1 [M+H] ⁺	A
119		422.14	423.2 [M+H] ⁺	A
120		422.08	423.1 [M+H] ⁺	A
121		450.09	451.1 [M+H] ⁺	D
122		446.14	447.2 [M+H] ⁺	A
123		466.08	467.3 [M+H] ⁺	A
124		447.13	448.2 [M+H] ⁺	A
125		483.12	484.3 [M+H] ⁺	D
126		433.12	434.2 [M+H] ⁺	A

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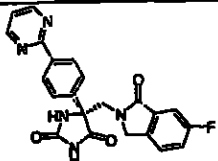
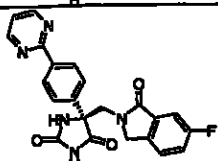
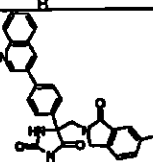
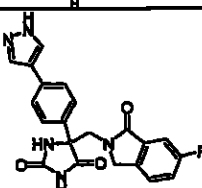
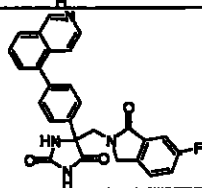
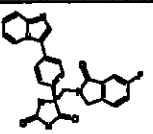
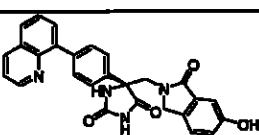
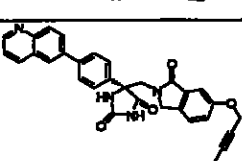
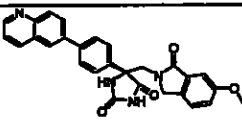
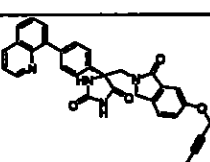
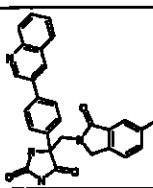
127		483.12	484.3 [M+H] ⁺	B
128		449.09	450.2 [M+H] ⁺	A
129		483.12	484.3 [M+H] ⁺	C
130		467.08	468.3 [M+H] ⁺	C
131		449.09	450.2 [M+H] ⁺	A
132		467.08	468.3 [M+H] ⁺	A
133		483.12	484.3 [M+H] ⁺	A
134		451.11	452.2 [M+H] ⁺	A
135		451.11	452.2 [M+H] ⁺	A
136		449.09	450.1 [M+H] ⁺	n/a

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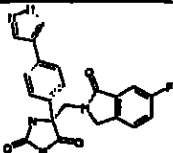
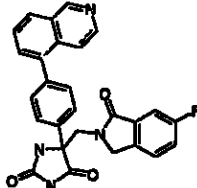
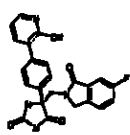
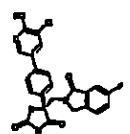
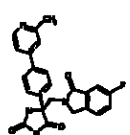
137		432.98	434.1 [M+H] ⁺	C
138		432.98	434.1 [M+H] ⁺	A
139		440.13	441.1 [M+H] ⁺	A
140		491.2	492.3 [M+H] ⁺	C
141		481.2	482.1 [M+H] ⁺	A
141		432.1	433.2 [M+H] ⁺	D
143		432.1	433.2 [M+H] ⁺	A
144		339.1	340 [M+H] ⁺	C
145		339.1	340 [M+H] ⁺	A
146		419.4	420.2 [M+H] ⁺	A
147		421.44	422.2 [M+H] ⁺	A
148		421.44	422.2 [M+H] ⁺	A
149		454.45	455.3 [M+H] ⁺	A

150		466.46	467.3 [M+H] ⁺	A
151		434.14	435.2[M+H] ⁺	A
152		434.14	435.1[M+H] ⁺	C
153		466.14	467.3[M+H] ⁺	C
154		435.11	436.2[M+H] ⁺	C
155		466.14	467.3[M+H] ⁺	A
156		435.11	436.1[M+H] ⁺	A
157		466.14	467.3[M+H] ⁺	C
158		466.14	467.3[M+H] ⁺	A
159		433.16	434.2[M+H] ⁺	A
160		472.10	473.3[M+H] ⁺	A

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161		417.12	418.2[M+H] ⁺	A
162		417.12	440.2[M+Na] ⁺	C
163		466.14	467.3[M+H] ⁺	B
164		405.12	406.2[M+H] ⁺	A
165		466.14	467.3[M+H] ⁺	A
166		455.44	456.3 [M+H] ⁺	n/a
167		464.15	465.3 [M+H] ⁺	A
168		516.18	517.1 [M+H] ⁺	C
169		478.16	479.3 [M+H] ⁺	A
170		516.18	517.3 [M+H] ⁺	n/a
171		466.46	467.3 [M+H] ⁺	B

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172		405.38	406.2 [M+H] ⁺	A
173		466.46	467.3 [M+H] ⁺	A
174		432.12	433.1 [M+H] ⁺	A
175		466.08	467.1 [M+H] ⁺	A
176		430.14	431.2 [M+H] ⁺	D

Proton NMR Spectral Data for Selected Compounds in Table 1000.

Compound 111. ¹H-NMR (500 MHz, DMSO-d₆) δ 9.0 (s, 1H), 8.7 9(d, J = 6.0 Hz, 2H), 7.92 (d, J = 8.7 Hz, 2H), 7.79 (d, J = 8.7 Hz, 2H), 7.76 (d, J = 6.0 Hz, 2H), 7.65 (m, 1H), 7.48 (m, 2H), 4.40 (d, J = 17.3 H, 1H), 4.31 (d, J = 17.3 Hz, 1H), 4.27 (d, J = 14.2 Hz, 1H), 4.14 (d, J = 14.2 Hz, 1H).

Compound 120. ¹H-NMR (500 MHz, DMSO-d₆) δ 8.99 (s, 1H), 8.03 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 3.3 Hz, 1H), 7.84 (d, J = 3.3 Hz, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H), 7.47 (m, 2H), 4.38 (d, J = 17.6 Hz, 1H), 4.28 (d, J = 17.6 Hz, 1H), 4.27 (d, J = 14.3 Hz, 1H), 4.13 (d, J = 14.3 Hz, 1H).

Compound 123. ¹H-NMR (500 MHz, DMSO-d₆) δ 8.99 (s, 1H), 7.84 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.66 (dd, J = 8.5, 4.6 Hz, 1H), 7.54 (d, J = 8.4 Hz,

2H), 7.49 (m, 2H), 6.65 (s, 1H), 4.40 (d, $J = 17.5$ Hz, 1H), 4.31 (d, $J = 17.5$ Hz, 1H), 4.29 (d, $J = 14.2$ Hz, 1H), 4.10 (d, $J = 14.2$ Hz, 1H).

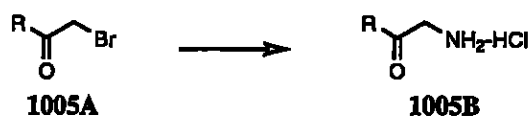
132

Compound 139. ^1H NMR (500 MHz, CD_3OD) δ 3.17-3.21 (m, 4H), 3.83-3.88 (m, 4H), 4.14-4.52 (m, 4H), 7.01 (d, $J = 8.8$ Hz, 2H), 7.47 (d, $J = 8$ Hz, 1H), 7.46-7.48 (m, 3H), 7.75 (s, 1H).

Compound 143. ^1H NMR (400 MHz, CDCl_3) δ 4.21-4.50 (m, 4H), 7.498 (d, $J = 0.8$ Hz, 1H), 7.52 (d, $J = 0.4$ Hz, 1H), 7.73-7.76 (m, 3H), 7.76-7.87 (m, 4H), 8.60 (d, $J = 6$ Hz, 2H).

Compound 155. ^1H NMR (500 MHz, CD_3OD) δ 8.84 (dd, $J = 1.89, 4.1$ Hz, 1H); 8.43 (dd, $J = 1.58, 8.2$ Hz, 1H); 7.99 (dd, $J = 1.58, 8.2$ Hz, 1H); 7.85 (m, 3H); 7.8 (dd, $J = 1.26$ Hz, 6.94 Hz, 1H); 7.75 (m, 3H), 7.70 (dd, $J = 7.25$ Hz, 0.95 Hz, 1H); 7.59 (dd, $J = 4.73$ Hz, 7.57 Hz, 1H); 7.58 (dd, $J = 4.4$ Hz, 8.2 Hz, 1H); 7.51 (dd, $J = 2.5$ Hz, 7.8 Hz, 1H); 7.40 (m, 1H); 4.54 (d, $J = 17.0$ Hz, 1H); 4.48 (d, $J = 17.0$ Hz, 1H); 4.48 (d, $J = 14.5$ Hz, 1H); 4.32 (1H, d, $J = 14.5$ Hz, 1H).

Example 1005:

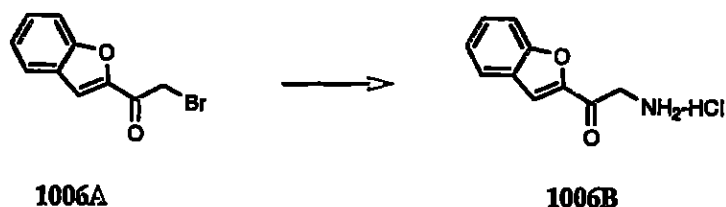


General procedure for example 1005

Compound **1005A** was treated with one equivalent of hexamethylene tetraamine in chloroform or other suitable solvent for about 5 hours. The product was collected by filtration and then treated with HCl in ethanol for one day to three days. The solid was then collected by filtration to give compound **1005B**.

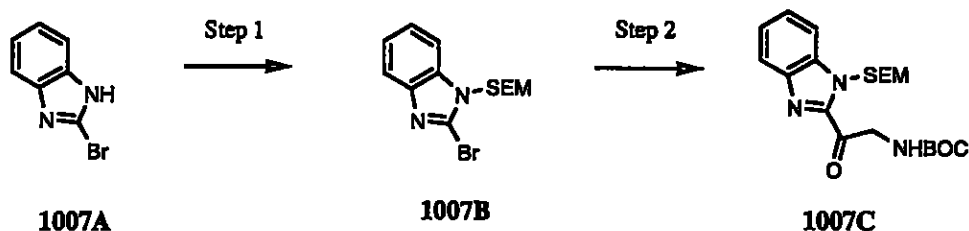
133

Example 1006



1-Benzofuran-2-yl-2-bromo-ethanone (**1006A**, 3.0g, 12.55 mmol), hexamethylene tetraamine (1.94 g, 13.80 mmol), and NaI (350 mg) were stirred in CHCl_3 (40 mL) for five hours. The solid was collected by filtration and dried under vacuum. The solid was then suspended in ethanol (30 mL) and HCl (conc, 36% in water, 10 mL) was added. The solution was stirred at 25 °C for 4 d. The solid was collected by filtration and washed by ethanol, dried under vacuum to give compound **1006B** (3.05 g, contained NH_4Cl).

Example 1007



Step 1

To a flame dried flask was added 2-bromo-1H-benzimidazole (**1007A**, 2.94 g, 14.92 mmol), anhydrous THF (75 mL), and NaH (95%, 490 mg, 19.4 mmol). The solution was stirred at 25 °C for 45 minutes; SEMCl (3.17 mL, 17.9 mmol) was added. The solution was stirred at 25 °C for 2.5 hours. Water (50 mL) and EtOAc (100 mL) were added. The aqueous layer was separated and extracted with EtOAc (100 mL) once. The organic layers were combined and concentrated under vacuum. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound **1007B** (3.6 g, 74%).

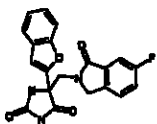
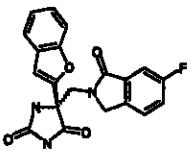
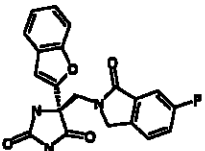
134

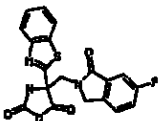
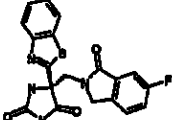
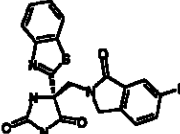
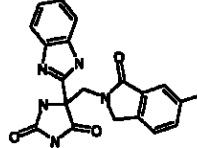
Step 2

To a flame dried flask was added compound 1007B (1.427 g, 4.35 mmol) and anhydrous ethyl ether/THF (2:1, 15 mL). The solution was cooled to -78°C. n-Butyllithium (1.6 M, 0.46 mL, 0.73 mmol) was added and stirred at -78 °C for 30 minutes. In another flamed dried pear shaped flask was added N-(tert-butoxycarbonyl)glycine-N'-methoxy-N'-methanamide (949 mg, 4.35 mmol) and anhydrous THF (2 mL). Isopropyl magnesium chloride (2 M, 2.5 mL, 5.0 mmol) was added at 0 °C. The solution was stirred at 0 °C for 5 minutes and was added into the compound 1003C solution via cannula at -78 °C. The solution was then gradually warmed up to -20 °C and stirred between -20 °C and 10 °C for 4 hours. Saturated NH₄Cl solution was added and the aqueous solution was extracted with EtOAc (50 mL) three times. The organic phases were combined and concentrated. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound 1007C (1.0 g, 57%).

The following compounds were prepared as described in Example 1, 14, 1005, 1006, and/or 1007.

Table 1001

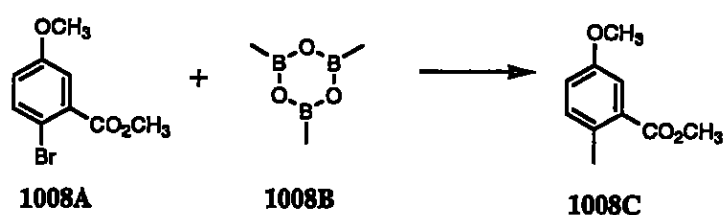
Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
177		379.10	380.1 [M+H] ⁺	A
178		379.10	380.1 [M+H] ⁺	A
179		379.10	380.1 [M+H] ⁺	D

180		396.07	397.1 [M+H] ⁺	B
181		396.07	397.1 [M+H] ⁺	A
182		396.07	397.1 [M+H] ⁺	B
183		379.11	380.1 [M+H] ⁺	A

Proton NMR Spectral Data for Selected Compounds in Table 1003.

Compound 181. ¹H-NMR (500 MHz, DMSO-d₆) δ 11.3 (s, 1H), 9.34 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.67 (m, 1H), 7.61 (m, 1H), 7.50 (m, 3H), 4.65 (d, J = 14.3 Hz, 1H), 4.44 (d, J = 17.3 Hz, 1H), 4.38 (d, J = 17.3 Hz, 1H), 4.34 (d, J = 14.3 Hz, 1H).

Example 1008



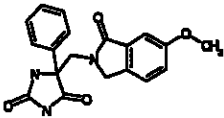
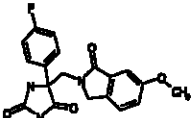
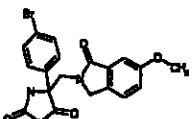
Compound **1008A** (20g, 81.61 mmol), **1008B** (13.36 mL, 97.93 mmol), Pd(dppf)Cl₂ (1.0g, 1.36 mmol), dioxane (350 mL), water (50 mL), and Cs₂CO₃

(22.5g, 163 mmol) were stirred at 110 °C (oil bath) under nitrogen for 16 hours. After cooling, the solid was removed by filtration. The solution was concentrated and purified by SGC (Hexane/EtOAc, 10:1) to give 1008C (12.1g, 80%).

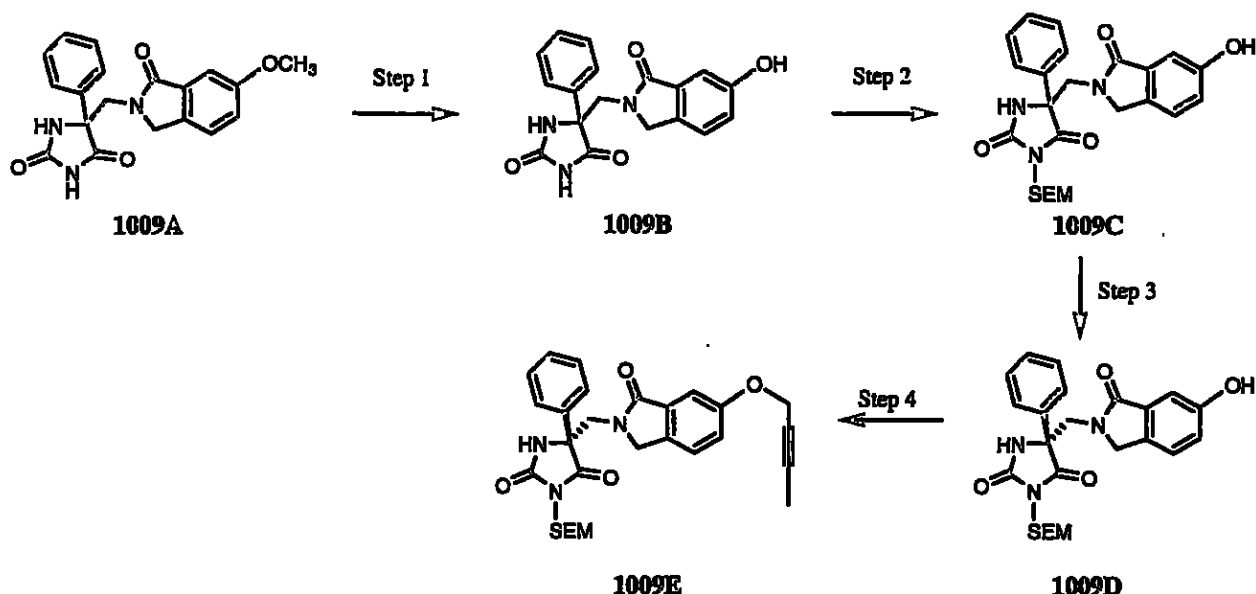
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The following compounds were prepared as described in Examples 14 and 1008.

Table 1002

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
184		351.12	352.1 [M+H] ⁺	A
185		369.11	370.1 [M+H] ⁺	A
186		429.03	430.2 [M+H] ⁺ 432.2 [M+Na] ⁺	A

Example 1009



Step 1

Compound **1009A** (1.18g, 3.36mmol) and pyridine hydrochloride (2.33g, 20.17 mmol) were added into a 20 mL microwave reactor tube and reacted at 200 °C for 1 hour. After cooling down, the solid was dissolved in DMF and purified by C18 chromatography (CH₃CN/water 5% to 90%, with 0.1% HCO₂H) to give compound **1009B** (0.87 g, 77%).

Step 2

Compound **1009B** (0.75 g, 2.22 mmol) was dissolved in DMF (12 mL). SEMCI (0.48 mL, 2.44 mmol) and DIPEA (0.775 mL, 4.44 mmol) were added and the solution was stirred at 25 °C for 4 hours. DMF was removed under vacuum and the product was purified by SGC (Hexane/EtOAc: 3:1 to 1:1) to give compound **1009C** (0.81 g, 78%).

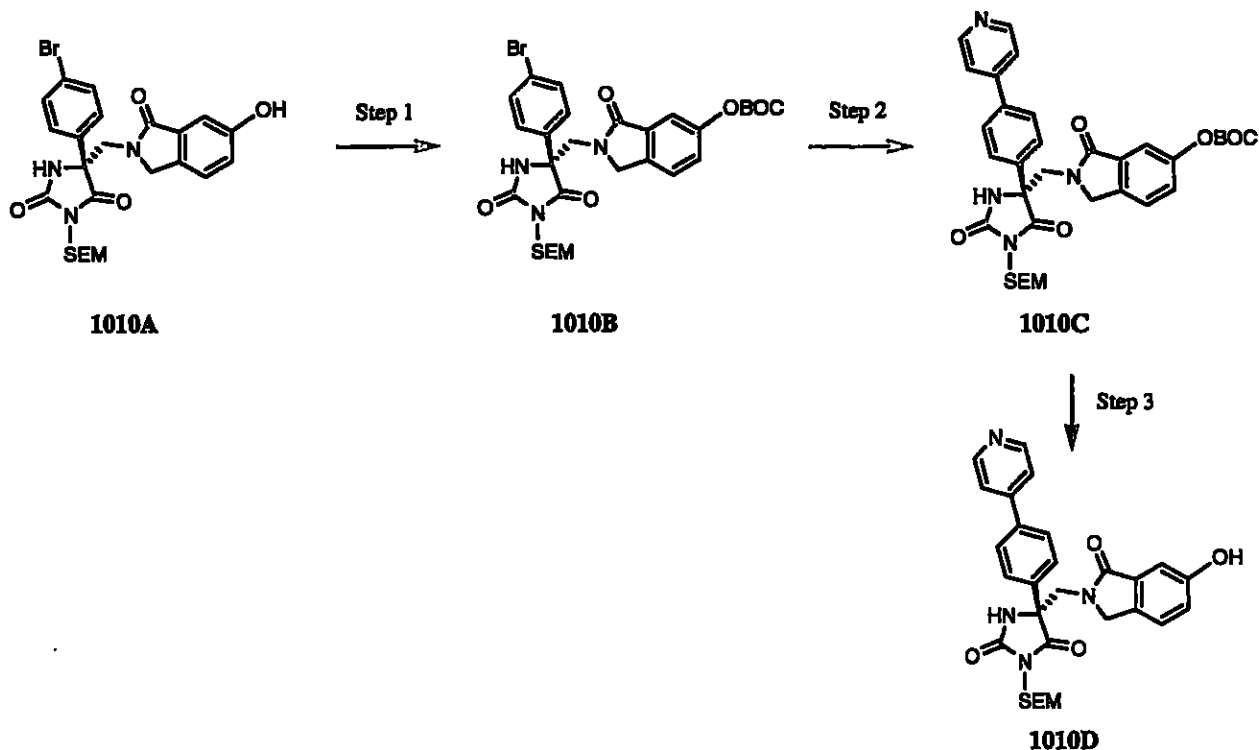
Step 3

Compound **1009C** was resolved on Chiralcel OD column by using Hexane and 2-propanol as mobile phase. The first peak was collected and concentrated to give compound **1009D**.

Step 4

Compound **1009D** (100mg, 0.214 mmol), 1-bromo-2-butyne (34 mg, 0.257 mmol), and Cs_2CO_3 (140 mg, 0.428 mmol) were stirred in DMF (2 mL) at 0 °C for 2 hours, then at 25 °C for overnight. Water (5 mL) was added and the aqueous solution was extracted with EtOAc (10 mL) three times. The organic phases were combined and concentrated. The product was purified by SGC (Hexane/EtOAc: 3:1) to give compound **1009E** (81 mg).

Example 1010



Step 1

Compound **1010A** (1.03g, 1.88 mmol), (BOC)₂O (493 mg, 2.26 mmol), and Cs₂CO₃ (741 mg, 2.26 mmol) were stirred overnight in CHCl₃ (20 mL). Water was added. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were concentrated and purified by SGC (Hexane/EtOAc 5% to 90%) to give compound **1010B** (1.01 g, 83%).

Step 2

To a dry flask was added compound 1010B (500 mg, 0.77 mmol) and 4-pyridyl boronic acid (190 mg, 1.55 mmol). The flask was vacuumed and

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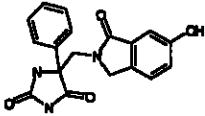
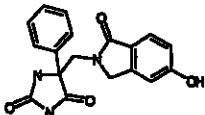
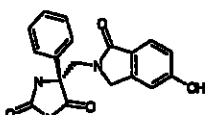
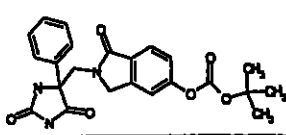
refilled with nitrogen three times. Pd(dppf)Cl₂ (28 mg, 0.04 mmol) was added and followed by addition of CH₃CN (5 mL) and K₂CO₃ (1M, 4 mL). The solution was stirred at 80 °C (oil bath) for 16 hours. After cooling down, CH₃CN (100 mL) was added and the solid was removed by filtration. The aqueous layer was separated and extracted once with EtOAc (20 mL). The organic solution was combined and concentrated. The product was purified by SGC (CH₂Cl₂/MeOH/NH₄OH: 20:1:0.1) to give compound 1010C.

Step 3

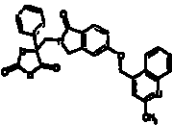
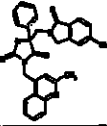
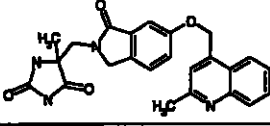
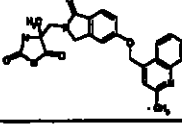
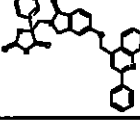
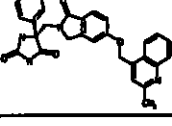
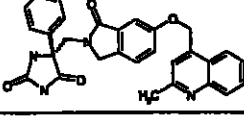
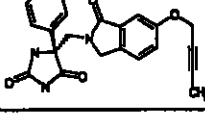
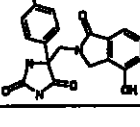
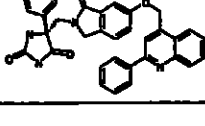
Compound 1010C obtained in step 2 was dissolved in MeOH (10 mL) and HCl (4M in dioxane, 3 mL) was added and stirred overnight at 25 °C. MeOH was then removed and the product was dried under vacuum to give compound 1010D (315 mg, 75% from compound 1010B).

The following compounds were prepared as described in Examples 14 and 1009 or 1010.

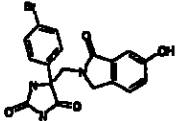
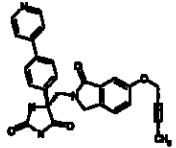
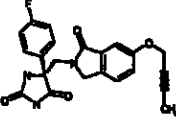
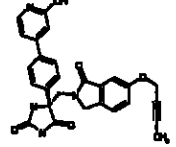
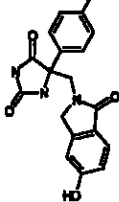
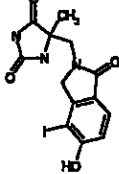
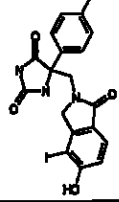
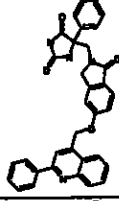
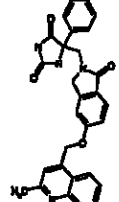
Table 1003

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
187		337.11	338.1 [M+H] ⁺	B
188		337.11	338.1 [M+H] ⁺ 360.1 [M+Na] ⁺	A
189		337.11	338.2 [M+H] ⁺ 360.2 [M+Na] ⁺	A
190		437.16	438.2 [M+H] ⁺	A

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191		492.18	493.3 [M+H] ⁺	A
192		492.18	493.3 [M+H] ⁺	C
193		430.16	431.1 [M+H] ⁺	A
194		430.16	431.1 [M+H] ⁺	A
195		554.20	555.1 [M+H] ⁺	B
196		492.16	493.1 [M+H] ⁺	A
197		492.16	493.1 [M+H] ⁺	A
198		389.14	390.1 [M+H] ⁺	A
199		355.10	356.1 [M+H] ⁺	C
200		554.20	555.1 [M+H] ⁺	B

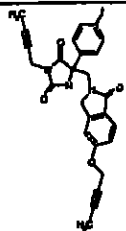
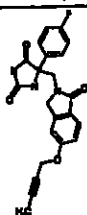
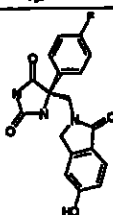
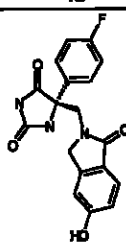
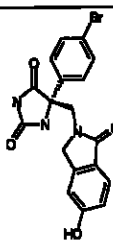
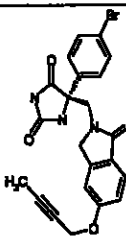
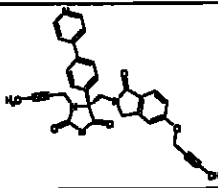
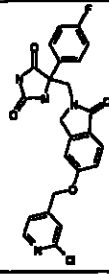
141

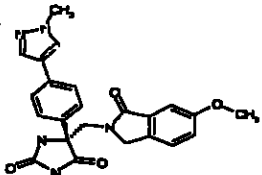
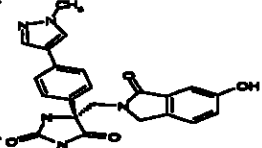
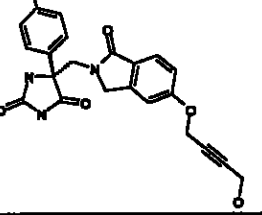
201		415.02	416.2 [M+H] ⁺	B
202		466.16	467.1 [M+H] ⁺	A
203		407.13	408.2 [M+H] ⁺	A
204		482.16	483.3 [M+H] ⁺	A
205		355.1	356 [M+H] ⁺	A
206		400.99	402 [M+H] ⁺	C
207		480.99	482 [M+H] ⁺	D
208		572.19	573 [M+H] ⁺	B
209		510.17	511 [M+H] ⁺	A

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218		452.1	453 [M+H] ⁺	B
219		409.14	410 [M+H] ⁺	A
220		411.16	412 [M+H] ⁺	A
221		531.19	532 [M+H] ⁺	B
222		485.1	486.488 [M+H] ⁺	A
223		446.14	447 [M+H] ⁺	A
224		465.21	466 [M+H] ⁺	C
225		558.09	559.561 [M+H] ⁺	A
226		487.04	488.490 [M+H] ⁺	A
227		591.11	592.1 [M+H] ⁺	B
228		519.1	520.1 [M+H] ⁺	C
229		528.1	529.4 [M+H] ⁺	B

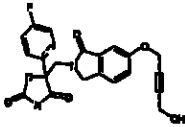
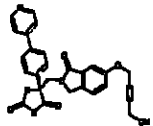
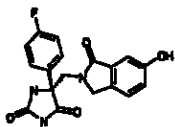
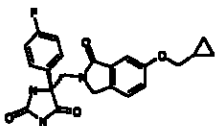
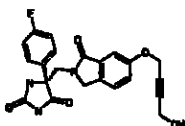
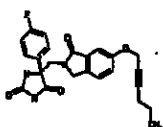
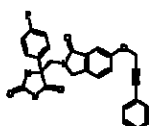
143

210		459.16	460 [M+H] ⁺	D
211		407.13	408 [M+H] ⁺	A
212		355.1	356 [M+H] ⁺	C
213		355.1	356 [M+H] ⁺	A
214		415.02	416.418 [M+H] ⁺	A
215		467.05	468.470 [M+H] ⁺	A
216		518.2	519 [M+H] ⁺	C
217		480.1	481 [M+H] ⁺	A

237		431.44	432.2 [M+H] ⁺	A
238		417.41	418.2 [M+H] ⁺	n/a
239		423.12	424.2 [M+H] ⁺	A

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240		423.12	424.2 [M+H] ⁺	A
241		482.16	483.3 [M+H] ⁺	A
242		355.10	356.2 [M+H] ⁺	A
243		409.14	410.2 [M+H] ⁺	A
244		423.12	424.1 [M+H] ⁺	n/a
245		435.16	436.2 [M+H] ⁺	n/a
246		469.14	470.3 [M+H] ⁺	n/a

Proton NMR Spectral Data for Selected Compounds in Table 1003.

Compound 198. ¹H-NMR (400 MHz, DMSO-d₆) δ 9.22 (s, 1H), 7.64 (m, 2H), 7.43 (m, 4H), 7.22 (t, J = 2.2 Hz, 1H), 7.16 (dd, J = 9.6, 1.2 Hz, 1H), 4.82 (d, J = 2.0 Hz, 2H), 4.16 (m, 4H), 3.33 (s, 3H).

Compound 203. ^1H -NMR (400 MHz, DMSO- d_6) δ 7.63 (dd, $J = 8.8, 5.6$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 1H), 7.13 (m, 4H), 4.80 (d, $J = 0.8$ Hz, 1H), 4.39 (d, $J = 17.6$ Hz, 1H), 4.17 (d, $J = 17.6$ Hz, 1H), 4.13 (d, $J = 13.6$ Hz, 1H), 3.71 (d, $J = 13.6$ Hz, 1H) 3.34 (s, 3H).

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Compound 213. ^1H NMR (500 Hz, CD_3OD) δ 4.11 (d, $J = 15$ Hz, 1H), 4.27 (d, $J = 15$ Hz, 1H), 4.29 (d, $J = 17$ Hz, 1H), 4.38 (d, $J = 17$ Hz, 1H), 6.84-6.89 (m, 2H), 7.16-7.21 (m, 2H), 7.56-7.60 (m, 1H), 7.71-7.76 (m, 2H)

Compound 219. ^1H NMR (500 Hz, CD_3OD) δ 0.36-0.40 (m, 2H), 0.61-0.68 (m, 2H), 1.25-1.35 (m, 1H), 3.91 (d, $J = 7$ Hz, 2H), 4.14 (d, $J = 15$ Hz, 1H), 4.30 (d, $J = 15$ Hz, 1H), 4.34 (d, $J = 17$ Hz, 1H), 4.43 (d, $J = 17$ Hz, 1H), 7.01-7.05 (m, 2H), 7.17-7.23 (m, 2H), 7.65-7.69 (m, 1H), 7.72-7.77 (m, 2H)

Compound 232. ^1H NMR (500 Hz, CD_3OD) δ 1.13 (t, $J = 8$ Hz, 3H), 2.21-2.27 (m, 2H), 4.15 (d, $J = 14$ Hz, 1H), 4.31 (d, $J = 14$ Hz, 1H), 4.36 (d, $J = 17$ Hz, 1H), 4.45 (d, $J = 17$ Hz, 1H), 4.79 (t, $J = 2$ Hz, 2H), 7.04-7.14 (m, 2H), 7.16-7.25 (m, 2H), 7.64-7.79 (m, 3H).

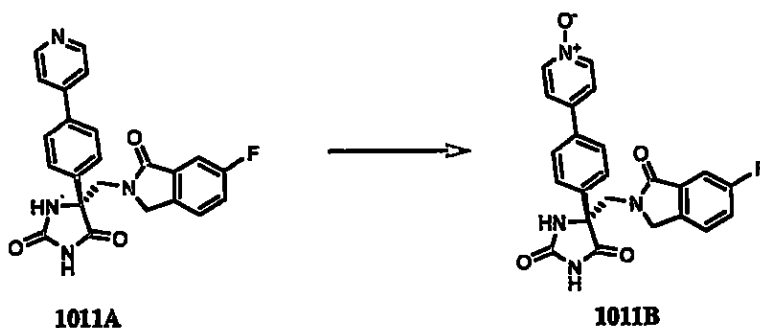
Compound 233. ^1H NMR (500 Hz, CD_3OD) δ 7.678 (d, $J = 8.5$ Hz, 1H); 7.455 (d, $J = 4.1$ Hz, 1H), 7.817 (d, $J = 4.1$ Hz, 1H); 7.099 (s, 1H); 7.052 (dd, $J = 2.207, 6.305$ Hz, 1H); 4.515 (d, $J = 17.3$ Hz, 1H), 4.450 (d, $J = 17.3$ Hz, 1H); 4.065 (d, $J = 14.5$ Hz, 1H); 3.89 (s, 3H); 3.87 (d, $J = 14.5$ Hz, 1H); 3.85 (m, 1H); 2.46 (m, 2H); 2.09 (m, 1H) 1.89 (m, 1H); 1.76 (m, 1H); 1.67 (m, 1H); 1.54 (m, 1H); 1.32 (m, 1H).

Compound 239. ^1H NMR (500 Hz, DMSO- d_6) δ 4.11 (d, $J = 15$ Hz, 1H), 4.27 (d, $J = 15$ Hz, 1H), 4.29 (d, $J = 17$ Hz, 1H), 4.38 (d, $J = 17$ Hz, 1H), 6.84-6.89 (m, 2H), 7.16-7.21 (m, 2H), 7.56-7.60 (m, 1H), 7.71-7.76 (m, 2H)

Compound 243. ^1H -NMR (500 MHz, CD_3OD) δ 8.53 (s, 1H), 7.67 (dd, $J = 8.5, 5$ Hz, 2H), 7.46 (d, $J = 8$ Hz, 1H), 7.27 (t, $J = 8.5$ Hz, 2H), 7.15 (m, 2H), 4.31 (d, $J = 17.0$ Hz, 1H), 4.22 (d, $J = 17$ Hz, 1H), 4.13 (d, $J = 14.2$ Hz, 1H),

4.06 (d, $J = 14.2$ Hz, 1H), 3.88 (d, $J = 6.5$ Hz, 2H), 3.35 (m, 2H), 1.22 (m, 1H), 0.57 (d, $J = 8$ Hz, 1H), 0.33 (d, $J = 5$ Hz, 1H).

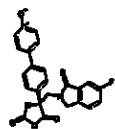
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Example 1011

To a solution of compound 1011A (100mg) in DMF (5 mL) was added *m*-chlorobenzoyl peroxide (MCPBA, 100mg). The solution was stirred overnight at 25 °C. The product was purified by C18 reverse phase chromatography (CH₃CN/water 5% to 90%, with 0.1% HCO₂H) to give compound 1011B (73 mg).

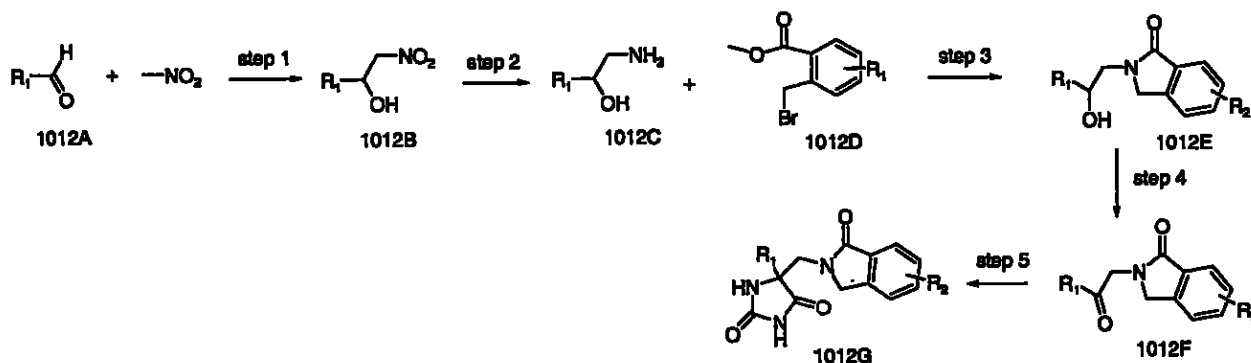
The following compounds were prepared as described in Examples 1010 and 1011.

Table 1004

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
247		432.12	433.1 [M+H] ⁺	A

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Example 1012.



In step 1, Compound **1012A** was treated with nitromethane and KO^tBu in a mixture of THF and *t*-BuOH for 2 to 12 h. Alternatively, compound **1012A** was treated with nitromethane and TBAF in a suitable solvent such as THF for 2 to 12 h. Compound **1012B** was purified by silica gel chromatography.

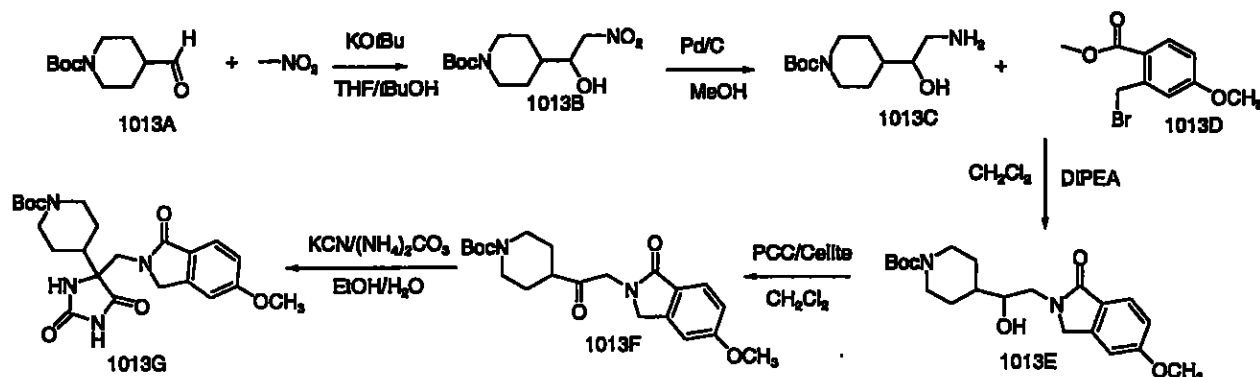
In step 2, Compound **1012B** was treated with Pd/C in a suitable solvent such as methanol, in a Parr shaker under H₂ atmosphere. After filtering off the catalyst and concentration of solvent, the product was used without further purification.

In step 3, the benzyl bromide (compound **1012D**) was mixed with compound **1012C**, DIPEA, and DMF. The solution was stirred at 0 °C to room temperature for 12 to 24 hours. The product was either removed by filtration or purified by silica gel chromatography.

In step 4, compound **1012E** was treated with PCC and Celite in a suitable solvent such as dichloromethane for 2 to 12 h. Compound **1012F** was purified by silica gel chromatography.

In step 5, compound **1012F** was reacted with potassium cyanide and ammonium carbonate in an appropriate alcohol and water solution, at 50 °C to 90 °C, for 5 to 48 hours. After cooling, water was added and compound **1012G** was collected by filtration.

Example 1013.



Compound 1013B: To a solution of THF (15 mL) and t-BuOH (15 mL) was added compound **1013A** (1.2 g, 5.6 mmol) and nitromethane (0.61 mL, 11.2 mmol) followed by addition of KO^tBu (0.63 g, 5.6 mmol). The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was adjusted to pH 6 using HOAc. The reaction mixture was diluted with EtOAc (30 mL), and was extracted with brine. The aqueous layer was extracted with EtOAc (30 mL x 2). The combined organic layers were washed with brine, dried, and concentrated to dryness. The crude material was purified via PTLC (25% EtOAc/Hexanes) to give 1.24 g (81%) of compound **1013B**.

Compound 1013C: Compound **1013B** (1.24 g, 4.5 mmol) was treated with Pd/C in methanol in a Parr shaker under H₂ atmosphere (50 psi) overnight. After filtering off the catalyst and concentration of solvent, compound **1013C** (1.1 g, 99%) was used without further purification.

150

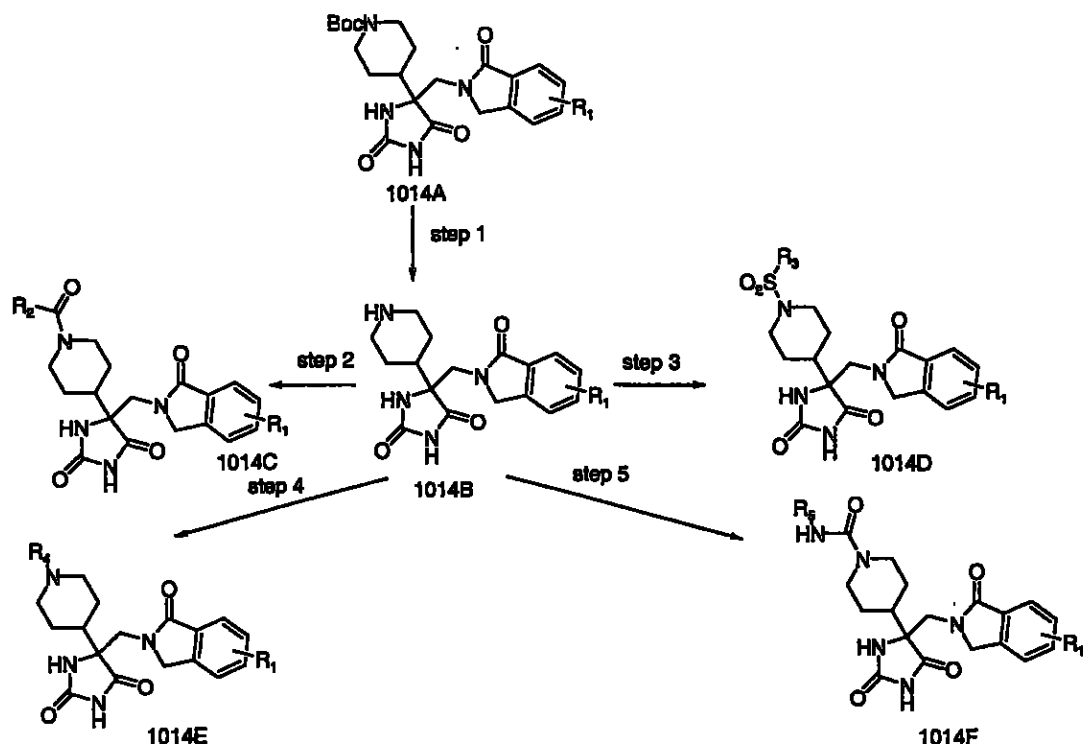
Compound 1013E: Compound 1013C (1.02 g, 4.2 mmol) was dissolved in dichloromethane (30 mL) at 0 °C. Compound 1013D (1.13 g, 4.2 mmol) and DIPEA (0.73 mL, 4.2 mmol) were added and the reaction was stirred at 0 °C and slowly warmed up to rt overnight. The reaction mixture was washed with HCl (1N, 50 mL) and brine (50 mL). The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (50% EtOAc/Hexanes) to give 0.88 g (54%) of compound 1013E.

Compound 1013F: Compound 1013E (0.88 g, 2.25 mmol) was dissolved in methylene chloride (30 mL). PCC (1.22 g, 5.63 mmol) and Celite (1.22 g) were added and the reaction mixture was stirred at 25 °C overnight. The solid was filtered off and the resulting solution was concentrated and purified via sgc (90% EtOAc/Hexanes) to give 0.62 g (71%) of compound 1013F.

Compound 1013G: Compound 1013F (1.01 g, 2.6 mmol), KCN (0.25 g, 3.9 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (0.75 g, 7.8 mmol) were suspended in a mixture of NH_3 in Methanol (7 N, 10 mL) and water (10 mL). The solution was stirred at 90 °C overnight. After cooling, water (20 mL) was added. The solid was filtered and washed with water three times. The solid was dried under vacuum to give compound 1013G (0.86 g, 72%).

Example 1014.

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Step 1.

Compound **1014A** was stirred with 2 to 20 equivalents of hydrogen chloride in methanol for 5 to 48 hours. The solvent was removed and the compound **1014B** could be used without further purification.

Step 2.

Compound **1014B** was treated with carboxylic anhydride and DIPEA to give compound **1014C** which was purified by silica gel chromatography.

Step 3.

Compound **1014B** was coupled with sulphonyl chloride compound to give compound **1014D**, which was purified by silica gel chromatography.

Step 4.

153

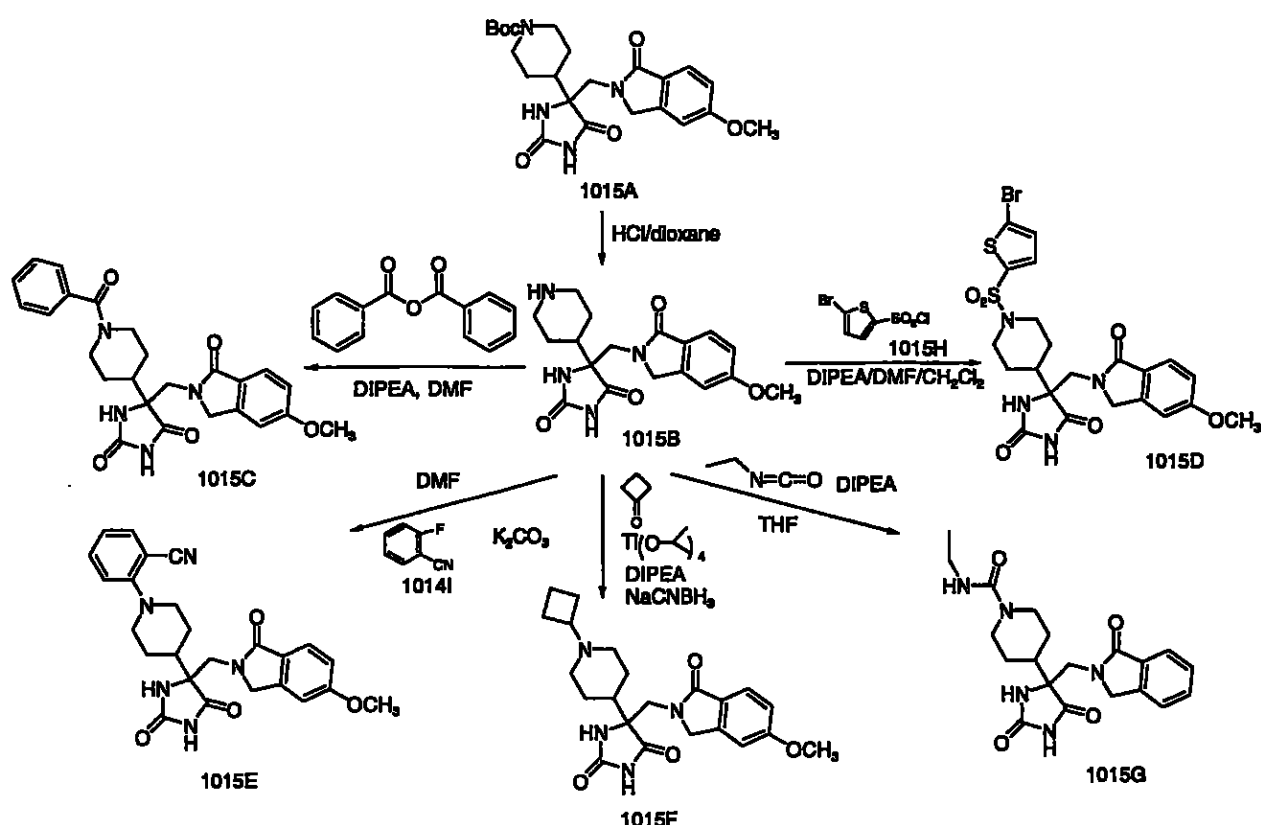
Compound 1014B was reacted with carbonyl compound under reductive amination conditions to give compound 1014E. Alternatively, compound 1014B was treated with a suitable electrophile and a base to give compound 1014E, which was purified by silica gel chromatography.

Step 5.

Compound 1014B was reacted with isocyanate compound and DIPEA to give compound 1014F, which was purified by silica gel chromatography.

Example 1015.

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Compound 1015B: Compound 1015A (0.86 g) was suspended in methanol (10 mL) and HCl (4M in dioxane, 10 mL) was added. The solution was stirred at 25 °C for 3 hours. Solvent was removed and the material was dried under vacuum to give compound 1015B (0.74 g, 99%).

Compound 1015C: Compound 1015B (40 mg, 0.11 mmol) and benzoic acid anhydride (25 mg, 0.11 mmol) were dissolved in DMF (1 mL). DIPEA (0.06 mL, 0.33 mmol) was added and the reaction mixture was stirred at room temperature overnight. Solvent was removed and the crude material was purified via sgc (5% NH₃•MeOH/CH₂Cl₂) to give 3.7 mg (7%) of compound 1015C.

Compound 1015D: Compound 1015B (40 mg, 0.11 mmol) and compound 1015H (30 mg, 0.11 mmol) were dissolved in DMF (1 mL). DIPEA (0.25 mL, 1.4 mmol) was added and the reaction mixture was stirred at room

temperature overnight. Solvent was removed and the crude material was purified via sgc (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 2.2 mg (3%) of compound 1015D.

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Compound 1015E: Compound 1015B (40 mg, 0.11 mmol) and compound 1015I (0.024 mL, 0.22 mmol) were dissolved in DMF (1 mL). K_2CO_3 (46 mg, 0.33 mmol) was added and the reaction mixture was stirred at 90 °C overnight. Solvent was removed and the crude material was purified via sgc (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 2.6 mg (5%) of compound 1015E.

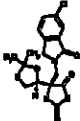
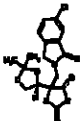
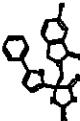
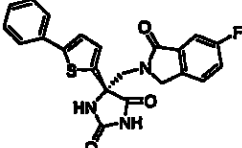
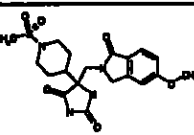
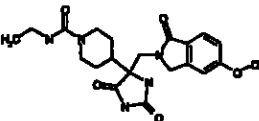
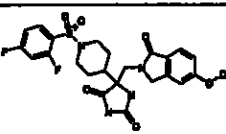
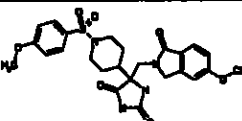
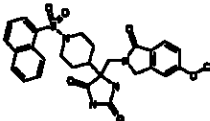
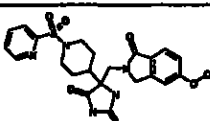
Compound 1015F: Compound 1015B (46 mg, 0.13 mmol) and cyclobutanone (0.2 mL) were stirred in methylene chloride (1 mL). Titanium tetraisopropoxide (0.045 mL, 0.15 mmol) was added followed by addition of DIPEA (0.027 mL, 0.16 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, NaCNBH_3 (41 mg, 0.65 mmol) was added and the mixture was stirred at rt overnight. The solvent was removed. The crude material was purified via PTLC (10% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 3.1 mg (6%) of compound 1015F.

Compound 1015G: Compound 1015B (80 mg, 0.24 mmol) and ethyl isocyanate (0.018 mL, 0.24 mmol) were dissolved in DMF (1 mL). DIPEA (0.17 mL, 0.97 mmol) was added and the reaction mixture was stirred at room temperature overnight. Solvent was removed and the crude material was purified via sgc (9% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 11 mg (11%) of compound 1015G.

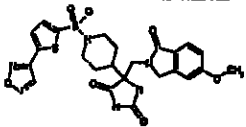
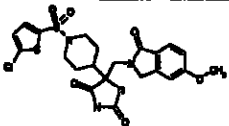
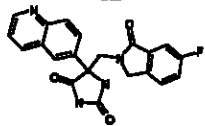
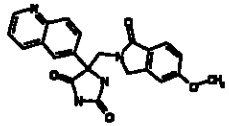
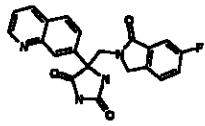
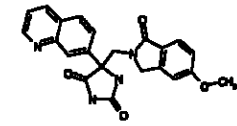
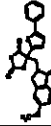
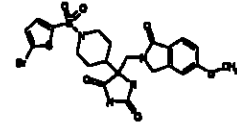
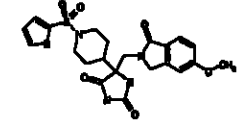
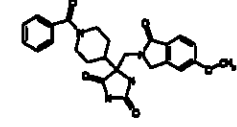
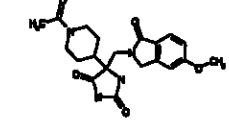
The following compounds were prepared as described in Examples 1012 to 1015.

Table 1005

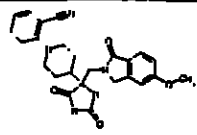
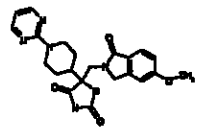
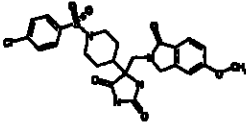
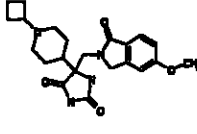
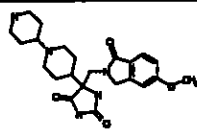
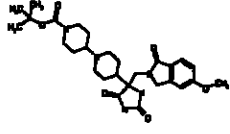
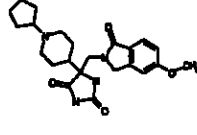
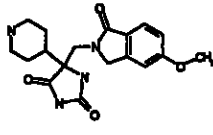
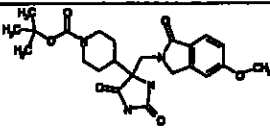
156

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nm)
248		379.09	380.1[M+H] ⁺	C
249		379.09	380.1[M+H] ⁺	C
250		421.09	422.1[M+H] ⁺	B
251		421.09	422.1[M+H] ⁺	A
252		436.14	437.1[M+H] ⁺	B
253		429.2	430.1[M+H] ⁺	B
254		534.14	535.1[M+H] ⁺	B
255		528.17	529.3[M+H] ⁺	B
256		548.17	549.3[M+H] ⁺	A
257		499.15	500.3[M+H] ⁺	B

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258		571.12	572.1[M+H] ⁺	A
259		538.07	539.1[M+H] ⁺	A
260		390.11	391.1[M+H] ⁺	A
261		402.13	403.2[M+H] ⁺	A
262		390.11	391.1[M+H] ⁺	A
263		402.13	403.1[M+H] ⁺	A
264		433.11	434.1[M+H] ⁺	A
265		582.02	585.1[M+H] ⁺	A
266		504.11	505.1[M+H] ⁺	A
267		462.19	463.1[M+H] ⁺	B
268		400.17	401.1[M+H] ⁺	A

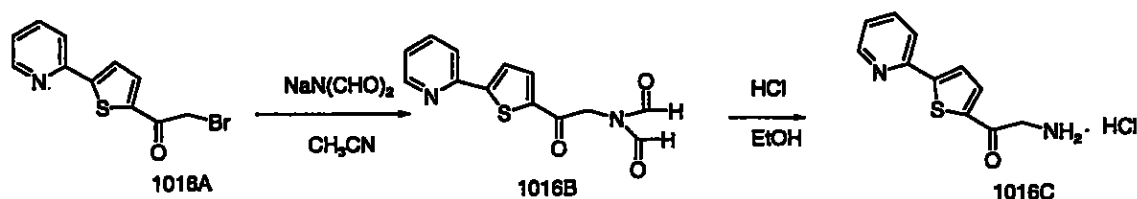
158

269		459.19	460.1[M+H] ⁺	B
270		436.19	437.2[M+H] ⁺	B
271		532.12	533.3[M+H] ⁺	B
272		412.21	413.2[M+H] ⁺	C
273		441.24	442.1[M+H] ⁺	C
274		541.29	542.3[M+H] ⁺	C
275		426.23	427.2[M+H] ⁺	C
276		358.16	359.1[M+H] ⁺	C
277		458.22	459.1[M+H] ⁺	B

Proton NMR Spectral Data for Selected Compounds in Table 1005.

159 189

Compound 262. ^1H NMR (500 Hz, CD_3OD) δ 8.921 (m, 1H); 8.433 (d, J = 8.6 Hz, 1H); 8.357 (s, 1H); 8.072 (m, 4H); 7.622 (m, 1H); 7.545 (m, 1H); 7.476 (m, 1H); 7.369 (m, 1H); 4.522 (d, J = 17 Hz, 1H); 4.510 (d, J = 14.5 Hz, 1H); 4.425 (d, J = 17 Hz, 1H), 4.350 (d, J = 14.5 Hz, 1H).

Example 1016.

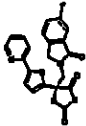
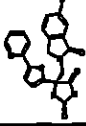
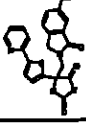
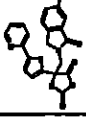
Compound 1016B: Compound 1016A (500 mg, 1.77 mmol) was suspended in CH_3CN (5 mL) followed by addition of $\text{NaN}(\text{CHO})_2$ (202 mg, 2.12 mmol). The reaction mixture was stirred at rt for 30 min before warmed up to 70 °C and stirred for 2 h. Solid was collected by suction filtration and washed with acetonitrile to give 1016B (380 mg, 78%) as brown solid.

Compound 1016C: Compound 1016B (380 mg, 1.38 mmol) was stirred with HCl (36% aq., 1 mL) and EtOH (10 mL) at rt for 2 days. It was then heated to 60 °C for 2 hr. Solvent was removed and it was dried under vacuum to give 1016C (345 mg, 98%). The material was used without further purification.

The following compounds were prepared as described in **Example 1016**, **Example 2** and **Example 8**.

Table 1006

160

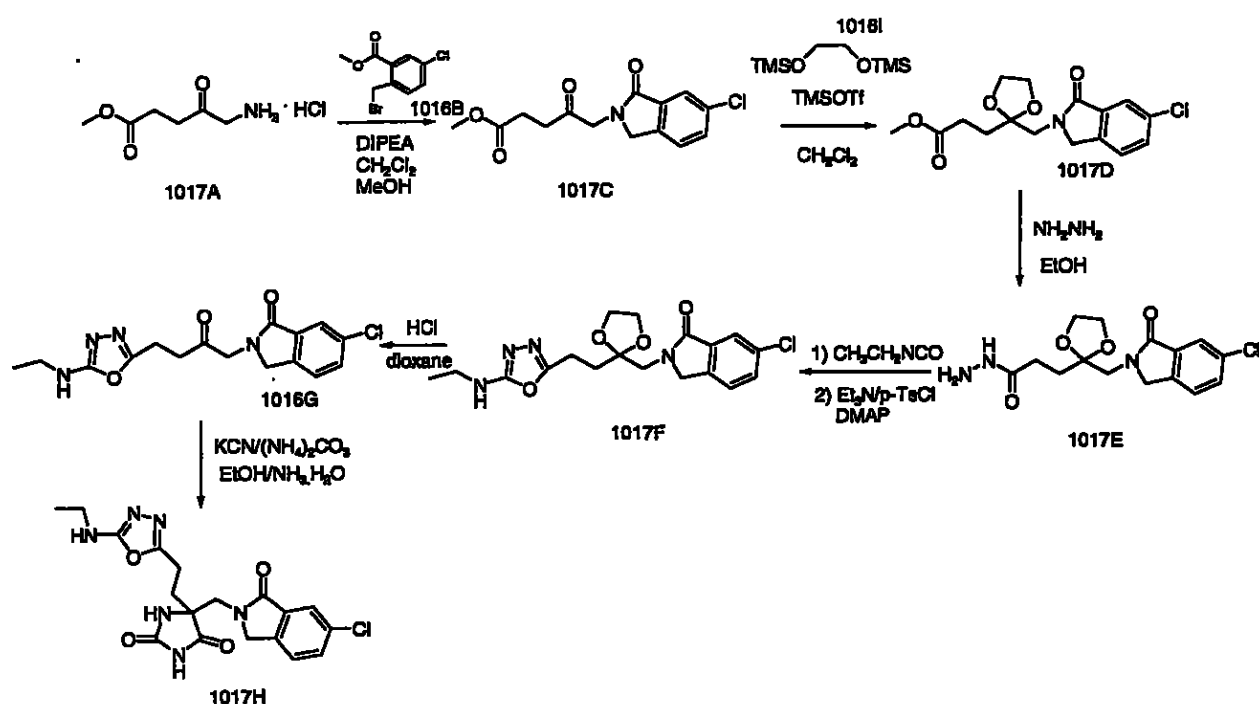
Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
278		422.08	423.1[M+H] ⁺	A
279		422.08	423.1[M+H] ⁺	C
280		420.9	421.1[M+H] ⁺	A
281		434.1	435.2[M+H] ⁺	A

Proton NMR Spectral Data for Selected Compounds in Table 1006.

Compound 278. ¹H NMR (500 Hz, CD₃OD) δ 8.503 (d, J = 4.73 Hz, 1H); 7.84 (m, 2H); 7.67 (d, J = 3.8 Hz, 1H); 7.56 (dd, J = 4.4 Hz, 8.5 Hz, 1H); 7.50 (dd, J = 2.5 Hz, 7.8 Hz, 1H); 7.38 (m, 1H); 7.33 (d, J = 4.1 Hz, 2H); 7.3 (m, 1H); 4.52 (d, J = 17 Hz, 1H); 4.45 (d, J = 17 Hz, 1H); 4.43 (d, J = 14.2 Hz, 1H); 4.28 (d, J = 14.2 Hz, 1H).

Example 1017.

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Compound 1017C: Compound **1017A** (1.5 g, 8.26 mmol) was dissolved in dichloromethane (20 mL) and methanol (10 mL) at 0 °C. Compound **1017B** (2.64 g, 10 mmol) and DIPEA (2.9 mL, 16.5 mmol) were added and the reaction was stirred at 0 °C and slowly warmed up to rt overnight. The reaction mixture was then heated to 50 °C and stirred for 2 h. The reaction mixture was washed with brine (50 mL). The organic layer was dried and concentrated to dryness. The crude material was purified via PTLC (50% EtOAc/hexanes) to give 0.7g (29%) of compound **1017C**.

Compound 1017D: Compound **1017C** (200 mg, 0.68 mmol) was stirred in CH₂Cl₂ (15 mL) at 0 °C followed by addition of compound **1017I** (0.5 mL, 2.04 mmol) and TMS-OTf (13 µL, 0.07 mmol). The reaction mixture was stirred at 0 °C to 5 °C for 6 hr before warmed up to rt and stirred overnight. The solvent was removed and the crude material was purified via PTLC (EtOAc) to give 0.21g (91%) of compound **1017D**.

Compound **1017E**: Compound **1017D** (210 mg, 0.62 mmol) was heated in a sealed tube with NH_2NH_2 (0.2 mL, 6.2 mmol) and EtOH (2 mL) at 60 °C overnight. Solvent was removed and gave crude material **1017E** (210 mg, 99%) which was used without further purification.

Compound **1017F**: Compound **1017E** (210 mg, 0.62 mmol) and ethyl isocyanate (59 μL , 0.74 mmol) were dissolved in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature overnight. To this mixture was added Et_3N (0.43 mL, 3.1 mmol), DMAP (15 mg, cat.) and *p*-TsCl (141 mg, 0.74 mmol). The reaction was stirred at rt overnight. Solvent was removed and the crude material was purified via sgc (10% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 60 mg (25%) of compound **1017F**.

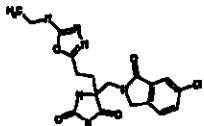
Compound **1017G**: Compound **1017F** (60 mg, 0.15 mmol) was heated in a sealed tube with HCl (3 mL, 4N in dioxane) at 65 °C for 48 hr. Solvent was removed and the crude material was purified via sgc (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 35 mg (66%) of compound **1017G**.

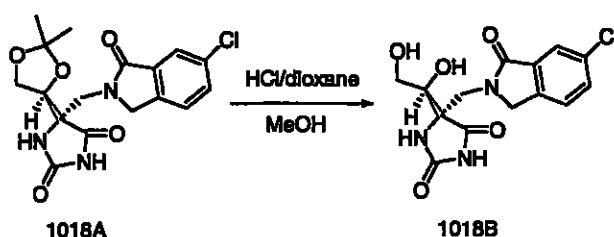
Compound **1017H**: Compound **1017G** (34 mg, 0.1 mmol), KCN (10 mg, 0.15 mmol), and $(\text{NH}_4)_2\text{CO}_3$ (30 mg, 0.3 mmol) were suspended in a mixture of $\text{NH}_3 \cdot \text{H}_2\text{O}$ (1 mL) and ethanol (1mL). The solution was stirred at 90 °C overnight. Solvent was removed and the crude material was purified via sgc (10% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 6 mg (15%) of compound **1017H**.

The following compounds were prepared as described in **Example 1017**

Table 1007

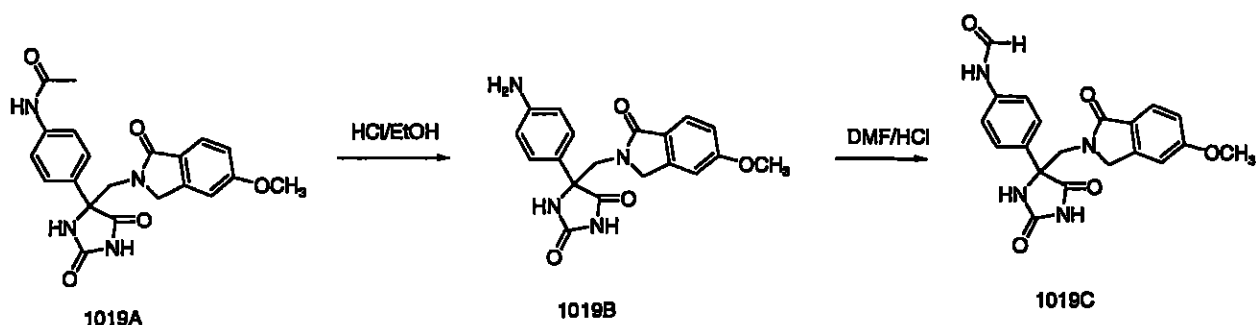
(63)

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
282		418.12	419.1[M+H] ⁺	B

Example 1018.

Compound 1018A: Compound 1018A was synthesized following procedures in Example 1012.

Compound 1018B: Compound 1018A (180 mg, 0.47 mmol) was stirred in MeOH (1 mL) at rt. HCl (3 mL, 4N in dioxane) was added and the reaction mixture was heated to 70 °C overnight. Solvent was evaporated. The crude material was taken up in water and the solid was collected by suction filtration to give 1018B (115 mg, 71%).

Example 1019.

Compound 1019A: Compound 1019A was synthesized following procedures described in Example 1012.

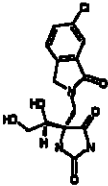
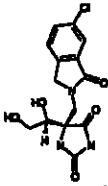
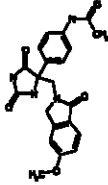
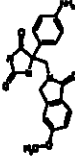
164

Compound 1019B: Compound 1019A (74 mg, 0.18 mmol) was dissolved in EtOH (2 mL) and HCl (0.4 mL, aq. 36%) was added and the reaction mixture was heated to 70 °C overnight. Solvent was removed and gave 1019B as a light yellow solid (74 mg, 99%).

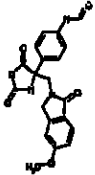
Compound 1019C: Compound 1019B (20 mg, 0.05 mmol) was stirred in DMF (1 mL) and HCl (cat., 4 N in dioxane) at 120 °C overnight. Solvent was removed and the crude material was purified via PTLC (9% NH₃•MeOH/CH₂Cl₂) to give 8 mg (37%) of Compound 1019C.

The following compounds were prepared as described in Example 1012, 1018 and 1019.

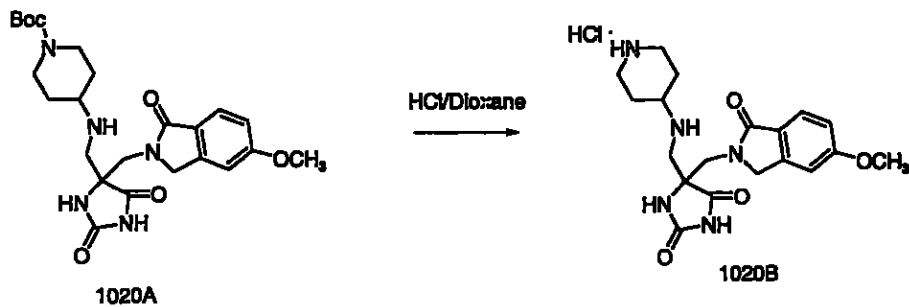
Table 1008

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
283		339.06	340.2[M+H] ⁺	B
284		339.06	340.2[M+H] ⁺	D
285		408.14	409.2[M+H] ⁺	A
286		366.13	367.1[M+H] ⁺	A

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287		394.13	395.2[M+H] ⁺	B
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Example 1020.

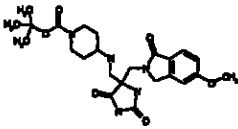
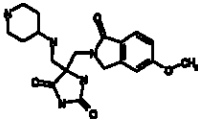


Compound 1020A: Compound 1020A was synthesized following the procedures described in Example 22.

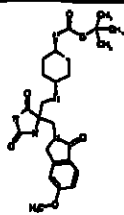
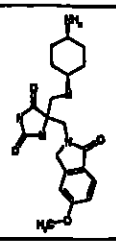
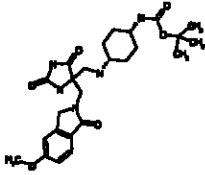
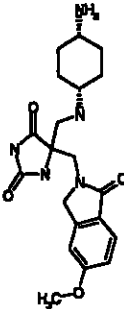
Compound 1020B: Compound 1020A (855 mg, 1.86 mmol) was stirred in MeOH (10 mL) and HCl (10 mL, 4N in dioxane) at rt for 2 hr. Solvent was removed and the material was dried to give 1020B (735 mg, 99%).

The following compounds were prepared as described in Example 22 and Example 1020.

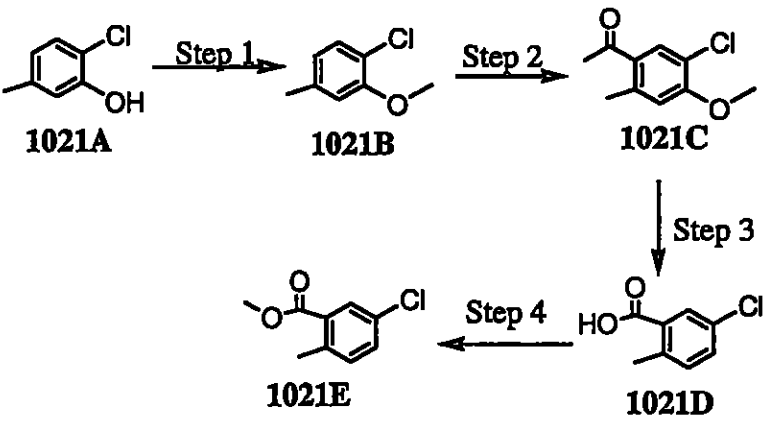
Table 1009

Compound #	Structure	Exact Mass	Mass Obsvd	KI (nM)
288		487.24	488.3[M+H] ⁺	B
289		387.19	388.1[M+H] ⁺	C

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290		501.26	502.3[M+H] ⁺	B
291		401.21	402.2[M+H] ⁺	C
292		501.26	502.3[M+H] ⁺	B
293		401.21	402.1[M+H] ⁺	B

Example 1021



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Step 1

DMF (100 mL), cesium carbonate (41.13 g, 126 mmol), and 2-chloro-5-methylphenol (1021A) (15.0 g, 105 mmol) were added to a flask. Methyl iodide (17.92 g, 126 mmol) was added dropwise via addition funnel. The reaction mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc, washed with water and brine, and dried with Na_2SO_4 . The resulting material was filtered, and concentrated to dryness. The crude product was purified via flash sgc using 1:4 EtOAc:hexanes as the mobile phase to give 15.93 g of 1021B.

Step 2

A flask containing AlCl_3 (2.55 g, 19.1 mmol), and LiCl (0.41 g, 9.6 mmol) was placed in a -30 °C cold bath. A solution of 1021B (1.0 g, 6.38 mmol) and acetyl chloride (0.75 g, 9.5 mmol) in 20 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred for 1 h at -30 °C, then allowed to warm to rt and stirred overnight at rt. The reaction mixture was poured into a mixture of ice and EtOAc. The organic layer was washed with water, saturated aq NaHCO_3 , and water, then dried with Na_2SO_4 , and concentrated to dryness to give 1.18 g of Compound 1021C.

Step 3

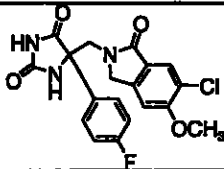
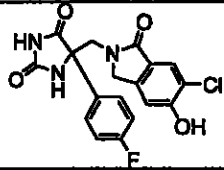
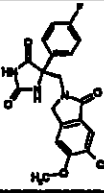
Sodium hydroxide (58 g, 1.45 mol) was dissolved in water (260 mL) and the flask was cooled in an ice-water bath. Bromine (19 mL) was added dropwise to the flask with stirring. The reaction mixture was stirred for 0.5 h after the addition was complete. The resulting solution was added dropwise to an ice-water cooled flask containing Compound 1021C (18.5 g, 93.1 mmol). After the addition was complete, the reaction mixture was allowed to warm to rt and left stirring overnight. The reaction mixture was heated at 40 °C for 2 h. NaHSO_3 (55 g) was added. The reaction mixture was stirred for 1 h. The resulting material was diluted with 10% aq NaOH and extracted with EtOAc to remove starting material. The aqueous layer was adjusted to pH 1 and extracted with additional EtOAc. The organic layer was dried with Na_2SO_4 , filtered, and concentrated to dryness to give 12.31 g of 1021D.

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Step 4
DMF (10 mL), Compound 1021D (0.50 g, 2.49 mmol), and K₂CO₃ (0.41 g, 2.96 mmol) were added to a flask. Methyl iodide (0.42 g, 2.96 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The reaction mixture was concentrated to dryness to give 0.52 g of 1021E.

The following compounds were prepared as described in step 1 in Example 14 and Example 1021.

Table 1010

Compound #	Structure	Exact Mass	Mass Obsvd	Ki (nM)
296		403.07	404.2 [M+H] ⁺	A
297		389.06	390.2 [M+H] ⁺	A
298		403.07	404.1 [M+H] ⁺	n/a

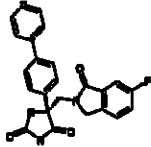
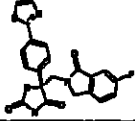
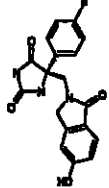
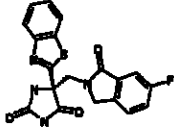
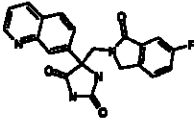
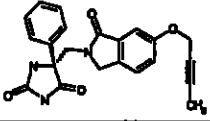
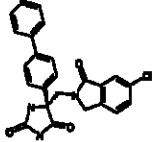
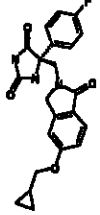
Proton NMR Spectral Data for Selected Compounds in Table 1010.

Compound 296. ¹H NMR (500 Hz, DMSO-d₆) δ 3.93 (s, 3H), 4.00 (d, J = 14 Hz, 1H), 4.19 (d, J = 14 Hz, 1H), 4.23 (d, J = 18 Hz, 1H), 4.34 (d, J = 18 Hz, 1H), 7.24-7.34 (m, 2H), 7.42 (s, 1H), 7.62-7.73 (m, 3H), 8.92 (s, 1H), 10.95 (s, 1H).

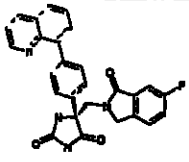
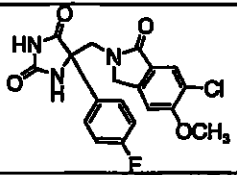
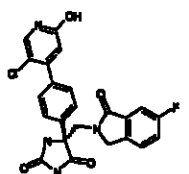
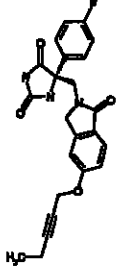
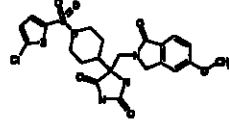
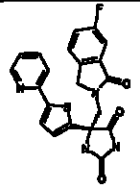
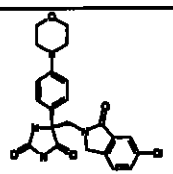
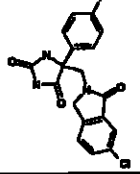
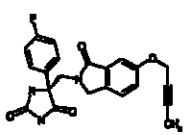
Specific TACE inhibitory activity (Ki values) of some representative compounds of the present invention are set forth below.

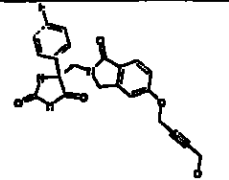
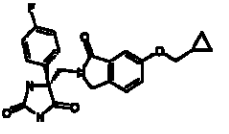
Table 1011

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Compound #	Structure	KI (nM)
111		0.46
120		4
213		0.8
181		3.17
262		4.91
198		1.29
143		1.87
219		2.4

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155		1.05
296		1.01
123		1.2
232		1.0
233		2.35
278		2.2
139		2.8
25		0.43
203		0.23

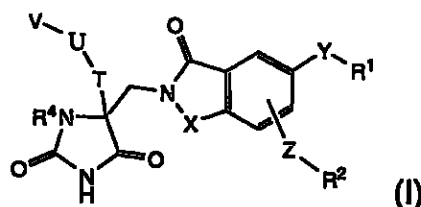
239		0.11
243		3.00

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It will be appreciated by those skilled in the art that changes could be made to the embodiments described above without departing from the broad inventive concept thereof. It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but it is intended to cover modifications that are within the spirit and scope of the invention, as defined by the appended claims.

THEREFORE, WE CLAIM:

1. A compound represented by Formula (I):



or a pharmaceutically acceptable salt, solvate or isomer thereof, wherein:

X is selected from the group consisting of $-S-$, $-C(R^4)_2-$ or $-N(R^4)-$;

T is selected from the group consisting of H (with U and V being absent), alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl, and arylalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of T is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

U is absent or present, and if present U is selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, and $-N(R^4)C(S)N(R^4)-$;

V is absent or present, and if present V is selected from the group consisting of alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of any of the aforementioned alkyl, aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties below;

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Y is absent or present, and if present Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

Z is absent or present, and if present Z is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, and $-S(O)_2-$;

n is 1 to 3;

R^1 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^1 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Y is present and Y is N, S or O, then R^1 is not halogen;

R^2 is selected from the group consisting of H, $-OR^4$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, alkylaryl, alkylheteroaryl and arylalkyl groups of R^2 is unsubstituted or optionally independently substituted with one to four R^{20} moieties which can be the same or different, each R^{20} moiety being independently selected from the group of R^{20} moieties below, with the proviso that when Z is present and Z is N, S or O, then R^2 is not halogen;

each R^4 is the same or different and is independently selected from the group consisting of H and alkyl;

R^{10} is selected from the group consisting of $-OR^4$, $-N(R^4)_2$, $-S(O)-$, $-S(O)_2-$, $-N(R^4)S(O)_2-$, $-S(O)_2N(R^4)-$, $-O(\text{fluoroalkyl})$, halogen, alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl, wherein each of the alkyl, fluoroalkyl, aryl, heteroaryl, heterocyclyl, cycloalkyl, alkylaryl and arylalkyl groups of R^{10} is unsubstituted or optionally independently substituted

with one to four R^{30} moieties which can be the same or different, each R^{30} moiety being independently selected from the group of R^{30} moieties below;

R^{20} is selected from the group consisting of halogen, alkyl, fluoroalkyl; and

R^{30} is selected from the group consisting of halogen, alkyl, and fluoroalkyl.

2. The compound of claim 1, wherein said isomer is a stereoisomer.

3. The compound of claim 1 wherein T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is $-O-$.

4. The compound of claim 1 wherein T is alkyl or aryl; X is $-C(R^4)_2-$; Y is absent; Z is absent or present, and if present Z is $-O-$; and R^2 is selected from the group consisting of alkylaryl and alkylheteroaryl.

5. The compound of claim 1 wherein T is alkyl or aryl; X is $-N(R^4)-$; Y is absent; Z is absent or present; R^2 is selected from the group consisting of H, halogen and alkyl; and if Z is present Z is $-O-$.

6. The compound of claim 1 wherein X is $-CH_2-$ or $-N(R^4)-$.

7. The compound of claim 6 wherein X is $-CH_2-$.

8. The compound of claim 6 wherein X is $-N(R^4)-$.

9. The compound of claim 8 wherein R^4 is H.

10. The compound of claim 1 wherein T is alkyl.

11. The compound of claim 10 wherein T is $-CH_3$.

12. The compound of claim 1 wherein T is aryl and said aryl is unsubstituted or optionally independently substituted with one to five R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.

13. The compound of claim 12 wherein R^{10} is halogen.

14. The compound of claim 12 wherein R^{10} is heteroaryl.

15. The compound of claim 12 wherein R^{10} is aryl.

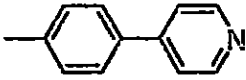
16. The compound of claim 1 wherein U selected from the group consisting of a covalent bond, $-N(R^4)-$, $-N(R^4)C(O)-$, and $-N(R^4)S(O)_2-$.

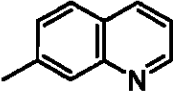
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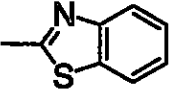
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17. The compound of claim 16 wherein U is a covalent bond.
18. The compound of claim 16 wherein U is $-N(R^4)-$.
19. The compound of claim 16 wherein U is $-N(R^4)C(O)-$.
20. The compound of claim 1 wherein V is selected from the group consisting of aryl, heteroaryl, heterocyclyl and cycloalkyl, said aryl, heteroaryl, heterocyclyl, and cycloalkyl being optionally fused with one or more moieties selected from the group consisting of aryl, heteroaryl, heterocyclyl, or cycloalkyl, wherein each of any of said aryl, heteroaryl, heterocyclyl and cycloalkyl is unsubstituted or optionally independently substituted with one to four R^{10} moieties which can be the same or different, each R^{10} moiety being independently selected from the group of R^{10} moieties.
21. The compound of claim 1 wherein Y is selected from the group consisting of a covalent bond, $-(C(R^4)_2)_n-$, $-C(O)-$ and $-O-$.
22. The compound of claim 21 wherein Y is $-O-$.
23. The compound of claim 21 wherein Y is $-(C(R^4)_2)_n-$.
24. The compound of claim 21 wherein Y is $-C(O)-$.
25. The compound of claim 21 wherein Y is a covalent bond.
26. The compound of claim 1 wherein R^1 is selected from the group consisting of $-OR^4$, H, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.
27. The compound of claim 26 wherein R^1 is H.
28. The compound of claim 26 wherein R^1 is alkylaryl.
29. The compound of claim 26 wherein R^1 is alkyl.
30. The compound of claim 26 wherein R^1 is fluoroalkyl.
31. The compound of claim 26 wherein R^1 is halogen.
32. The compound of claim 26 wherein R^1 is $-OR^4$.
33. The compound of claim 32 wherein R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_3$.
34. The compound of claim 32 wherein R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{OH}$.
35. The compound of claim 32 wherein R^4 is $-\text{CH}_2-$ .
36. The compound of claim 29 wherein said alkyl is $-\text{CH}_3$.
37. The compound of claim 29 wherein said alkyl is $-\text{CH}_2\text{CH}_3$.

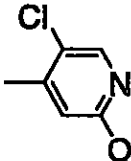
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38. The compound of claim 1 wherein T, U, and V when taken together form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -CH₂-.

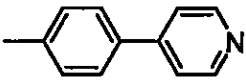
39. The compound of claim 1 wherein T, U, and V when taken together form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

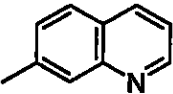
40. The compound of claim 1 wherein T, U, and V when taken together form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

41. The compound of claim 1 wherein T, U, and V when taken together

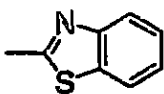
form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

42. The compound of claim 1 wherein T, U, and V when taken together form  and R¹ is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

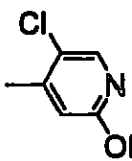
43. The compound of claim 1 wherein T, U, and V when taken together form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

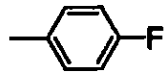
44. The compound of claim 1 wherein T, U, and V when taken together form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

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45. The compound of claim 1 wherein T, U, and V when taken together form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

46. The compound of claim 1 wherein T, U, and V when taken together

form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

47. The compound of claim 1 wherein T, U, and V when taken together form  and R² is selected from the group consisting of F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, and -OCH₂-.

48. The compound of claim 30 wherein said fluoroalkyl is -CH₂CF₃.

49. The compound of claim 31 wherein said halogen is selected from the group consisting of -Br, -Cl and -F.

50. The compound of claim 32 wherein R⁴ is -CH₃.

51. The compound of claim 29 wherein said alkyl is substituted with one to four R²⁰ moieties which can be the same or different, each R²⁰ moiety being independently selected from the group of R²⁰ moieties.

52. The compound of claim 51 wherein R²⁰ is aryl.

53. The compound of claim 1 wherein Z is selected from the group consisting of a covalent bond, -N(R⁴)-, -(C(R⁴)₂)_n-, -C(O)- and -O-.

54. The compound of claim 53 wherein Z is -O-.

55. The compound of claim 53 wherein Z is a covalent bond.

56. The compound of claim 53 wherein Z is -N(R⁴)-.

57. The compound of claim 53 wherein Z is -C(O)-.

58. The compound of claim 53 wherein R⁴ is alkyl.

59. The compound of claim 58 wherein said alkyl is -CH₃.

60. The compound of claim 53 wherein R^2 is selected from the group consisting of $-OR^4$, hydrogen, alkyl, fluoroalkyl, alkylaryl, halogen, and heteroaryl.

61. The compound of claim 60 wherein R^2 is hydrogen.

62. The compound of claim 60 wherein R^2 is alkyl.

63. The compound of claim 60 wherein R^2 is alkylaryl.

64. The compound of claim 60 wherein R^2 is fluoroalkyl.

65. The compound of claim 64 wherein said fluoroalkyl is $-\text{CH}_2\text{CF}_3$.

66. The compound of claim 60 wherein R^2 is halogen.

67. The compound of claim 66 wherein said halogen is selected from the group consisting of $-\text{Br}$, $-\text{Cl}$ and $-\text{F}$.

68. The compound of claim 60 wherein R^2 is heteroaryl.

69. The compound of claim 60 wherein R^4 is $-\text{CH}_3$.

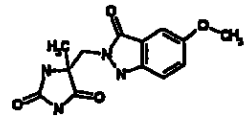
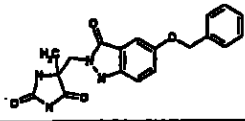
70. The compound of claim 60 wherein R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_3$.

71. The compound of claim 60 wherein R^4 is $-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{OH}$.

72. The compound of claim 60 wherein R^4 is $-\text{CH}_2$ .

73. The compound of claim 60 wherein said alkyl is $-\text{CH}_3$.

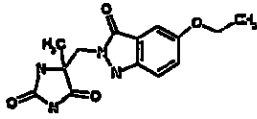
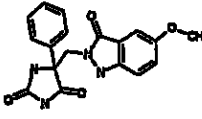
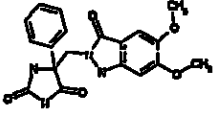
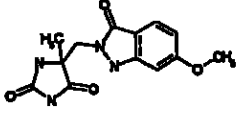
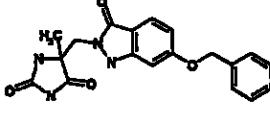
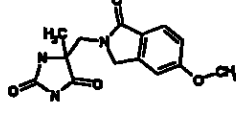
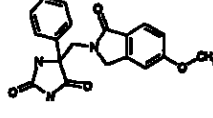
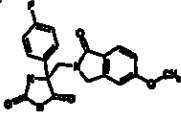
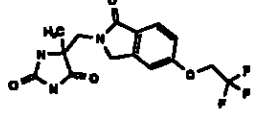
74. A compound exhibiting inhibitory activity of a tumor necrosis factor-alpha-converting enzyme (TACE), tumor necrosis factor-alpha (TNF- α), matrix metalloproteinases (MMPs), a disintegrin and metalloproteases (ADAMs) or any combination thereof, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

Compound #	Structures
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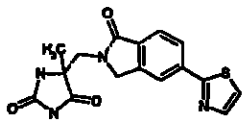
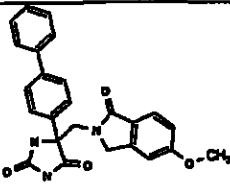
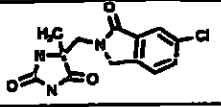
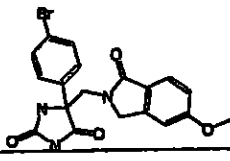
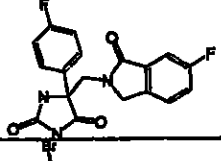
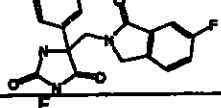
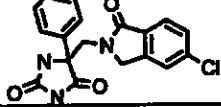
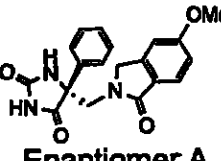
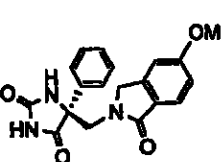
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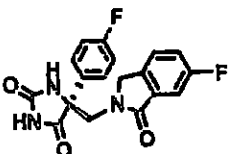
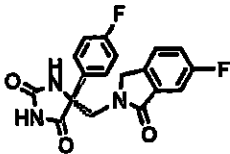
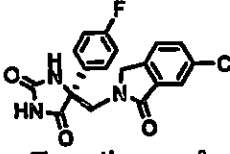
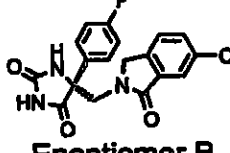
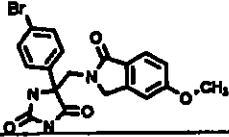
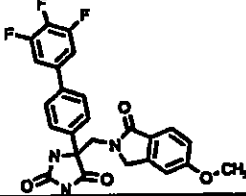
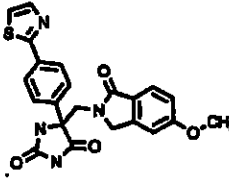
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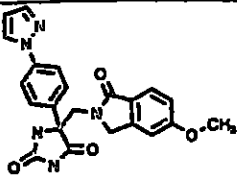
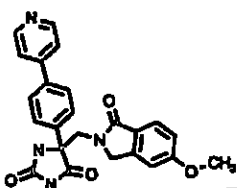
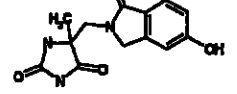
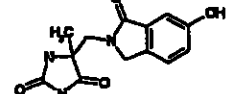
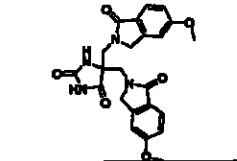
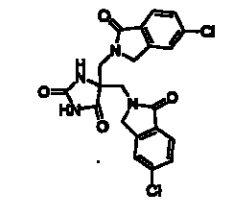
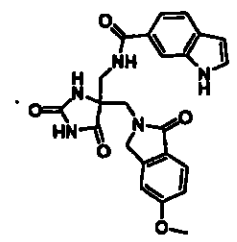
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20	 Enantiomer A
21	 Enantiomer B

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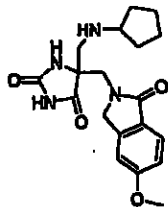
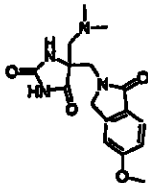
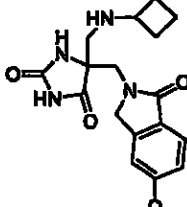
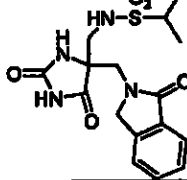
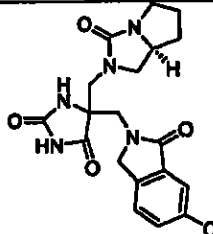
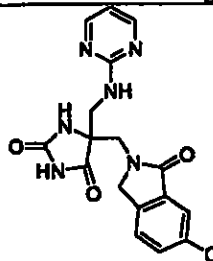
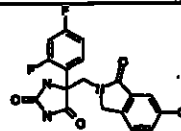
22	 Enantiomer A
23	 Enantiomer B
24	 Enantiomer A
25	 Enantiomer B
26	 Enantiomer A
27	 Enantiomer B
28	 Enantiomer A

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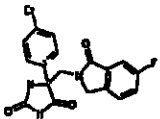
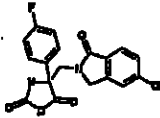
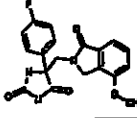
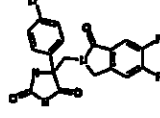
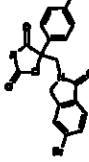
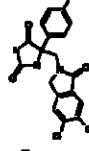
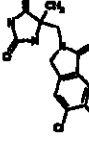
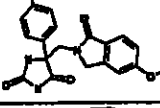
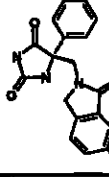
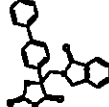
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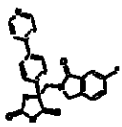
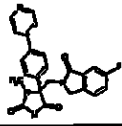
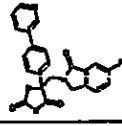
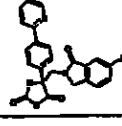
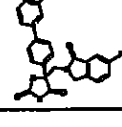
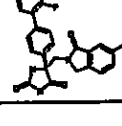
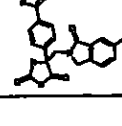
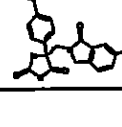
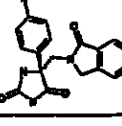
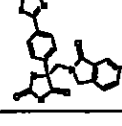
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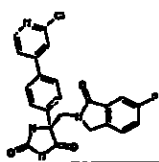
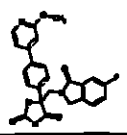
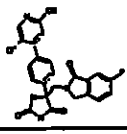
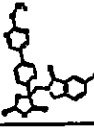
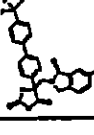
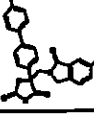
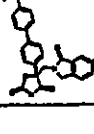
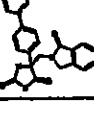
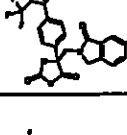
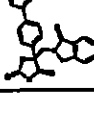
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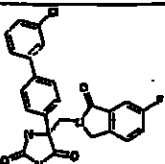
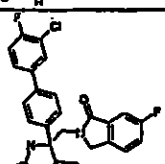
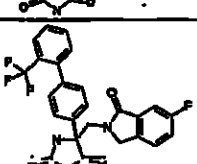
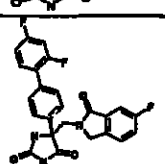
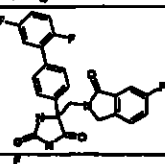
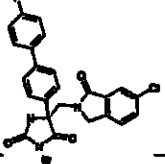
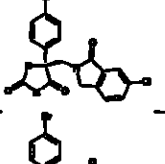
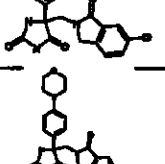
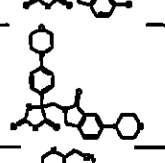
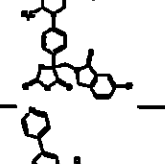
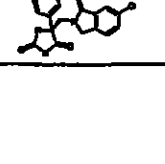
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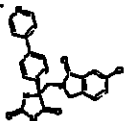
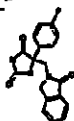
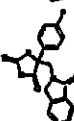
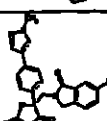
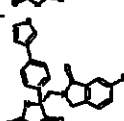
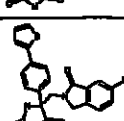
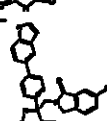
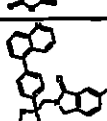
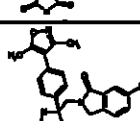
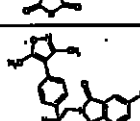
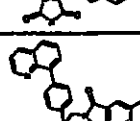
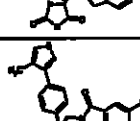
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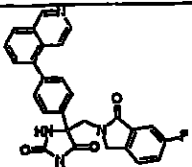
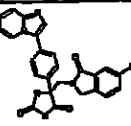
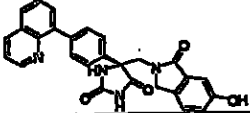
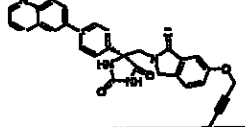
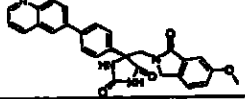
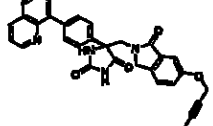
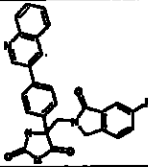
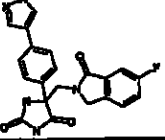
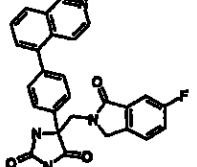
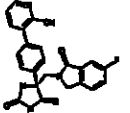
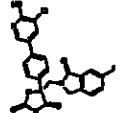
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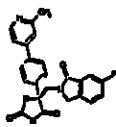
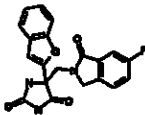
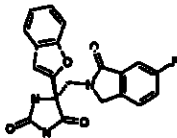
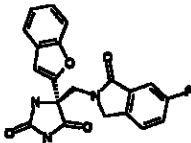
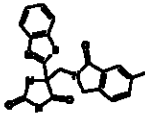
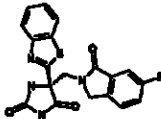
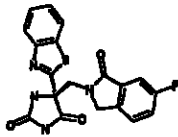
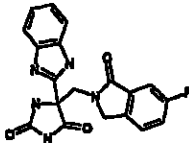
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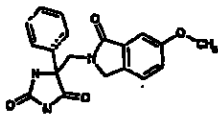
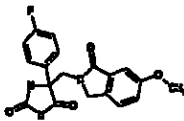
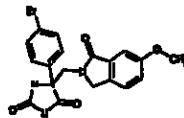
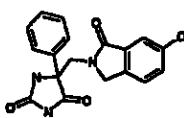
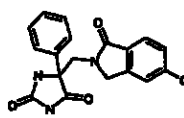
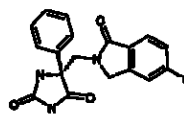
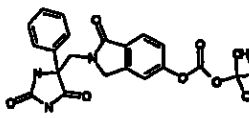
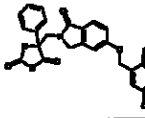
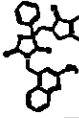
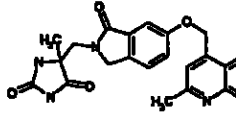
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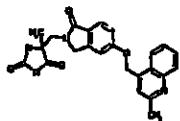
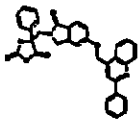
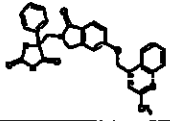
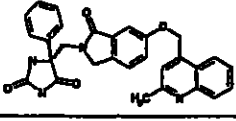
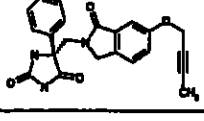
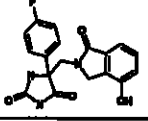
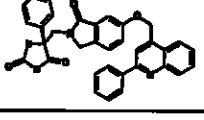
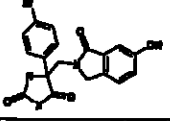
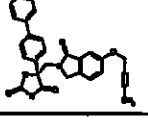
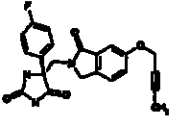
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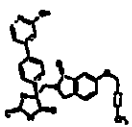
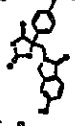
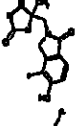
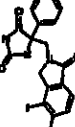
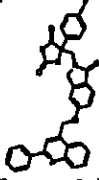
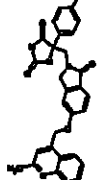
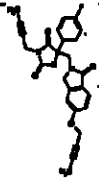
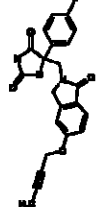
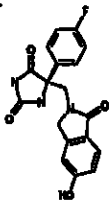
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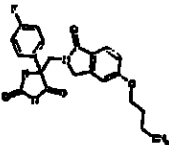
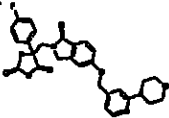
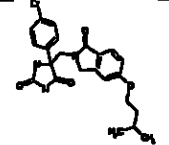
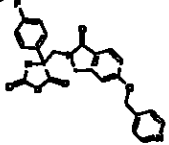
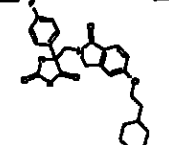
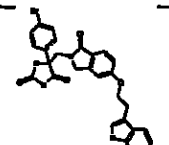
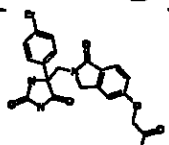
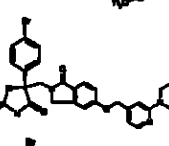
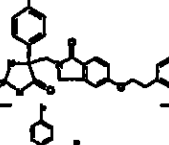
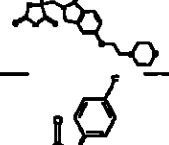
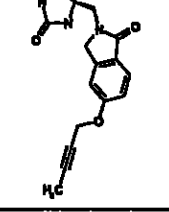
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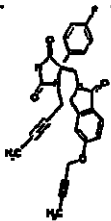
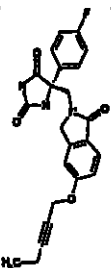
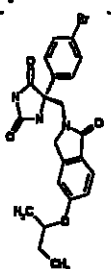
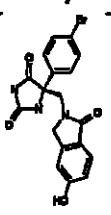
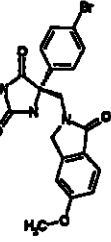
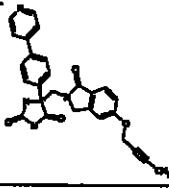
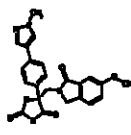
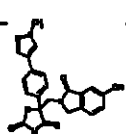
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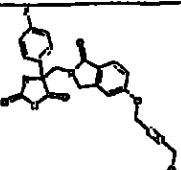
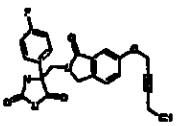
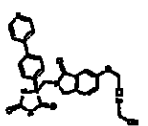
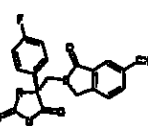
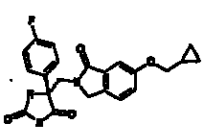
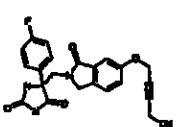
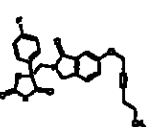
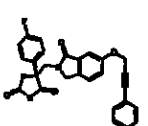
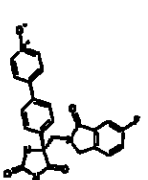
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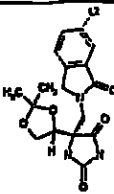
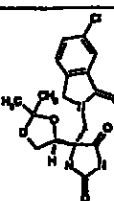
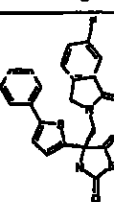
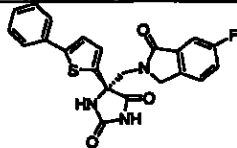
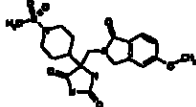
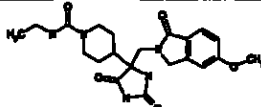
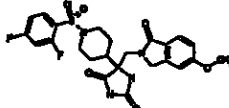
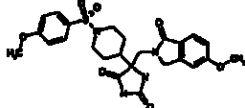
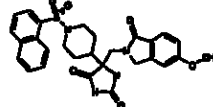
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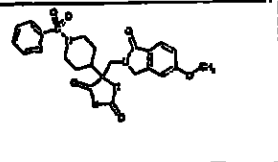
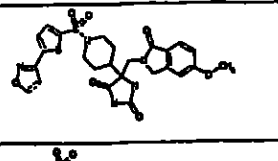
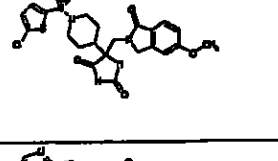
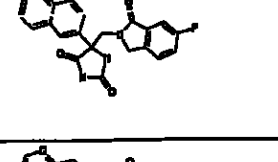
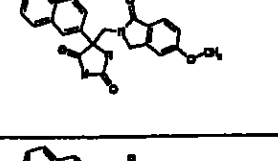
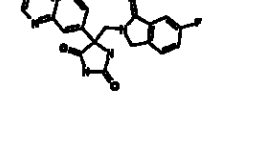
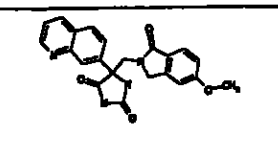
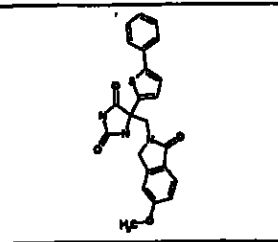
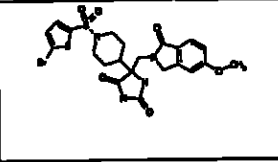
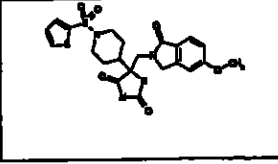
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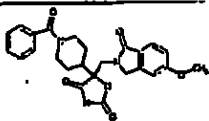
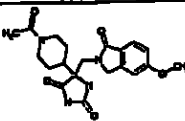
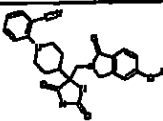
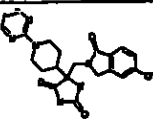
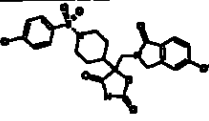
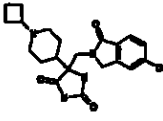
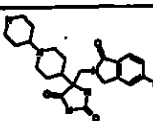
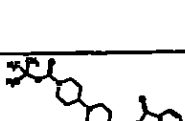
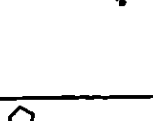
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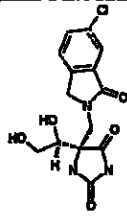
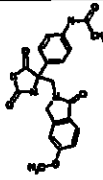
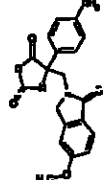
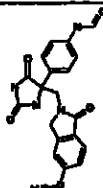
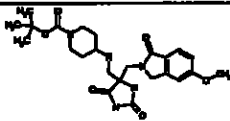
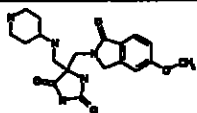
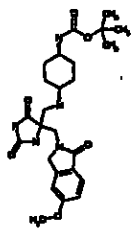
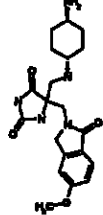
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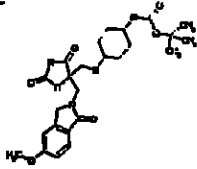
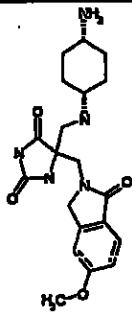
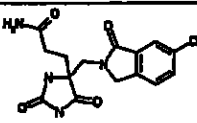
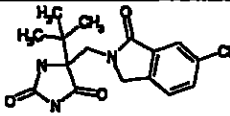
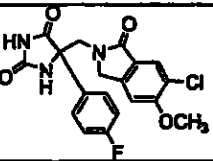
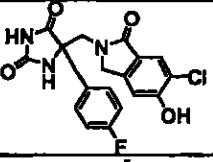
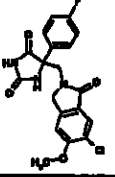
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RECTIFIED SHEET (RULE 91) ISA/EP

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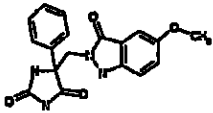
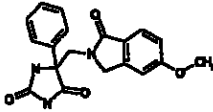
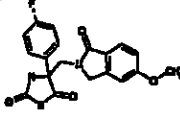
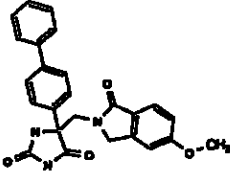
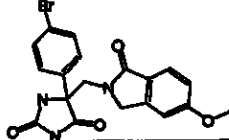
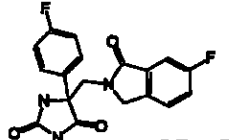
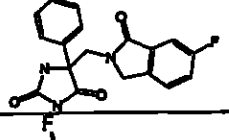
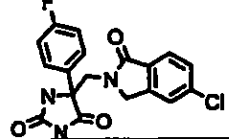
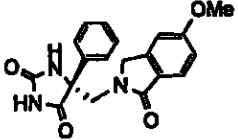
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75. The compound of claim 74, wherein said compound is selected from the compounds of structures listed below:

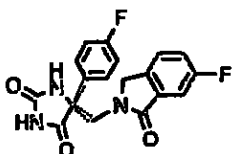
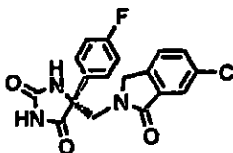
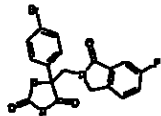
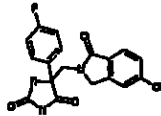
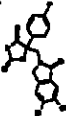
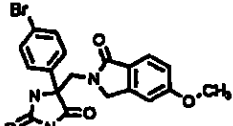
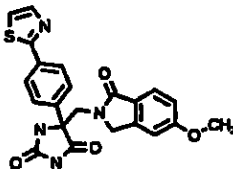
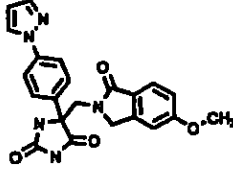
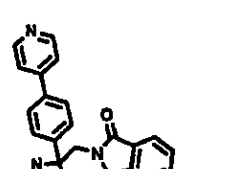
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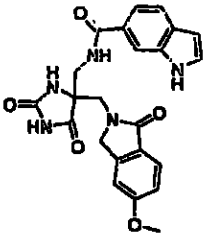
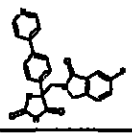
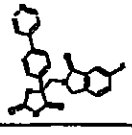
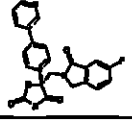
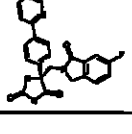
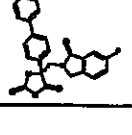
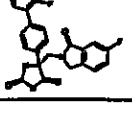
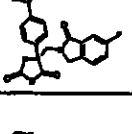
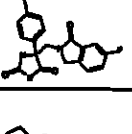
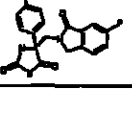
Compound #	Structure
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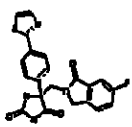
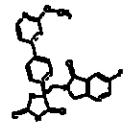
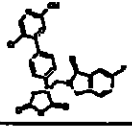
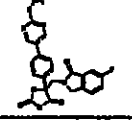
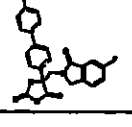
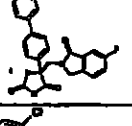
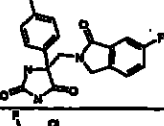
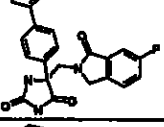
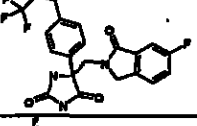
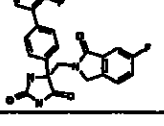
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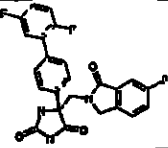
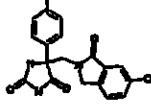
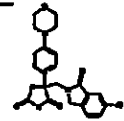
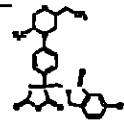
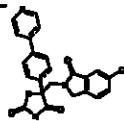
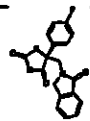
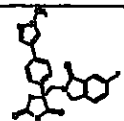
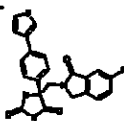
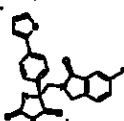
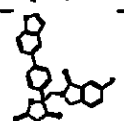
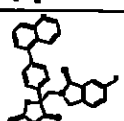
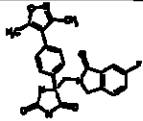
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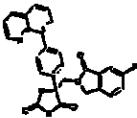
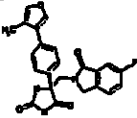
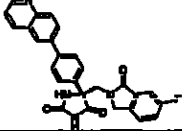
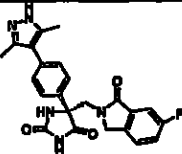
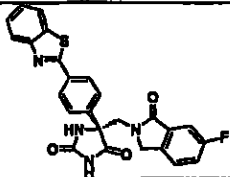
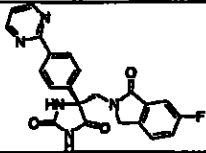
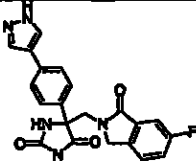
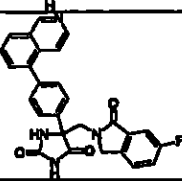
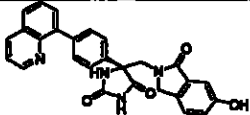
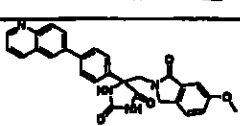
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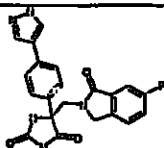
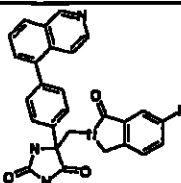
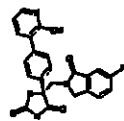
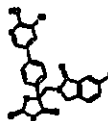
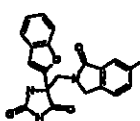
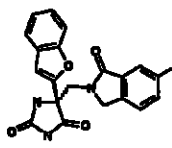
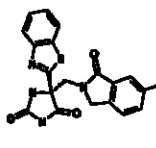
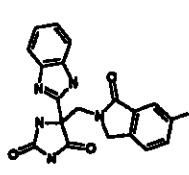
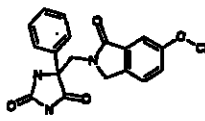
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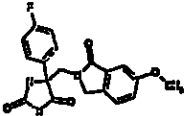
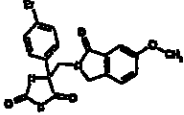
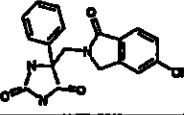
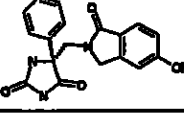
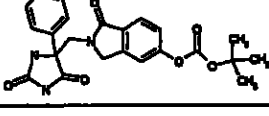
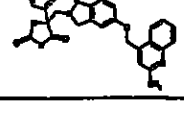
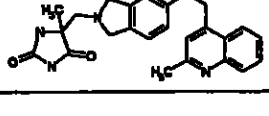
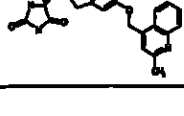
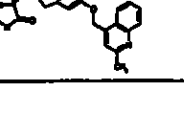
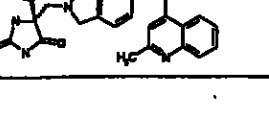
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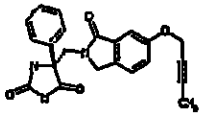
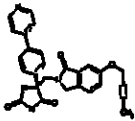
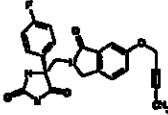
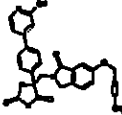
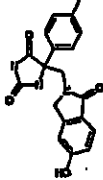
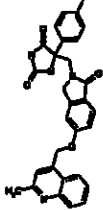
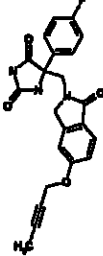
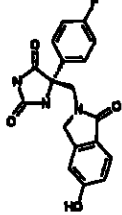
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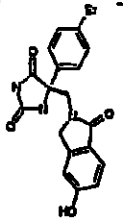
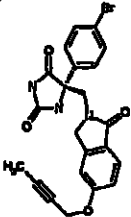
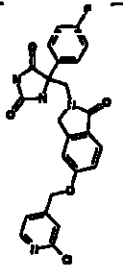
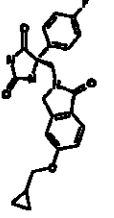
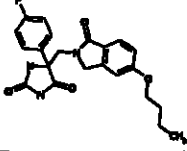
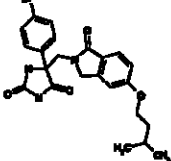
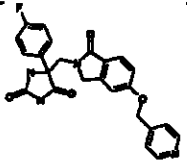
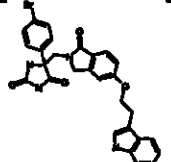
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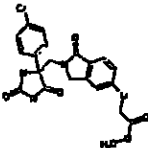
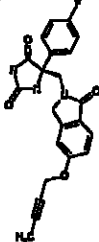
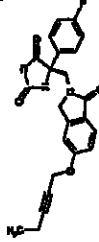
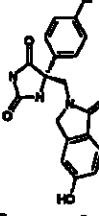
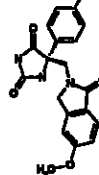
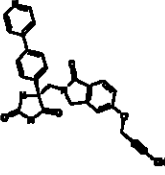
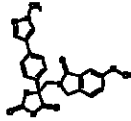
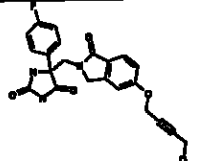
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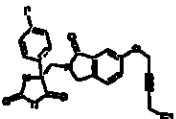
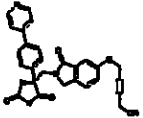
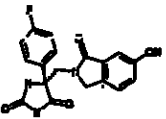
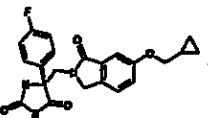
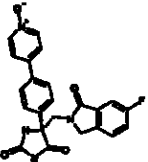
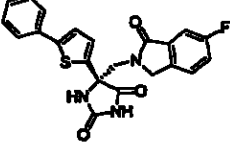
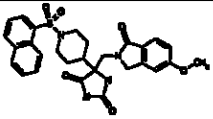
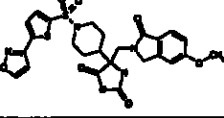
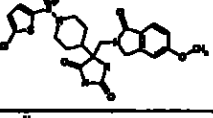
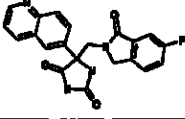
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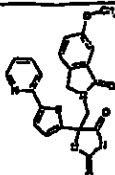
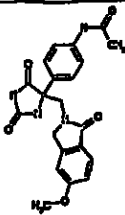
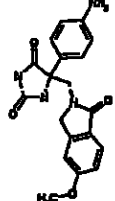
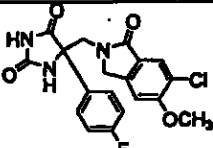
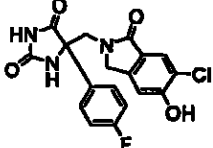
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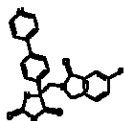
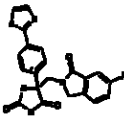
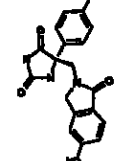
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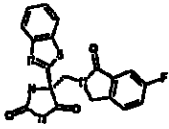
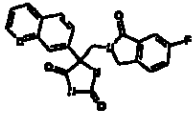
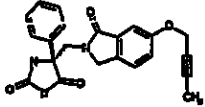
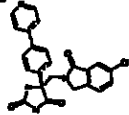
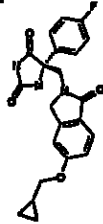
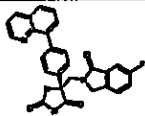
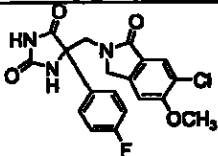
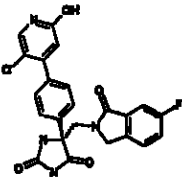
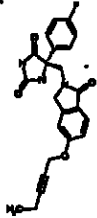
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76. The compound of claim 75, wherein said compound is selected from the compounds of structures listed below:

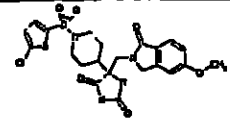
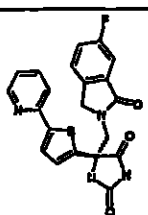
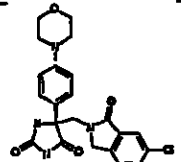
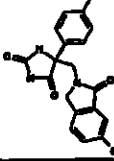
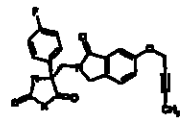
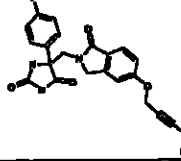
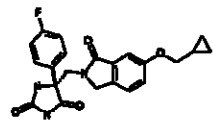
Compound #	Structure
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RECTIFIED SHEET (RULE 91) ISA/EP

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77. The pharmaceutical composition of claim 1 additionally comprising at least one pharmaceutically acceptable carrier.

78. A method of treating disorders associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

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79. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with TACE, TNF- α , MMPs, ADAMs, or any combination thereof.

80. A method of preparing a pharmaceutical composition for treating the disorders associated with TACE, TNF- α , MMPs, ADAMs or any combination thereof, said method comprising bringing into intimate contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

81. A pharmaceutical composition for treating disorders associated with TACE, TNF- α , MMP, ADAM or any combination thereof in a subject comprising, administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

82. A compound of claim 1 in purified form.

83. A method of treating a condition or disease mediated by TACE, MMPs, TNF- α , aggrecanase, or any combination thereof in a subject comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

84. A method of treating a condition or disease selected from the group consisting of rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, inflammatory bowel disease, multiple sclerosis and psoriasis in a subject, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

85. A method of treating a condition or disease selected from the group consisting of fever, cardiovascular conditions, hemorrhage, coagulation, cachexia, anorexia, alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease and HIV infection in a subject comprising administering to the subject in need of such treatment a

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therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

86. A method of treating a condition or disease selected from the group consisting of septic shock, haemodynamic shock, sepsis syndrome, post ischaemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancers such as cutaneous T-cell lymphoma, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, inflammatory bowel diseases such as Crohn's disease and colitis, osteo and rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, adult Still's disease, urethritis, Wegener's granulomatosis, Behcehe disease, Sjogren's syndrome, sarcoidosis, polymyositis, dermatomyositis, multiple sclerosis, sciatica, complex regional pain syndrome, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV, non-insulin dependent diabetes mellitus, systemic lupus erythematosus, glaucoma, sarcoidosis, idiopathic pulmonary fibrosis, bronchopulmonary dysplasia, retinal disease, scleroderma, osteoporosis, renal ischemia, myocardial infarction, cerebral stroke, cerebral ischemia, nephritis, hepatitis, glomerulonephritis, cryptogenic fibrosing aveolitis, psoriasis, transplant rejection, atopic dermatitis, vasculitis, allergy, seasonal allergic rhinitis, reversible airway obstruction, adult respiratory distress syndrome, asthma, chronic obstructive pulmonary disease (COPD) and bronchitis in a subject comprising administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

87. A method of treating a condition or disease associated with COPD, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

88. A method of treating a condition or disease associated with rheumatoid arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

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89. A method of treating a condition or disease associated with Crohn's disease, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

90. A method of treating a condition or disease associated with psoriasis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

91. A method of treating a condition or disease associated with ankylosing spondylitis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

92. A method of treating a condition or disease associated with sciatica, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

93. A method of treating a condition or disease associated with complex regional pain syndrome, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

94. A method of treating a condition or disease associated with psoriatic arthritis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof.

95. A method of treating a condition or disease associated with multiple sclerosis, comprising: administering to the subject in need of such treatment a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate or isomer thereof, in combination with a compound selected from the group consisting of Avonex®, Betaseron, Copaxone or other compounds indicated for the treatment of multiple sclerosis.

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96. The method of claim 83 further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of disease modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 selective (COX-2) inhibitors, COX-1 inhibitors, immunosuppressives, biological response modifiers (BRMs), anti-inflammatory agents and H1 antagonists.

97. A method of claim 84, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDs, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

98. A method of claim 85, further comprising administering to said subject a therapeutically effective amount of at least one medicament selected from the group consisting of DMARDs, NSAIDs, COX-2 inhibitors, COX-1 inhibitors, immunosuppressives, BRMs, anti-inflammatory agents and H1 antagonists.

COMPUESTOS PARA EL TRATAMIENTO DE TRASTORNOS**INFLAMATORIOS****ANTECEDENTES DE LA INVENCION****Campo de la Invención**

Esta invención se refiere generalmente a novedosos derivados de hidantoína que pueden inhibir metaloproteinasas de matriz (MMPs, correspondiente a "matrix metalloproteinases"), una desintegrina y metaloproteasas (ADAMs) y/o enzima convertidora del factor alfa de necrosis tumoral (TACE correspondiente a "tumor necrosis factor alpha - converting enzyme") y al hacerlo se evita la liberación del factor alfa de necrosis tumoral (TNF- α), composiciones farmacéuticas que comprenden tales compuestos y métodos de tratamiento utilizando tales compuestos.

Descripción

La osteoartritis y la artritis reumatoidea (OA y AR, respectivamente) son enfermedades destructivas del cartílago articular caracterizadas por la erosión localizada de la superficie del cartílago. Los hallazgos han demostrado que el cartílago articular de las cabezas femorales de pacientes con OA, por ejemplo, tenían una incorporación reducida de sulfato radiorotulado con respecto a los controles, sugiriendo que debe haber un aumento del índice de degradación del cartílago en la OA (Mankin et al. J. Bone Joint Surg. 52A (1970) 424-434). Existen cuatro clases de enzimas degradantes de proteína en células de mamífero: serina, cisteína, aspártico y metaloproteasas. La evidencia disponible sustenta la creencia de que son las metaloproteasas las responsables de la degradación de la matriz extracelular del cartílago articular en la OA y la AR. El aumento de las actividades de colagenasas y estromelisina se ha encontrado en el cartílago de la OA y la actividad se correlaciona con la severidad de la lesión (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983,

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63-68 y Ibid. 27, 1984, 305-312). Adicionalmente, se ha identificado la agrecanasa (una metaloproteasa recientemente identificada) que provee el producto de disociación específico de proteoglicano, encontrado en pacientes con AR y OA (Lohmander L. S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Las metaloproteasas (MPs) han sido implicadas como las enzimas clave en la destrucción de cartílago y hueso de mamífero. Puede esperarse que la patogénesis de tales enfermedades puede modificarse en forma beneficiosa mediante la administración de inhibidores de MP (véase Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

Las MMPs son una familia de más de 20 enzimas diferentes que están involucradas en una variedad de procesos biológicos importantes en la ruptura no controlada de tejido conectivo, incluyendo proteoglicano y colágeno, conduciendo a la resorción de la matriz extracelular. Esta es una característica de muchas afecciones patológicas, tales como la AR y la OA, ulceración córnea, epidérmica o gástrica; metástasis tumoral o invasión tumoral; enfermedad periodontal y enfermedad ósea. Normalmente, estas enzimas catabólicas son estrechamente reguladas en el nivel de su síntesis así como también en su nivel de actividad extracelular a través de la acción de inhibidores específicos, tales como alfa-2-macroglobulinas y TIMPs (inhibidor de tejido de MPs), los cuales forman complejos inactivos con las MMP's.

El factor alfa de necrosis tumoral (TNF- α) es una citoquina asociada a las células que es procesada de una forma de precursor de 26 kDa hasta una forma activa de 17 kd. Ver Black R.A. "Tumor necrosis factor-alpha converting enzyme" Int J Biochem Cell Biol. Enero 2002; 34(1):1-5 y Moss ML, White JM, Lambert MH, Andrews RC. "TACE and other ADAM proteases as targets for drug discovery" Drug Discov Today. 1 de Abril de 2001;6(8):417-426, cada uno de los cuales se incorpora como referencia en la presente invención.

Se ha demostrado que TNF- α juega un rol pivotal en las respuestas inmunes e inflamatorias. La expresión inapropiada o la sobreexpresión de TNF- α es un sello distintivo de una cantidad de enfermedades, incluyendo la AR, enfermedad de Crohn, esclerosis múltiple, soriasis y sepsis. La inhibición de la producción de TNF- α se ha mostrado que es beneficiosa en muchos modelos preclínicos de enfermedad inflamatoria, haciendo la inhibición de la producción de TNF- α o señalamiento de un objetivo atractivo para el desarrollo de fármacos anti-inflamatorios novedosos.

TNF- α es un mediador primario en seres humanos y animales de la inflamación, fiebre y respuestas de fase aguda, similares a las observadas durante la infección aguda y choque. El exceso de TNF- α ha demostrado ser letal. El bloqueo de los efectos de TNF- α con anticuerpos específicos puede ser beneficioso en una variedad de afecciones, incluyendo enfermedades autoinmunes tales como AR (Feldman et al, Lancet, (1994) 344, 1105), diabetes mellitus no dependiente de insulina (Lohmander L. S. et al., Arthritis Rheum. 36 (1993) 1214-22) y enfermedad de Crohn (Macdonald T. et al., Clin. Exp. Immunol. 81 (1990) 301).

Los compuestos que inhiben la producción de TNF- α son, por ende, de importancia terapéutica para el tratamiento de trastornos inflamatorios. Recientemente, se ha demostrado que las metaloproteasas, tales como TACE, son capaces de convertir TNF- α de su forma inactiva a su forma activa (Gearing et al Nature, 1994, 370, 555). Puesto que la producción en exceso de TNF- α se ha notado en diversas patologías también caracterizadas por la degradación del tejido mediada por MMP, compuestos los cuales inhiben tanto la producción de MMPs como de TNF- α también pueden tener una ventaja en particular en enfermedades donde ambos mecanismos están involucrados.

Un método para inhibir los efectos perjudiciales de TNF- α consiste en inhibir la enzima, TACE antes de que pueda procesar TNF- α a su forma soluble. TACE es un miembro de la familia ADAM de las proteínas de membrana tipo I e interviene en el corte proteolítico ("shedding") de ectodominios de diversas proteínas de adhesión y señalamiento ancladas a membrana. TACE ha ganado cada vez más importancia en el estudio de diversas enfermedades, incluyendo enfermedad inflamatoria, debido a su rol en la disociación de TNF- α de su secuencia "tallo" y así liberando la forma soluble de la proteína TNF- α (Black R.A. Int J Biochem Cell Biol. 2002 34,1-5).

Existen numerosas patentes y publicaciones las cuales describen inhibidores de MMP a base de hidroxamato, sulfonamida, hidantoína, carboxilato y/o lactama.

Las patentes de los Estados Unidos 6.677.355 y 6.534.491(B2), describen compuestos que son derivados de ácido hidroxámico e inhibidores de MMP.

La Patente de los Estados Unidos 6.495.565 describe derivados de lactama que son inhibidores potenciales de MMPs y/o TNF- α .

Las Publicaciones PCT WO2002/074750, WO2002/096426, WO20040067996, WO2004012663, WO200274750 y WO2004024721 describen derivados de hidantoína que son inhibidores potenciales de MMPs.

Las Publicaciones PCT WO2004024698 y WO2004024715 describen derivados de sulfonamida que son inhibidores potenciales de MMPs.

Las Publicaciones PCT WO2004056766, WO2003053940 y WO2003053941 también describen inhibidores potenciales de TACE y MMPs.

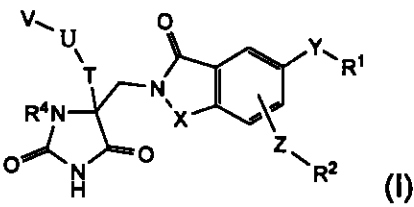
Existe una necesidad en la técnica de inhibidores de MMPs, ADAMs, TACE, y TNF- α , los cuales pueden ser útiles como compuestos anti-inflamatorios y agentes terapéuticos protectores del cartílago. La inhibición de TNF- α , TACE y/o otras MMPs puede prevenir la degradación del cartílago por estas enzimas,

aliviando de ese modo las patologías de la OA y la AR así como también de muchas otras enfermedades auto-inmunes.

SÍNTESIS DE LA INVENCION

En sus muchas realizaciones, la presente invención provee una clase novedosa de compuestos como inhibidores de TACE, la producción de TNF-α, MMPs, ADAMs o cualquier combinación de los mismos, métodos para la preparación de tales compuestos, composiciones farmacéuticas que comprenden uno o más compuestos de ese tipo, métodos para preparar formulaciones farmacéuticas que comprenden uno o más compuestos de ese tipo, y métodos de tratamiento, prevención, inhibición o mejora de una o más enfermedades asociadas con TACE, TNF-α, MMPs, ADAMs o cualquier combinación de los mismos utilizando tales compuestos o composiciones farmacéuticas.

En una realización, la presente solicitud describe un compuesto, o sales o solvatos farmacéuticamente aceptables de dicho compuesto, teniendo dicho compuesto la estructura general que se muestra en la fórmula (I):



o su sal, solvato o isómero farmacéuticamente aceptable, en donde:

X se selecciona del grupo formado por -S-, -C(R⁴)₂- o -N(R⁴)-;

T se selecciona del grupo formado por H (estando U y V ausentes), alquilo, alquenilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo, y arilalquilo, estando dicho arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo opcionalmente fusionado con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en

donde cada uno de cualquiera de los grupos alquilo, alquenilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo antes mencionados de T

está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} es independientemente seleccionada del grupo de porciones R^{10} que aparecen más adelante;

U está ausente o presente, y si está presente U se selecciona del grupo formado por un enlace covalente, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, y $-N(R^4)C(S)N(R^4)-$;

V está ausente o presente, y si está presente V se selecciona del grupo formado por alquilo, arilo, heteroarilo, heterociclilo y cicloalquilo, dicho arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo están opcionalmente fusionados con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en donde cada uno de cualquiera de los antes mencionados alquilo, arilo, heteroarilo, heterociclilo y cicloalquilo está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente del grupo de porciones R^{10} que aparecen más adelante;

Y está ausente o presente, y si está presente Y se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, y $-S(O)_2-$;

Z está ausente o presente, y si está presente Z se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, y $-S(O)_2-$;

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n es 1 a 3;

R^1 se selecciona del grupo formado por H, $-OR^4$, halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo de R^1 está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} que aparecen más adelante, con la condición de que cuando Y está presente e Y es N, S o O, entonces R^1 no es halógeno;

R^2 se selecciona del grupo formado por H, $-OR^4$, halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo de R^2 está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} que aparecen más adelante, con la condición de que cuando Z está presente y Z es N, S o O, entonces R^2 no es halógeno;

cada R^4 es igual o diferente y se selecciona independientemente del grupo formado por H y alquilo;

R^{10} se selecciona del grupo formado por $-OR^4$, $-N(R^4)_2$, $-S(O)-$, $-S(O)_2-$, $-N(R^4)S(O)_2-$, $-S(O)_2N(R^4)-$, $-O(\text{fluoralquilo})$, halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo de R^{10} está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{30} las cuales pueden ser iguales o

diferentes, cada porción R^{30} se selecciona independientemente del grupo de porciones R^{30} que aparecen más adelante;

R^{20} se selecciona del grupo formado por halógeno, alquilo, fluoralquilo; y

R^{30} se selecciona del grupo formado por halógeno, alquilo, y fluoralquilo.

Los compuestos de la Fórmula I pueden ser útiles como inhibidores de TACE y pueden ser útiles en el tratamiento y prevención de enfermedades asociadas con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos.

DESCRIPCIÓN DETALLADA DE LA INVENCION

En sus diversas realizaciones, la presente invención provee una clase novedosa de inhibidores de TACE, la producción de TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, composiciones farmacéuticas que contienen uno o más de los compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más compuestos de ese tipo, y métodos de tratamiento, prevención o mejora de uno o más de los síntomas de la inflamación.

En una realización, la presente invención provee compuestos los cuales son representados mediante la Fórmula estructural (I) que aparece en lo que antecede o su sal, solvato o isómero farmacéuticamente aceptable, en donde las diversas porciones son según lo descrito anteriormente.

En otra realización, el isómero al que se hace referencia en el párrafo precedente es un estereoisómero.

En una realización, T es alquilo o arilo; X es $-C(R^4)_2-$; Y está ausente; Z está ausente o presente; R^2 se selecciona del grupo formado por H, halógeno y alquilo; y si Z está presente Z es -O-.

En otra realización, T es alquilo o arilo; X es $-C(R^4)_2-$; Y está ausente; Z está ausente o presente, y si está presente Z es -O-; y R^2 se selecciona del grupo formado por alquilarilo y alquilheteroarilo.

En otra realización, T es alquilo o arilo; X es $-N(R^4)-$; Y está ausente; Z está ausente o presente; R^2 se selecciona del grupo formado por H, halógeno y alquilo; y si Z está presente Z es $-O-$.

En otra realización, X es $-CH_2-$ o $-N(R^4)-$.

En aun otra realización, X es $-CH_2-$.

En aun otra realización, X es $-N(R^4)-$.

En otra realización, R^4 es H.

En otra realización, T es alquilo.

En aun otra realización, T es $-CH_3$.

En aun otra realización, T es arilo y dicho arilo está no sustituido u opcional e independientemente sustituido con una a cinco porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente del grupo de porciones R^{10} .

En otra realización, R^{10} es halógeno.

En aun otra realización, R^{10} es heteroarilo.

En aun otra realización, R^{10} es arilo.

En una realización U se selecciona del grupo formado por un enlace covalente, $-N(R^4)-$, $-N(R^4)C(O)-$, y $-N(R^4)S(O)_2-$.

En aun otra realización U es un enlace covalente.

En aun otra realización U es $-N(R^4)-$.

En aun otra realización, U es $-N(R^4)C(O)-$.

En otra realización, V se selecciona del grupo formado por arilo, heteroarilo, heterociclilo y cicloalquilo, dicho arilo, heteroarilo, heterociclilo, y cicloalquilo está opcionalmente fusionado con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, o cicloalquilo, en donde cada uno de cualquiera de dicho arilo, heteroarilo, heterociclilo y cicloalquilo está no sustituido u opcional e independientemente sustituido con una a cuatro porciones

R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente del grupo de porciones R^{10} .

En otra realización, Y se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-C(O)-$ y $-O-$.

En aun otra realización, Y es $-O-$.

En aun otra realización, Y es $-(C(R^4)_2)_n-$.

En aun otra realización, Y es $-C(O)-$.

En otra realización, Y es un enlace covalente.

En una realización, R^1 se selecciona del grupo formado por $-OR^4$, H, alquilo, fluoralquilo, alquilarilo, halógeno, y heteroarilo.

En otra realización, R^1 es H.

En aun otra realización, R^1 es alquilarilo.

En aun otra realización, R^1 es alquilo.

En aun otra realización, R^1 es fluoralquilo.

En una realización adicional, R^1 es halógeno.

En otra realización, R^1 es $-OR^4$.

En otra realización, donde R^1 es $-OR^4$, R^4 es $-CH_2C\equiv CCH_3$.

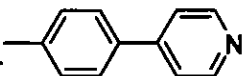
En otra realización, donde R^1 es $-OR^4$, R^4 es $-CH_2C\equiv CCH_2OH$.

En otra realización, donde R^1 es $-OR^4$, R^4 es $-CH_2-$ .

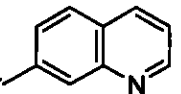
En otra realización, el alquilo es $-CH_3$.

En aun otra realización, el alquilo es $-CH_2CH_3$.

En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta

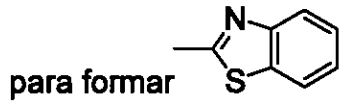
para formar  y R^1 se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2-$ .

En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta

para formar  y R^1 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

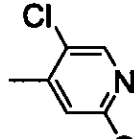
En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



y R^1 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar OH y R^1 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

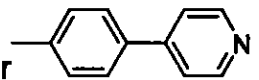
En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar y R^1 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

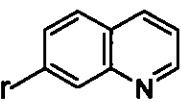
En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar y R^2 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

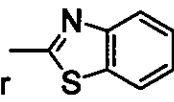
En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar y R^2 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

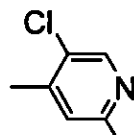
En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar y R^2 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta



para formar OH y R^2 se selecciona del grupo formado por F, Cl, OH,

236 241

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

En otra realización, en la fórmula (I), T, U, y V se toman en forma conjunta

para formar  y R^2 se selecciona del grupo formado por F, Cl, OH,

$-\text{OCH}_2\text{C}\equiv\text{CCH}_3$, $-\text{OCH}_2\text{C}\equiv\text{CCH}_2\text{OH}$, $-\text{OCH}_3$, y $-\text{OCH}_2$ -.

En otra realización, el fluoralquilo es $-\text{CH}_2\text{CF}_3$.

En una realización, halógeno se selecciona del grupo formado por Br, -Cl y -F.

En otra realización, R^4 es $-\text{CH}_3$.

En aun otra realización, alquilo de R^1 está sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} .

En otra realización, R^{20} es arilo.

En otra realización, Z se selecciona del grupo formado por un enlace covalente, $-\text{N}(\text{R}^4)-$, $-(\text{C}(\text{R}^4)_2)_n-$, $-\text{C}(\text{O})-$ y $-\text{O}-$.

En aun otra realización, Z es $-\text{O}-$.

En aun otra realización, Z es un enlace covalente.

En aun otra realización, Z es $-\text{N}(\text{R}^4)-$.

En una realización adicional, Z es $-\text{C}(\text{O})-$.

En otra realización, R^4 es alquilo.

En otra realización, R^2 se selecciona del grupo formado por $-\text{OR}^4$, H, alquilo, fluoralquilo, alquilarilo, halógeno, y heteroarilo.

En otra realización en donde R^2 es $-\text{OR}^4$, R^4 es $-\text{CH}_2\text{C}\equiv\text{CCH}_3$.

En otra realización en donde R^2 es $-\text{OR}^4$, R^4 es $-\text{CH}_2\text{C}\equiv\text{CCH}_2\text{OH}$.

En otra realización en donde R^2 es $-\text{OR}^4$, R^4 es $-\text{CH}_2$ -.

En aun otra realización, R^2 es hidrógeno.

En aun otra realización, R^2 es alquilo.

En aun otra realización, R^2 es alquilarilo.

En aun otra realización, R^2 es fluoralquilo.

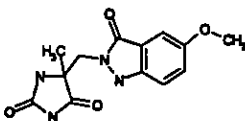
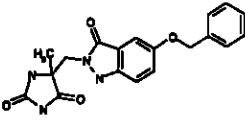
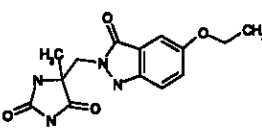
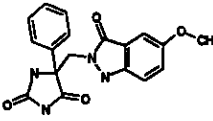
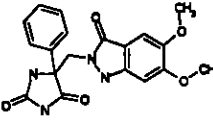
En otra realización, R^2 es $-\text{CH}_2\text{CF}_3$.

En aun otra realización, R^2 es halógeno.

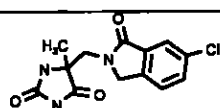
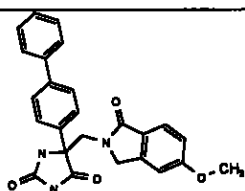
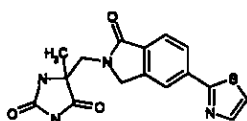
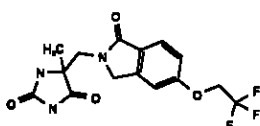
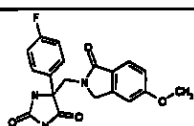
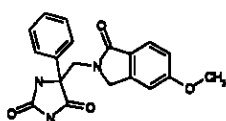
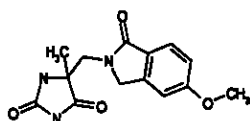
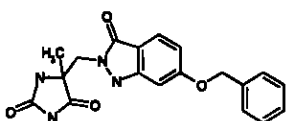
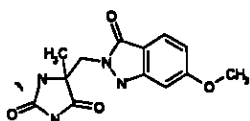
En otra realización, R² es heteroarilo.
En otra realización, R⁴ es -CH₃.

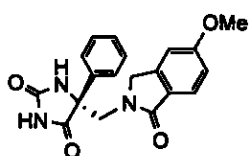
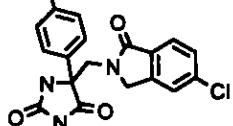
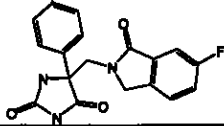
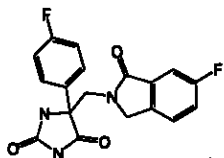
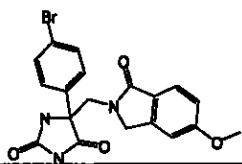
Otra realización de la invención describe los siguientes compuestos mostrados en la **Tabla A** que aparece a continuación.

Tabla A

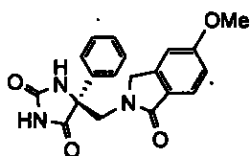
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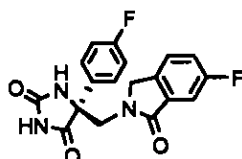




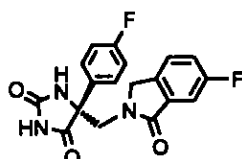
Enantiómero A



Enantiómero B

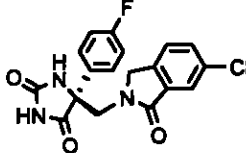
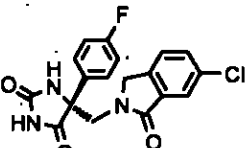
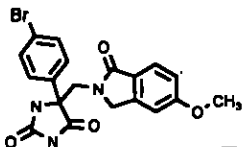
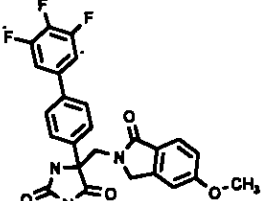
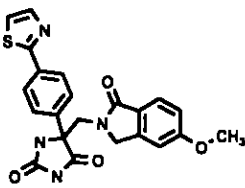
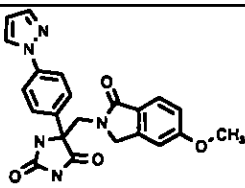
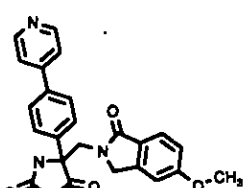
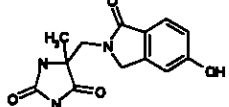
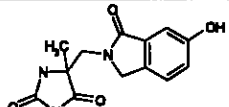


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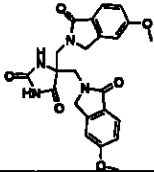
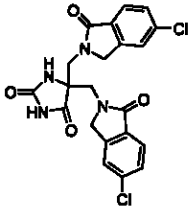
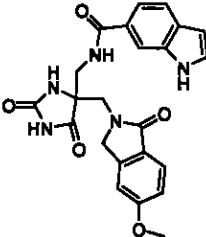
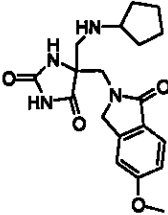
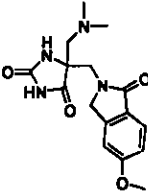
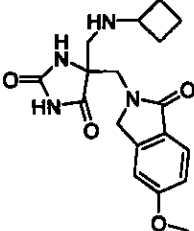


Enantiómero B

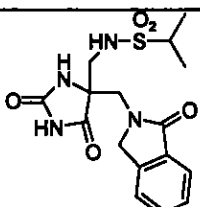
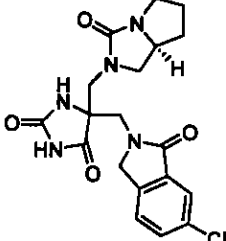
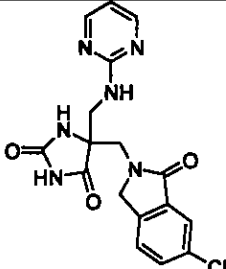
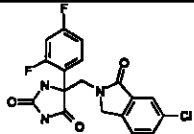
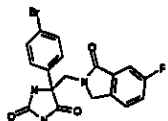
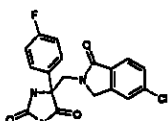
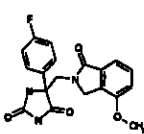
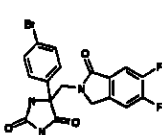
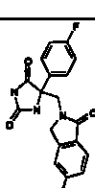
240 ~~245~~
14

 Enantiómero A
 Enantiómero B








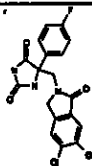
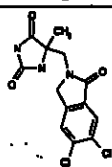
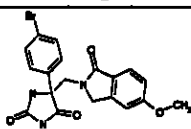
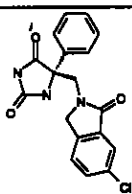
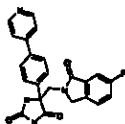
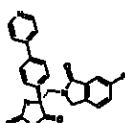
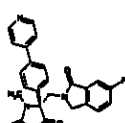
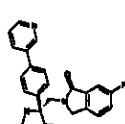
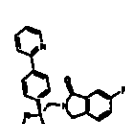
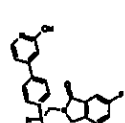
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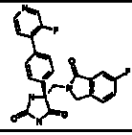
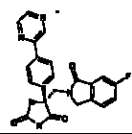
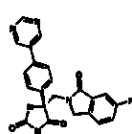
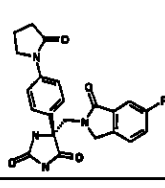
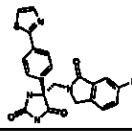
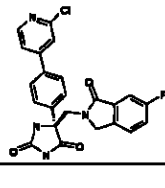
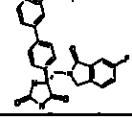
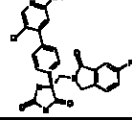
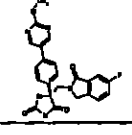
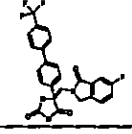
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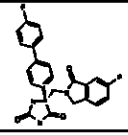
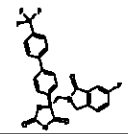
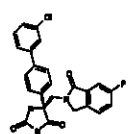
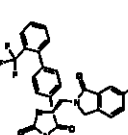
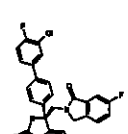
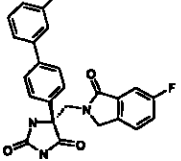
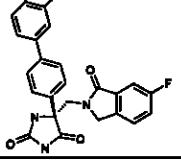
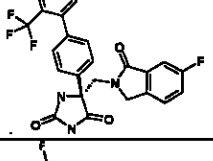
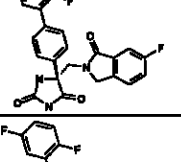
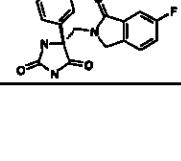
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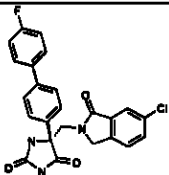
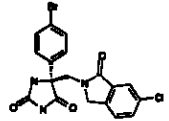
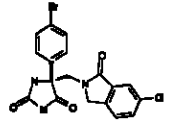
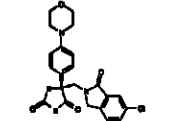
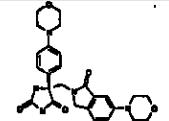
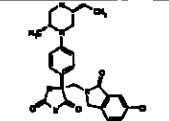
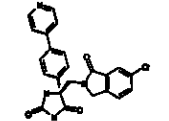
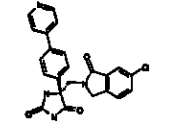
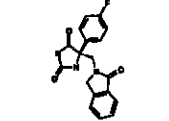
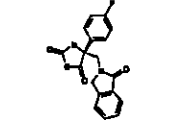
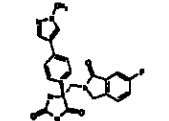
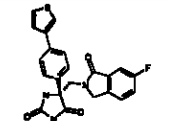
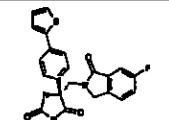











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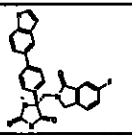
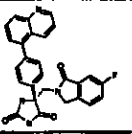
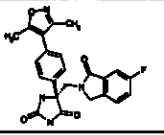
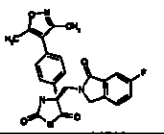
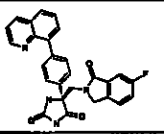
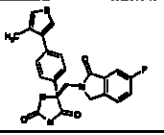
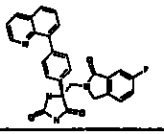
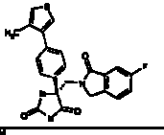
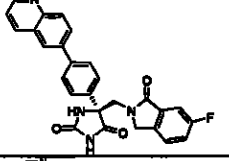
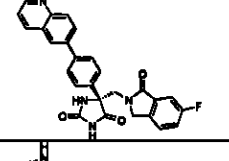
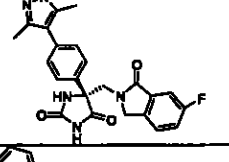
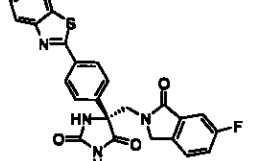
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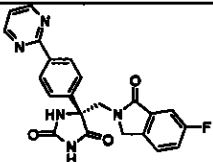
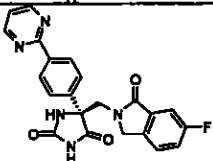
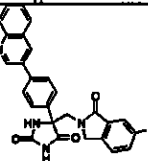
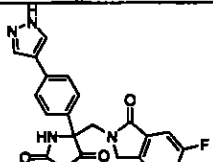
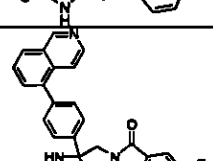
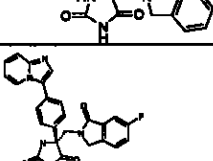
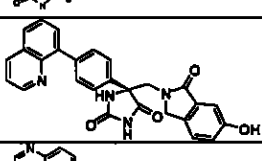
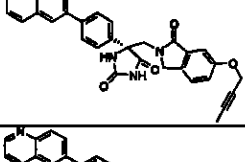
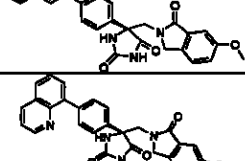
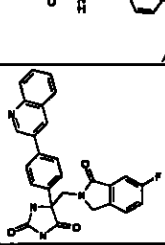














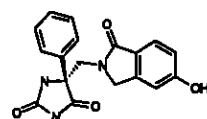
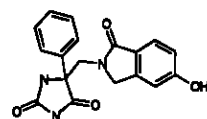
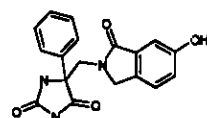
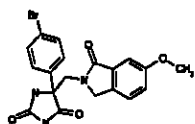
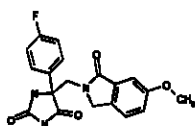
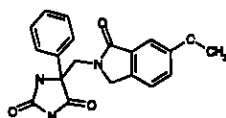
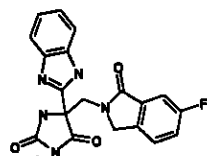
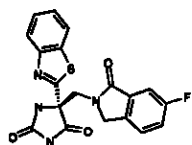
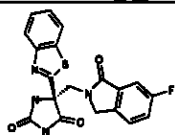
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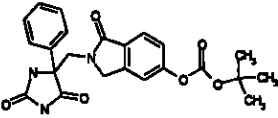
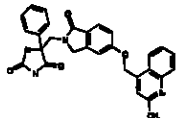
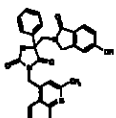
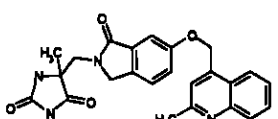
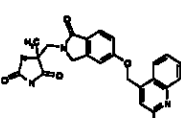
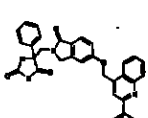
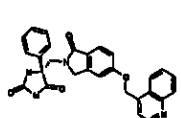
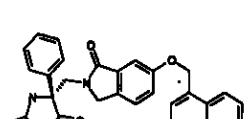
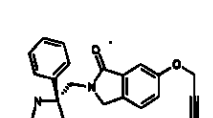
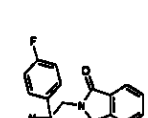













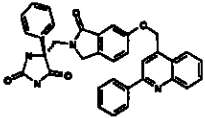
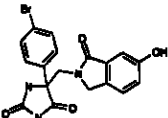
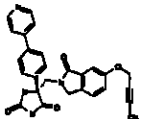
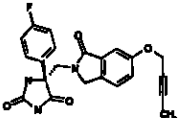
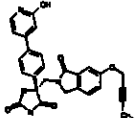
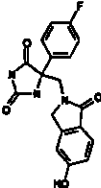
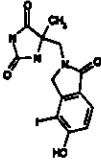
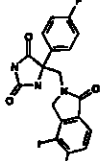
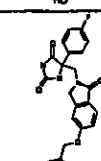
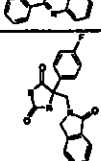
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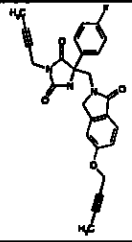
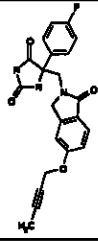
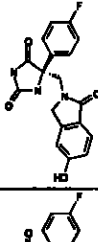
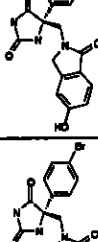
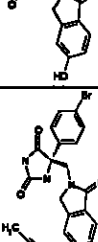
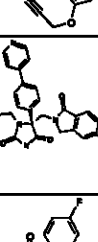
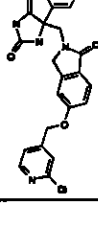
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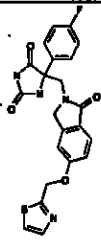
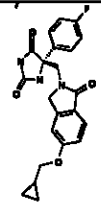
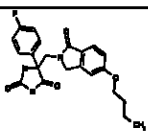
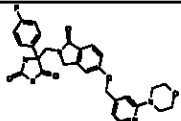
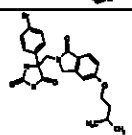
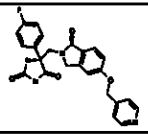
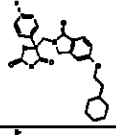
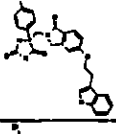
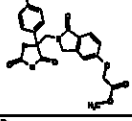
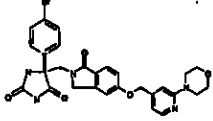
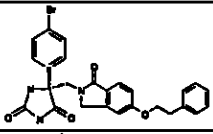
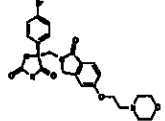











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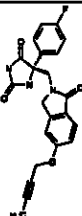
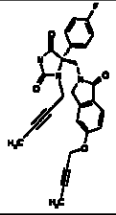
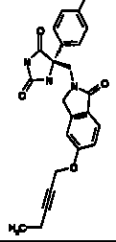
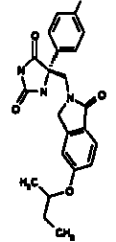
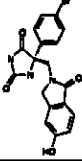
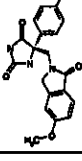
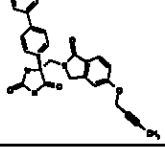
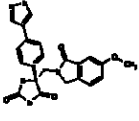
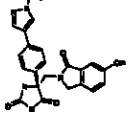
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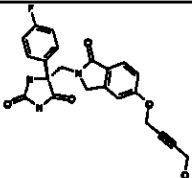
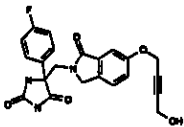
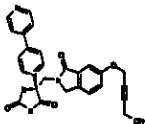
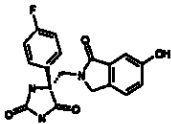
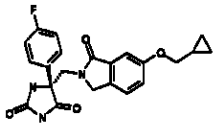
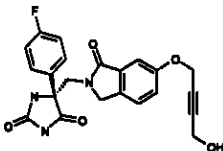
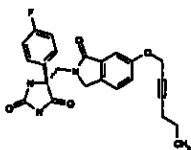
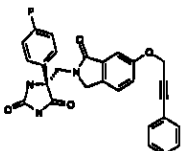
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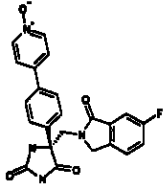
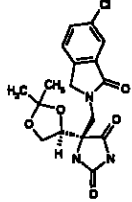
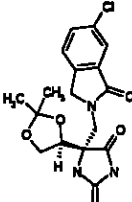
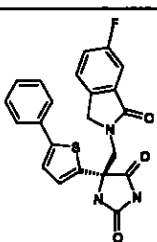
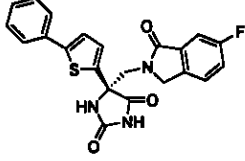
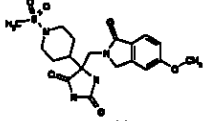
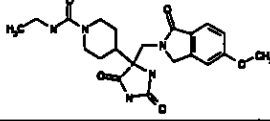
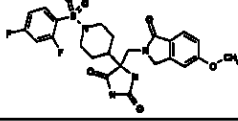
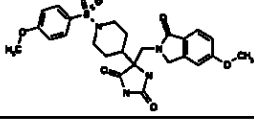
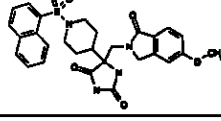
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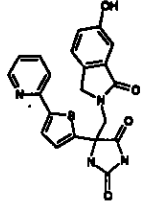
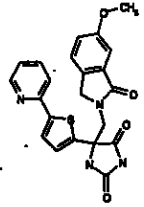
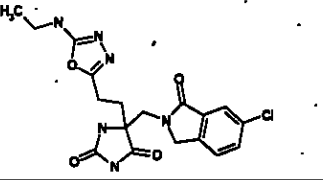
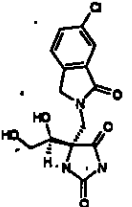
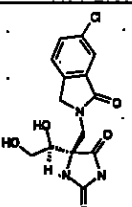
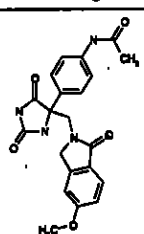
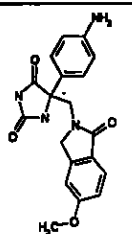
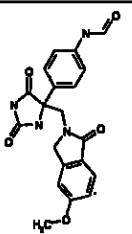
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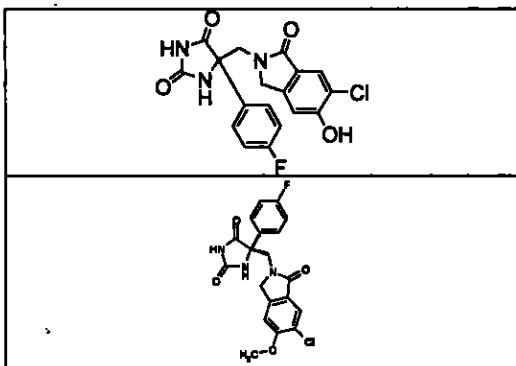
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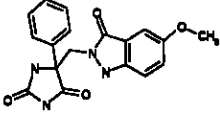
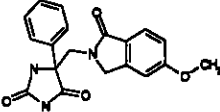
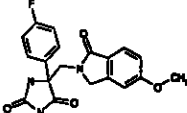
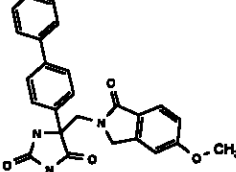
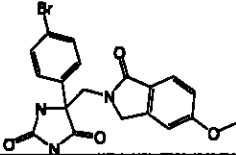
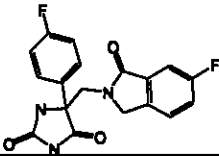
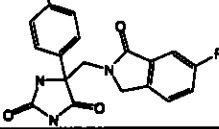
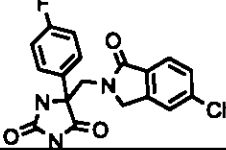
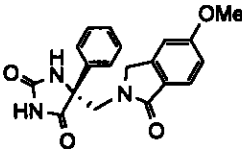
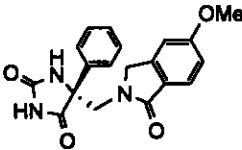
262 267



. Otra realización de la invención describe los compuestos preferidos mostrados en la Tabla B que aparece a continuación:

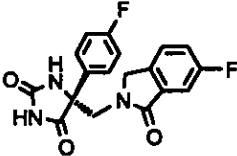
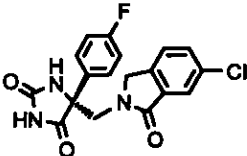
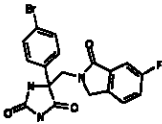
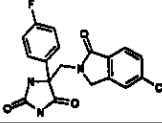
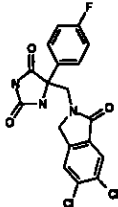
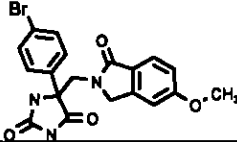
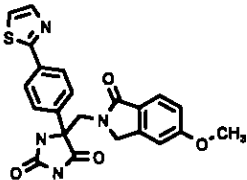
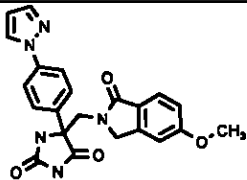
Tabla B

263 268

Estructura










Enantiómero A

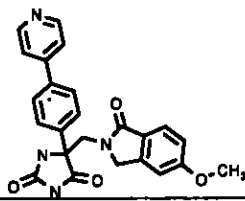
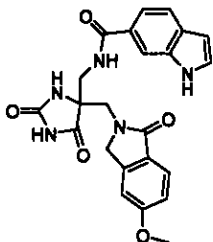
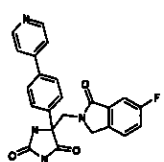
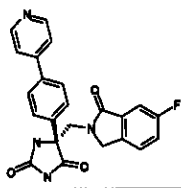
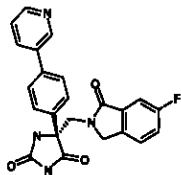
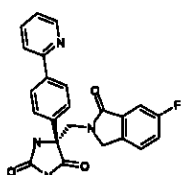
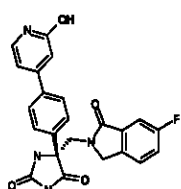
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269
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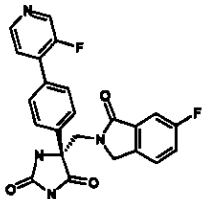
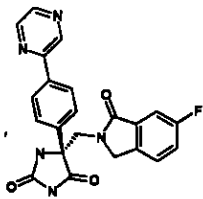
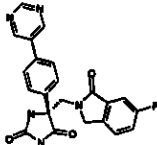
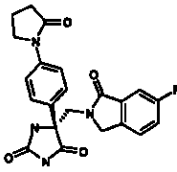
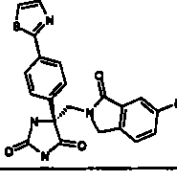
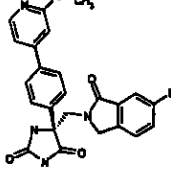
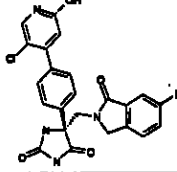

Enantiómero B

Enantiómero B







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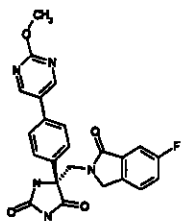
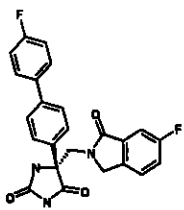
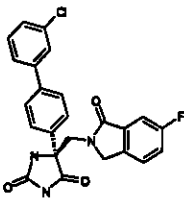
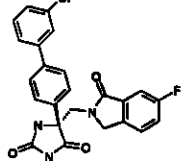
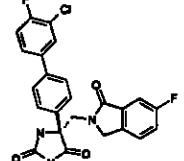
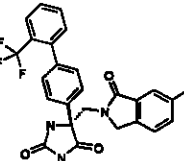
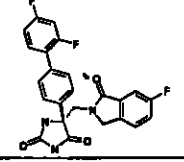
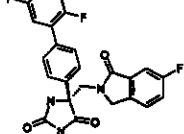
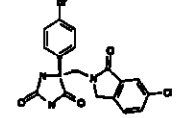
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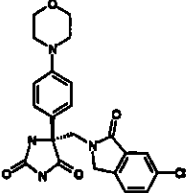
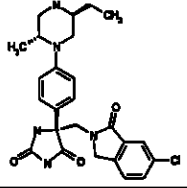
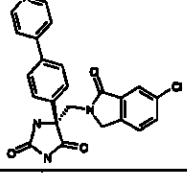
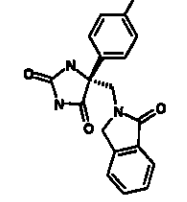
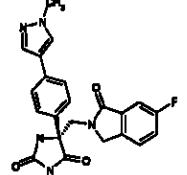
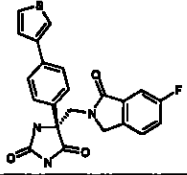
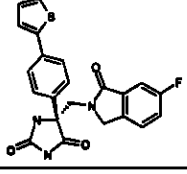
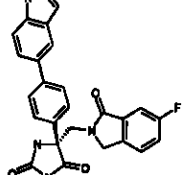
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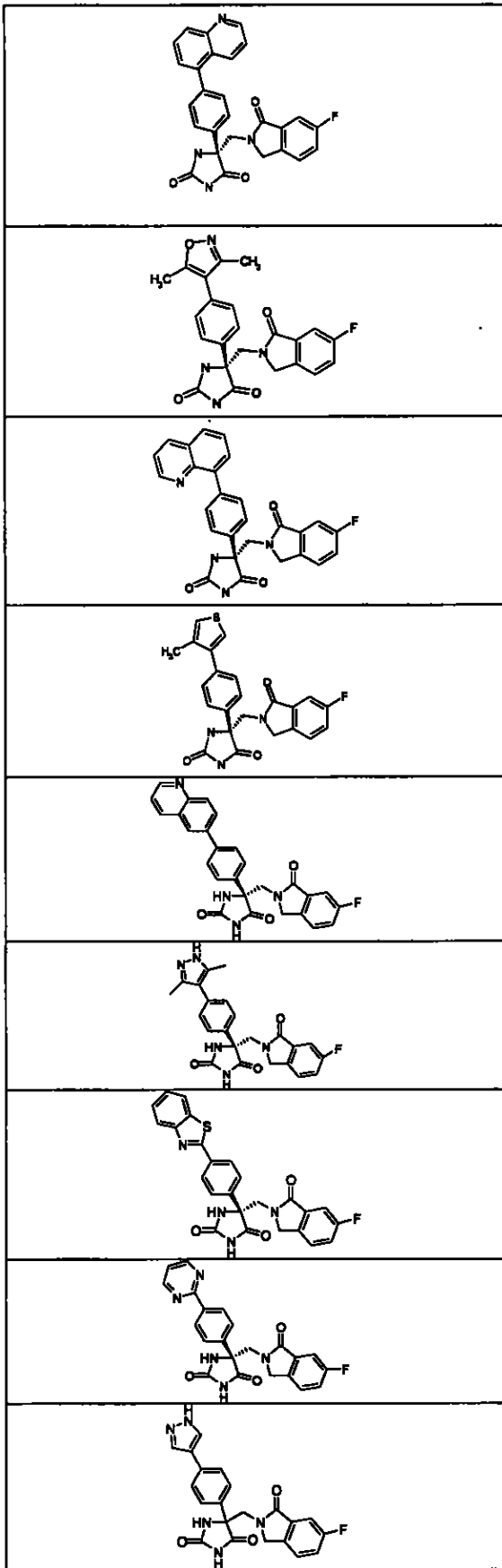
267 - 71/2

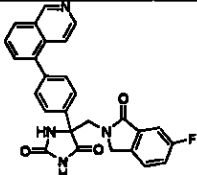
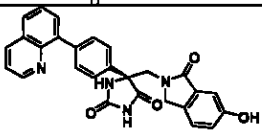
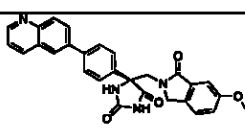
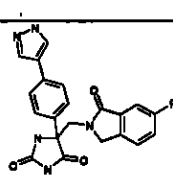
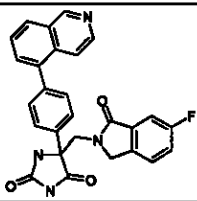
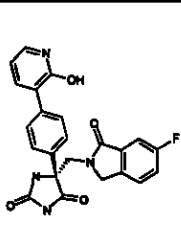
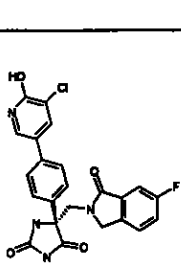
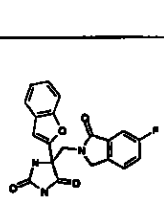
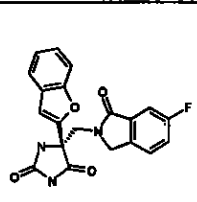
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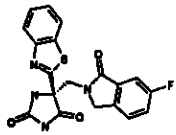
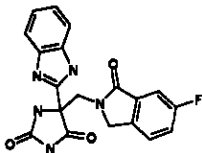
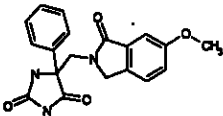
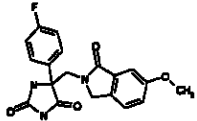
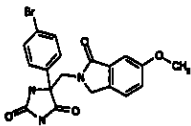
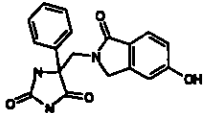
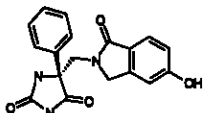
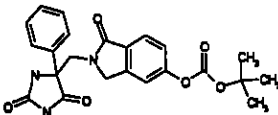
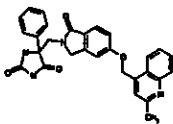
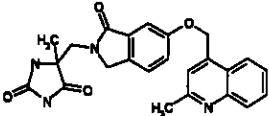
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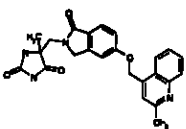
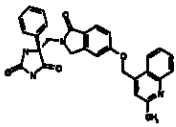
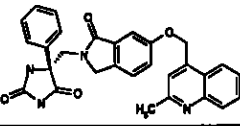
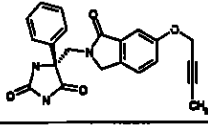
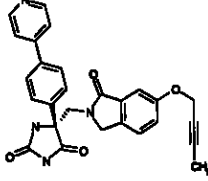
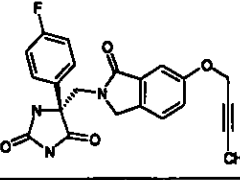
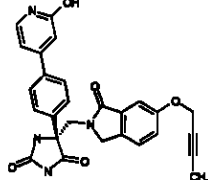
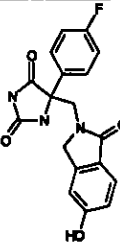
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271 206

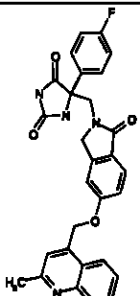
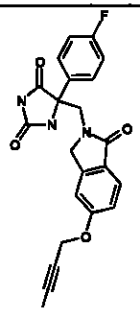
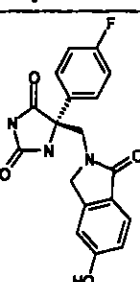
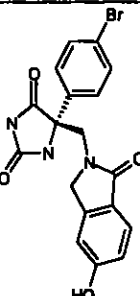
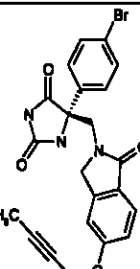











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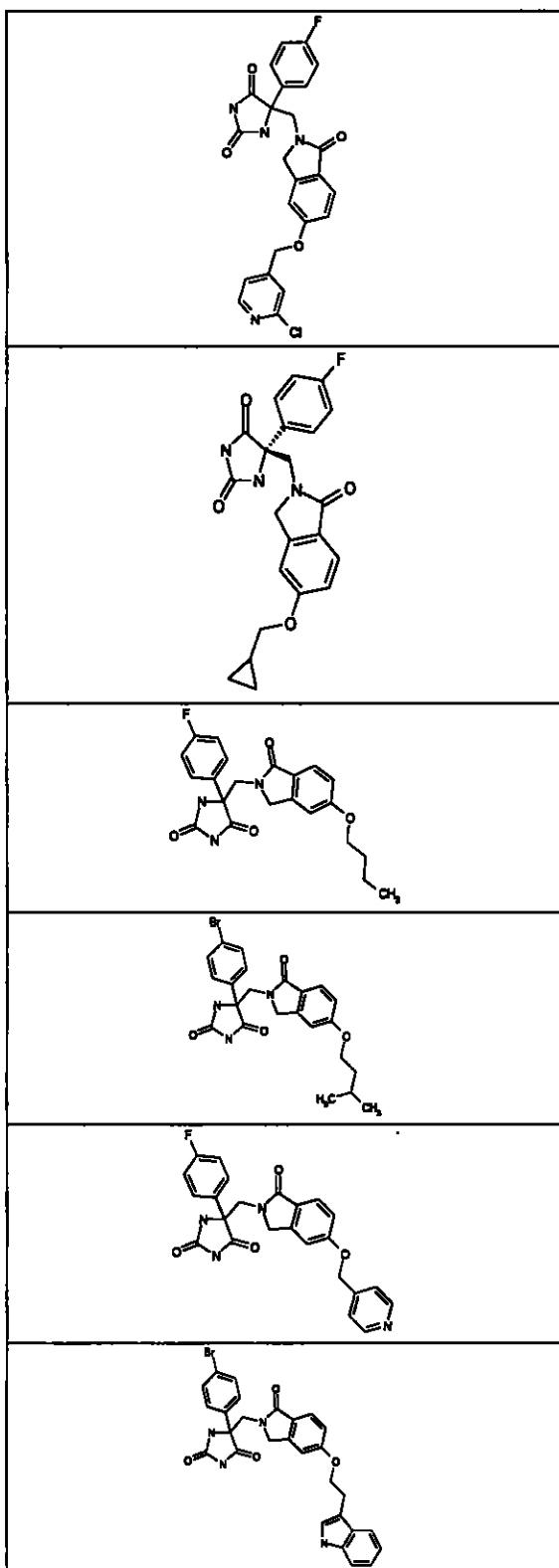









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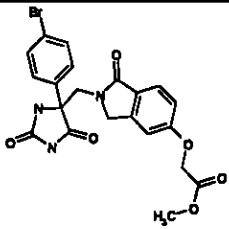
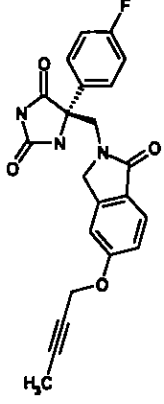
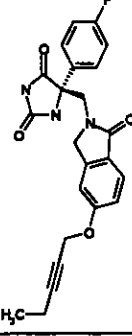
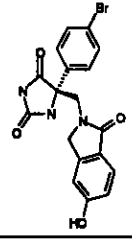
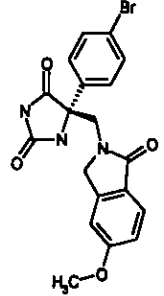
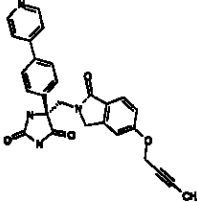
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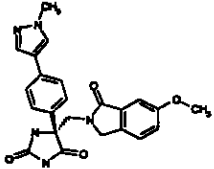
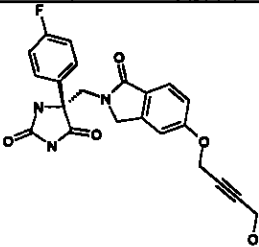
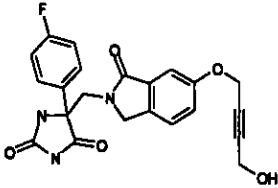
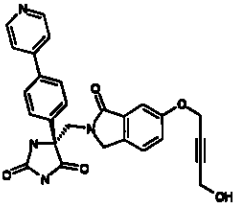
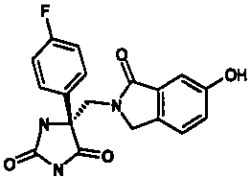
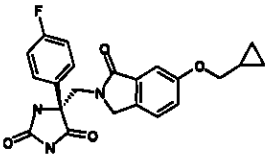
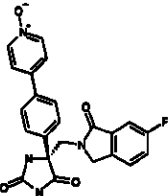
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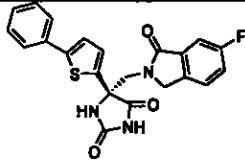
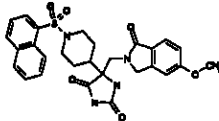
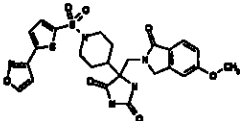
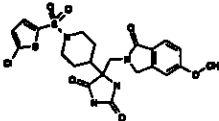
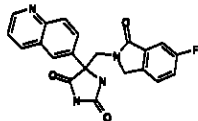
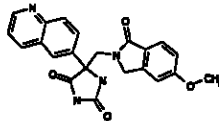
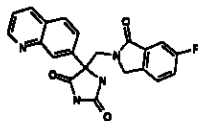
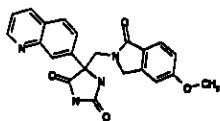
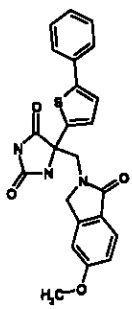
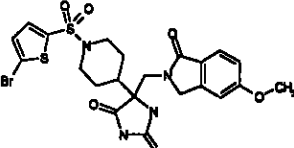







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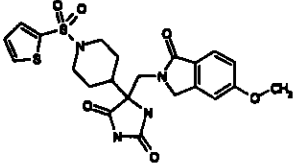
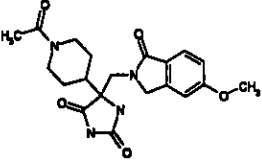
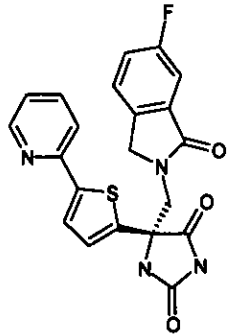
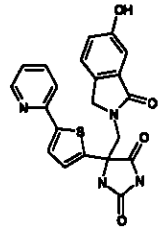
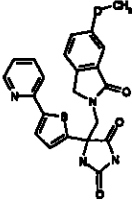
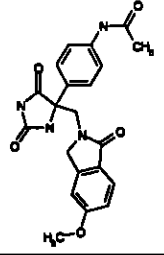
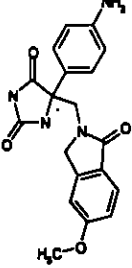
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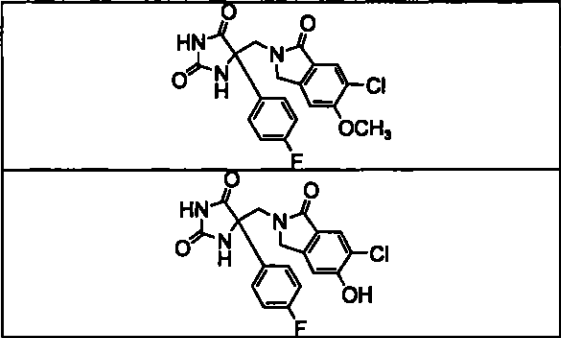











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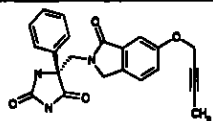
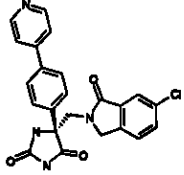
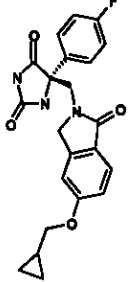
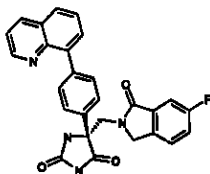
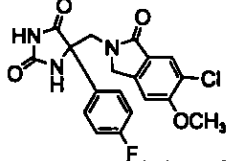
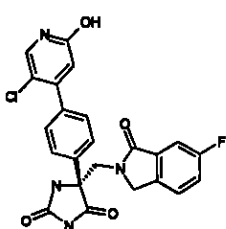
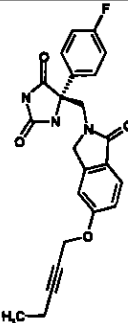
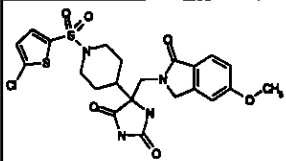


Otra realización de la invención describe los compuestos más preferidos mostrados en la **Tabla C** que aparece a continuación.

Tabla C

Estructura

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Según se utilizó anteriormente, y a lo largo de esta descripción, los siguientes términos, a menos que se indique lo contrario, se entenderán con las siguientes acepciones:

"Paciente" incluye tanto humanos como animales.

"Mamíferos" significa humanos y otros animales mamíferos.

"Alquilo" significa un grupo de hidrocarburos alifáticos que puede ser recto o ramificado y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo que más se prefieren contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferiores tales como metilo, etilo o propilo, están unidos a una cadena de alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. El grupo alquilo podría sustituirse con uno o más sustituyentes que podrían ser el mismo o diferentes, cada sustituyente se selecciona independientemente del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxilo, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)₂, carboxi y -C(O)O-alquilo. Algunos ejemplos no limitantes de grupos alquilo adecuados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquenilo" significa un grupo de hidrocarburos alifáticos que contiene por lo menos un enlace doble carbono-carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos poseen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferentemente alrededor de 2 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena de alquenilo lineal. "Alquenilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. Algunos ejemplos no

limitantes de grupos alqueno adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo de hidrocarburos alifáticos que contiene por lo menos un enlace triple carbono-carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos poseen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y con mayor preferencia aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. Algunos ejemplos no limitantes de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butenilo y 3-metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo podría sustituirse con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona independientemente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillos aromáticos multicíclicos o monocíclicos que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, preferentemente alrededor de 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede sustituirse opcionalmente con uno o más "sustituyentes del sistema de anillos" que pueden ser iguales o diferentes, y son según lo que se define en este trabajo. Algunos ejemplos no limitantes de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillos aromáticos monocíclicos o multicíclicos que comprende aproximadamente 5 hasta aproximadamente 14 átomos del anillo, preferentemente alrededor de 5 hasta aproximadamente 10

átomos del anillo, en los cuales uno o más de los átomos del anillo es un elemento distinto del carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos del anillo. El "heteroarilo" puede opcionalmente sustituirse con uno o más "sustituyentes del sistema de anillo" que puede ser el mismo o diferentes, y son según se define en este trabajo. El prefijo aza, oxa o tia antes del nombre de raíz heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como un átomo de anillo. Un átomo de nitrógeno de un heteroarilo puede oxidarse opcionalmente al N-óxido correspondiente. Algunos ejemplos no limitantes de heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridona (incluyendo piridonas N-sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, bencimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo, etcétera. El término "heteroarilo" también se refiere a porciones de heteroarilo parcialmente saturadas tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo, etcétera.

"Aralquilo" o "arilalquilo" significa un grupo arilo-alquilo en el cual el arilo y el alquilo son según se describió anteriormente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Algunos ejemplos no limitantes de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace a la porción madre es a través del alquilo.

"Alquilarilo" significa un grupo alquilo-arilo en el cual el alquilo y el arilo son según se describió anteriormente. Los alquilarilos preferidos comprenden un

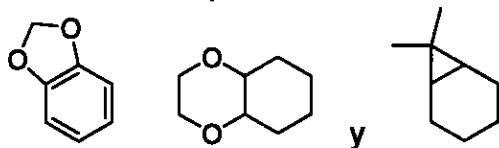
grupo alquilo inferior. Un ejemplo no limitante de un grupo alquilarilo adecuado es toliilo. El enlace a la porción madre es a través del arilo.

"Cicloalquilo" significa un sistema de anillos no aromáticos mono o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, preferentemente alrededor de 5 hasta aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos del anillo. El cicloalquilo puede opcionalmente sustituirse con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son según se definió anteriormente. Algunos ejemplos no limitantes de cicloalquilos monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, etcétera. Algunos ejemplos no limitantes de cicloalquilos multicíclicos adecuados incluyen 1-decalinilo, norbornilo, adamantilo, etcétera, así como también especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo, etcétera.

"Halógeno" se refiere a flúor, cloro, bromo, o yodo. Los preferidos son flúor, cloro y bromo.

"Sustituyente de sistema de anillo" significa un sustituyente unido a un sistema de anillos aromáticos o no aromáticos el cual, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillos. Los sustituyentes del sistema de anillos pueden ser iguales o diferentes, cada uno se selecciona independientemente del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxilo, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcóxicarbonilo, arilóxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(\text{alquilo})$, G_1G_2N- , $G_1G_2N\text{-alquil-}$, $G_1G_2NC(O)-$,

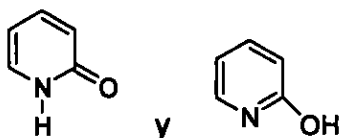
$G_1G_2NSO_2-$ y $-SO_2NG_1G_2$, en donde G_1 y G_2 pueden ser iguales o diferentes y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema de anillos" también puede referirse a una porción simple que simultáneamente reemplaza dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema de anillos. Algunos ejemplos de tal porción son metilendioxi, etilendioxi, $-C(CH_3)_2-$, etcétera, los cuales forman porciones tales como, por ejemplo:



"Heterociclilo" se refiere a un sistema de anillos multicíclico o monocíclico saturado no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos del anillo, preferentemente alrededor de 5 hasta aproximadamente 10 átomos del anillo, en el cual uno o más de los átomos en el sistema de anillos es un elemento que no sea carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. No hay átomos de oxígeno y/o de azufre adyacentes presentes en el sistema de anillos. Los heterociclilos preferidos contienen alrededor de 5 hasta aproximadamente 6 átomos del anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo de anillo. Cualquier $-NH$ en un anillo heterociclilo podría existir protegido tal como, por ejemplo, como un grupo $-N(Boc)$, $-N(CBz)$, $-N(Tos)$, etcétera; tales protecciones también se consideran parte de esta invención. El heterociclilo puede opcionalmente sustituirse con uno o más "sustituyentes del sistema de anillos" que pueden ser iguales o diferentes, y son como se definen en este trabajo. El átomo de nitrógeno o de azufre del heterociclilo puede opcionalmente oxidarse al N-óxido, S-óxido o S,S-dióxido correspondiente. Algunos ejemplos no limitantes de anillos heterocíclicos monocíclicos adecuados incluyen piperidilo,

pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, etcétera.

Debería señalarse que las formas tautoméricas tales como, por ejemplo, las porciones:



se consideran equivalentes en ciertas realizaciones de esta invención.

"Alquinilalquilo" se refiere a un grupo alquinil-alquilo en el cual los alquinilo y los alquilo son como se describieron anteriormente. Los alquinilalquilos preferidos contienen un grupo alquinilo inferior y alquilo inferior. El enlace con la porción madre es a través del alquilo. Algunos ejemplos no limitantes de grupos alquinilalquilo adecuados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquilo en el cual el heteroarilo y el alquilo son como se describieron anteriormente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Algunos ejemplos no limitantes de grupos aralquilo adecuados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace con la porción madre es a través del alquilo.

"Hidroxialquilo" se refiere a un grupo HO-alquilo en el cual el alquilo es como se definió previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Algunos ejemplos no limitantes de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" se refiere a un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, en los cuales los varios grupos son como se describieron previamente. El enlace con la porción madre es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Algunos ejemplos no limitantes de grupos acilo adecuados incluyen formilo, acetilo y propanoílo.

"Aroilo" significa un grupo aril-C(O)- en el cual el grupo arilo es como se definió previamente. El enlace a la porción madre es a través del carbonilo. Algunos ejemplos no limitantes de grupos adecuados incluyen benzoílo y 1-naftoílo.

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es según se describió anteriormente. Algunos ejemplos no limitantes de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace a la porción madre es a través del oxígeno etéreo.

"Arioxi" se refiere a un grupo aril-O- en el cual el grupo arilo es como se describió previamente. Algunos ejemplos no limitantes de grupos arioxi adecuados incluyen fenoxi y naftoxi. El enlace con la porción madre es a través del oxígeno etéreo.

"Aralquiloxi" se refiere a un grupo aralquil-O- en el cual el grupo aralquilo es como se definió anteriormente. Algunos ejemplos no limitantes de grupos aralquiloxi adecuados incluyen benciloxi y 1- ó 2-naftalenmetoxi. El enlace a la porción madre es a través del oxígeno etéreo.

"Alquiltio" se refiere a un grupo alquil-S- en el cual el grupo alquilo es según se definió previamente. Algunos ejemplos no limitantes de grupos alquiltio adecuados incluyen metiltio y etiltio. El enlace a la porción madre es a través del azufre.

"Arlitio" se refiere a un grupo aril-S- en el cual el grupo arilo es como se describió anteriormente. Algunos ejemplos no limitantes de grupos arilitio adecuados incluyen feniltio y naftiltio. El enlace a la porción madre es a través del azufre.

"Aralquiltio" se refiere a un grupo aralquil-S- en el cual el grupo aralquilo es como se describió previamente. Un ejemplo no limitante de un grupo aralquiltio adecuado es benciltio. El enlace a la porción madre es a través del azufre.

"Alcoxicarbonilo" se refiere a un grupo alquil-O-CO-. Algunos ejemplos no limitantes de grupos alcoxicarbonilo adecuados incluyen metoxycarbonilo y etoxycarbonilo. El enlace a la porción madre es a través del carbonilo.

"Ariloxycarbonilo" se refiere a un grupo aril-O-C(O)-. Algunos ejemplos no limitantes de grupos ariloxycarbonilo adecuados incluyen fenoxycarbonilo y naftoxycarbonilo. El enlace a la porción madre es a través del carbonilo.

"Aralcoxicarbonilo" se refiere a un grupo aralquil-O-C(O)-. Un ejemplo no limitante de un grupo aralcoxicarbonilo adecuado es benciloxycarbonilo. El enlace a la porción madre es a través del carbonilo.

"Alquilsulfonilo" se refiere a un grupo alquil-S(O₂)-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace a la porción madre es a través del sulfonilo.

"Arielsulfonilo" se refiere a un grupo aril-S(O₂)-. El enlace a la porción madre es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado se reemplazan con una selección del grupo indicado, siempre y cuando la valencia normal del átomo designado bajo las circunstancias existentes no esté excedida, y que la sustitución dé como resultado un compuesto estable. Las combinaciones de sustituyentes y/o variables son admisibles solo si tales combinaciones dan como resultado compuestos estables. Por "compuesto estable" o "estructura estable" se denota un compuesto que es suficientemente contundente para sobrevivir el aislamiento a un grado útil de pureza de una mezcla de reacción, y la formulación en un agente terapéutico eficaz.

El término "opcionalmente sustituido" denota sustitución opcional con los grupos, radicales o porciones especificados.

El término "aislado" o "en forma aislada" para un compuesto se refiere al estado físico de dicho compuesto luego de ser aislado a partir de un proceso

sintético o una fuente natural o una combinación de los mismos. El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto luego de haberse obtenido a partir de un proceso o procesos de purificación descritos en este trabajo o bien conocidos por el experto en la técnica, en pureza suficiente para ser caracterizables mediante técnicas analíticas estándares descritas en este trabajo o bien conocidas por los expertos en la técnica.

Debería señalarse asimismo que cualquier carbono así como también heteroátomo con valencias insatisfechas en el texto, esquemas, ejemplos y Tablas de este trabajo se supone que poseen el número suficiente de átomo/s de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo está en forma modificada para prevenir efectos secundarios no deseados en el lado protegido cuando el compuesto está sujeto a una reacción. Los grupos protectores adecuados serán reconocidos por aquellos expertos en la técnica así como también por referencia a los libros de texto estándares tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, Nueva York.

Cuando cualquier variable (por ejemplo, arilo, heterociclo, R^2 , etcétera) aparece más de una vez en cualquier constituyente o en la Fórmula I, su definición en cada aparición es independiente de su definición en cualquier otra aparición.

Según se utiliza en este trabajo, el término "composición" intenta abarcar un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto que se origine como resultado, directa o indirectamente, a partir de la combinación de los ingredientes especificados en las cantidades especificadas.

Los profármacos y los solvatos de los compuestos de la invención también se contemplan en este trabajo. El término "profármaco", según se utiliza en este trabajo, denota un compuesto que es un precursor del fármaco el cual, luego de la administración a un sujeto, experimenta una conversión química mediante procesos metabólicos o químicos para rendir un compuesto de la Fórmula I o una sal y/o solvato del mismo. Un debate acerca de profármacos se proporciona en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, ambos de los cuales se incorporan en este trabajo como referencia.

"Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física involucra grados variantes de enlace iónico y covalente, incluyendo enlace de hidrógeno. En ciertos casos el solvato será capaz de aislamiento, por ejemplo cuando una o más moléculas de solvente se incorporan en el entramado de cristal del sólido cristalino. "Solvato" abarca ambos solvatos de fase de solución y aislable. Algunos ejemplos no limitantes de solvatos adecuados incluyen etanolatos, metanolatos, etcétera. "Hidrato" es un solvato en donde la molécula de solvente es H₂O.

"Cantidad efectiva" o "cantidad terapéuticamente efectiva" pretende describir una cantidad de compuesto o una composición de la presente invención efectiva en la inhibición de TACE, la producción de TNF- α , MMPs, ADAMS o cualquier combinación de las mismas y así producir el efecto terapéutico, mejorador, inhibitorio o preventivo deseado.

Los compuestos de la Fórmula I pueden formar sales que también se encuentran dentro del alcance de la invención. Se entiende que la referencia a un compuesto de la Fórmula I en este trabajo incluye referencia a las sales del

mismo, a menos que se indique lo contrario. El término "sal/es", según se utiliza en este trabajo, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, así como también sales básicas formadas con bases inorgánicas y/u orgánicas. Además, cuando un compuesto de la Fórmula I contiene tanto una porción básica, tal como, aunque no limitada a piridina o imidazol, como una porción ácida, tal como, aunque no limitada a un ácido carboxílico, podrían formarse zwitteriones ("sales internas") y están incluidos dentro del término "sal/es" según se utiliza en este trabajo. Se prefieren las sales farmacéuticamente (es decir, no tóxicas, fisiológicamente) aceptables, aunque otras sales también son útiles. Podrían formarse sales de los compuestos de la Fórmula I, por ejemplo, mediante la reacción de un compuesto de la Fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en donde la sal se precipite o en un medio acuoso seguido por liofilización.

Algunas sales de adición de ácido ejemplificantes incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos,) etcétera. Por añadidura, los ácidos que generalmente se consideran adecuados para la formación de sales farmacéuticamente útiles de compuestos farmacéuticos básicos son abordados, por ejemplo, por P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use*. (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, Nueva York; y en *The Orange Book* (Food &

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Drug Administration, Washington, D.C. en su sitio en internet). Estas descripciones se incorporan en este trabajo a modo de referencia a las mismas.

Algunas sales básicas ejemplificantes incluyen sales de amonio, sales de metal alcalino tales como sales de sodio, litio, y potasio, sales de metales alcalinotérreos tales como sales de calcio y de magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como dicitohexilaminas, t-butilaminas, y sales con aminoácidos tales como arginina, lisina, etcétera. Los grupos básicos que contienen nitrógeno podrían cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo cloruros, bromuros y yoduros de metilo, etilo, y butilo), dialquilsulfatos (por ejemplo sulfatos de dimetilo, sulfato de dietilo, y sulfato de dibutilo), haluros de cadena larga (por ejemplo cloruros, bromuros y yoduros de decilo, de laurilo, y de estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Todas estas sales ácidas y sales base pretenden ser sales farmacéuticamente aceptables dentro del alcance de la invención y todas las sales ácidas y base se consideran equivalentes a las formas libres de los compuestos correspondientes para propósitos de la invención.

Los compuestos de la Fórmula I, y las sales, los solvatos y los profármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o iminoéter). Todas estas formas tautoméricas están contempladas en este trabajo como parte de la presente invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos, etcétera) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y profármacos de los compuestos así como también las sales y los solvatos de los profármacos), tales como aquellos que podrían existir debido a carbonos asimétricos en varios sustituyentes, incluyendo formas enantioméricas (que pueden existir aún en ausencia de carbonos asimétricos), formas

rotaméricas, atropisómeros, y formas diastereoméricas, están contemplados dentro del alcance de la invención, porque son isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención podrían, por ejemplo, estar sustancialmente libres de otros isómeros, o podrían mezclarse, por ejemplo, como racematos o con todo los otros estereoisómeros, o estereoisómeros seleccionados. Los centros quirales de la presente invención pueden poseer la configuración S ó R según fue definido por IUPAC 1974 Recommendations. La utilización de los términos "sal", "solvato" "profármaco", etcétera, pretende ser aplicada de igual manera a la sal, al solvato y al profármaco de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o profármacos de los compuestos de la invención.

Las formas polimórficas de los compuestos de la Fórmula I, y de las sales, solvatos y profármacos de los compuestos de la Fórmula I, pretenden estar incluidos en la presente invención.

Los compuestos de acuerdo con la invención presentan propiedades farmacológicas; en particular, los compuestos de la Fórmula I pueden ser inhibidores de la actividad de TACE, TNF- α y/o MMP.

En un aspecto, la invención proporciona una composición farmacéutica que comprende como ingrediente activo por lo menos un compuesto de la fórmula 1.

En otro aspecto, la invención proporciona una composición farmacéutica de la fórmula 1 que comprende de forma adicional por lo menos un portador farmacéuticamente aceptable.

En otro aspecto, la invención proporciona un método para el tratamiento de trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, dicho método comprende administrar a un paciente

necesitado de tal tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de por lo menos un compuesto de la fórmula 1.

En otro aspecto, la invención proporciona una utilización de un compuesto de la fórmula 1 para la elaboración de un medicamento para el tratamiento de trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos.

Los compuestos de la Fórmula I pueden presentar actividad anti-inflamatoria y/o actividad inmunomoduladora al mismo tiempo que pueden ser útiles en el tratamiento de enfermedades que incluyen, aunque no se limitan a, choque séptico, choque hemodinámico, síndrome séptico, lesión por reperfusión pos-isquémica, malaria, infección micobacteriana, meningitis, soriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo de injertos, cánceres tales como linfoma cutáneo de células T, enfermedades que involucran angiogénesis, enfermedades autoinmunes, dermatitis, enfermedades inflamatorias del intestino tales como enfermedad de Crohn y colitis, OA y artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still del adulto, ureitis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión radiógena, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus insulina no dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad de la retina, esclerodermia, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, alveolitis fibrosante criptogénica, soriasis, rechazo de órganos, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías respiratorias, síndrome de distress

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respiratorio del adulto, asma, enfermedad pulmonar obstructiva crónica (COPD, correspondiente al término en inglés "chronic obstructive pulmonary disease") y/o bronquitis. Está contemplado que un compuesto de esta invención pueda ser útil en el tratamiento de una o más de las enfermedades mencionadas.

En otro aspecto, la invención proporciona un método para preparar una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, dicho método comprende poner en contacto íntimo por lo menos un compuesto de la fórmula 1 y por lo menos un portador farmacéuticamente aceptable.

En otro aspecto, la invención proporciona un compuesto de la fórmula (I) que exhibe TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, actividad inhibitoria, que incluye enantiómeros, estereoisómeros y tautómeros de dicho compuesto, y sales o solvatos farmacéuticamente aceptables de dicho compuesto, dicho compuesto se selecciona a partir de compuestos de estructuras enumeradas en la **Tabla A** expuesta en lo que antecede.

En otro aspecto, la invención proporciona una composición farmacéutica para el tratamiento de trastornos asociados con TACE, TNF- α , MMP, ADAM o cualquier combinación de los mismos en un sujeto que comprende, la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, solvato o isómero farmacéuticamente aceptable del mismo.

En otro aspecto, la invención proporciona un compuesto de la fórmula 1 en forma purificada.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad mediadas por TACE, MMPs, TNF- α , agreganasa, o cualquier combinación de los mismos en un sujeto que comprende: la administración al sujeto necesitado de dicho tratamiento de una cantidad

terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad seleccionadas del grupo que consiste en artritis reumatoidea, osteoartritis, periodontitis, gingivitis, úlcera de córnea, crecimiento de tumor sólido e invasión tumoral por metástasis secundarias, glaucoma neovascular, enfermedad inflamatoria del intestino, esclerosis múltiple y soriasis en un sujeto, que comprende: la administración a un sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, solvato, o isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad seleccionada del grupo que consiste en fiebre, afecciones cardiovasculares, hemorragia, coagulación, caquexia, anorexia, alcoholismo, respuesta en fase aguda, infección aguda, choque, reacción de injerto versus huésped, enfermedad autoinmune e infección por VIH en un sujeto, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, solvato o isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad seleccionadas del grupo que consiste en choque séptico, choque hemodinámico, síndrome séptico, lesión por reperfusión pos-isquémica, malaria, infección micobacteriana, meningitis, soriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo de injerto, cánceres tales como linfoma cutáneo de células T, enfermedades que involucran angiogénesis, enfermedades autoinmunes, dermatitis, enfermedades inflamatorias del intestino tal como la enfermedad de Crohn y colitis, osteoartritis y

artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still del adulto, uveítis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión radiógena, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus insulina no-dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad de la retina, esclerodermia, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, alveolitis fibrosante criptogénica, soriasis, rechazo de trasplante, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías respiratorias, síndrome de distress respiratorio del adulto, asma, enfermedad pulmonar obstructiva crónica (COPD, correspondiente al término en inglés "chronic obstructive pulmonary disease") y bronquitis en un sujeto, que comprende la administración al sujeto necesitado de dicho tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato, o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con COPD, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la reivindicación 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con artritis reumatoidea, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato, o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con la enfermedad de Crohn, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con soriasis, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con espondilitis anquilosante, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con ciática, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con el síndrome de dolor regional complejo, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con artritis psoriásica, que comprende: la administración a un sujeto necesitado de dicho tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad asociadas con la esclerosis múltiple, que comprende: la administración al sujeto necesitado de tal tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptables del mismo, en combinación con un compuesto seleccionado del grupo que consiste en Avonex®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de esclerosis múltiple.

Adicionalmente, un compuesto de la presente invención podría coadministrarse o utilizarse en combinación con fármacos antirreumáticos modificadores de la enfermedad (DMARDS, correspondiente al término en inglés "disease-modifying antirheumatic drugs") tales como metotrexato, azatioprina, leflunomida, pencilinamina, sales de oro, mofetil micofenolato, ciclofosfamida y otro fármacos similares. Éstos también podrían coadministrarse con o utilizarse en combinación con fármacos anti-inflamatorios no esteroides (NSAIDs, correspondiente al término en inglés "non-steroidal anti-inflammatory drugs") tales como piroxicam, naproxeno, indometacina, ibuprofeno, etcétera; inhibidores selectivos de cicloxigenasa-2 (COX-2) tales como Vioxx® y Celebrex®; inmunosupresores tales como esteroides, ciclosporina, Tacrolimus, rapamicina, etcétera; modificadores de respuesta biológica (BRMs, correspondiente al término en inglés "biological response modifiers") tales como Enbrel®, Remicade®, antagonistas de IL-1, anti-CD40, anti-CD28, IL-10, moléculas anti-adhesión,

etcétera; y otros agentes anti-inflamatorios tales como inhibidores de quinasa p38, inhibidores de PDE4, otros inhibidores de TACE químicamente distintos, antagonistas receptores de quimioquina, Talidomida y otros inhibidores de moléculas pequeñas de la producción de citoquina pro-inflamatoria.

Además, un compuesto de la presente invención podría coadministrarse o utilizarse en combinación con un antagonista H1 para el tratamiento de rinitis alérgica estacional y/o asma. Algunos antagonistas H1 adecuados podrían ser, por ejemplo, Claritin®, Clarinex®, Allegra®, o Zyrtec®.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad mediadas por TACE, MMPs, TNF- α , agrecanasa, o cualquier combinación de los mismos en un sujeto, que comprende: la administración al sujeto necesitado de tal tratamiento una cantidad terapéuticamente efectiva de por lo menos un compuesto de la fórmula 1 o una sal, un solvato o un isómero farmacéuticamente aceptable del mismo en combinación con una cantidad terapéuticamente efectiva de por lo menos un medicamento seleccionado del grupo que consiste en fármacos antirreumáticos modificadores de enfermedad (DMARDS), NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, modificadores de respuesta biológica (BRMs), agentes anti-inflamatorios y antagonistas H1.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad seleccionadas del grupo que consiste en artritis reumatoidea, osteoartritis, periodontitis, gingivitis, úlcera de córnea, crecimiento tumoral sólido e invasión tumoral por metástasis secundaria, glaucoma neovascular, enfermedad inflamatoria de intestino, esclerosis múltiple y soriasis en un sujeto, que comprende: la administración al sujeto necesitado de dicho tratamiento de una cantidad terapéuticamente efectiva de por lo menos un compuesto de la reivindicación 1 o una sal, un solvato o un isómero

farmacéuticamente aceptables del mismo en combinación con una cantidad terapéuticamente efectiva de por lo menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, BRMs, agentes anti-inflamatorios y antagonistas H1.

En otro aspecto, la invención proporciona un método para el tratamiento de una afección o enfermedad seleccionada del grupo que consiste en choque séptico, choque hemodinámico, síndrome séptico, lesión por reperfusión pos-isquémica, malaria, infección micobacteriana, meningitis, soriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo de injerto, cánceres tales como linfoma cutáneo de células T, enfermedades que involucran angiogénesis, enfermedades autoinmunes, dermatitis, enfermedades inflamatorias del intestino tales como enfermedad de Crohn y colitis, osteoartritis y artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still del adulto, ureitis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, daño radiógeno, lesión alveolar hiperóxica, enfermedad periodontal, VIH, diabetes mellitus insulina no dependiente, lupus sistémico eritematoso, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad de la retina, esclerodermia, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, alveolitis fibrosante criptogénica, soriasis, rechazo de trasplante, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías respiratorias, síndrome de distress respiratorio del adulto, asma, enfermedad pulmonar obstructiva crónica (COPD, correspondiente al término en inglés "chronic obstructive pulmonary disease") y bronquitis en un sujeto, que comprende: la administración al sujeto necesitado de dicho tratamiento de una

cantidad terapéuticamente efectiva de por lo menos un compuesto de la reivindicación 1 o una sal, un solvato o un isómero farmacéuticamente aceptable del mismo en combinación con una cantidad terapéuticamente efectiva de por lo menos un medicamento seleccionado del grupo que consiste en DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, BRMs, agentes anti-inflamatorios y antagonistas de H1.

En otro aspecto, la invención proporciona un método para el tratamiento de artritis reumatoidea que comprende la administración de un compuesto de la fórmula I en combinación con un compuesto seleccionado de la clase que consiste en un inhibidor de COX-2, por ejemplo Celebrex® o Vioxx®; un inhibidor de COX-1, por ejemplo Feldene®; un inmunosupresor, por ejemplo metotrexato o ciclosporina; un esteroide, por ejemplo β -metasona; y un compuesto anti-TNF- α , por ejemplo Enbrel® o Remicade®; un inhibidor de PDE IV, u otras clases de compuestos indicados para el tratamiento de artritis reumatoidea.

En otro aspecto, la invención proporciona un método para el tratamiento de esclerosis múltiple que comprende la administración de un compuesto de la fórmula I en combinación con un compuesto seleccionado del grupo que consiste en Avonex®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de esclerosis múltiple.

La actividad de TACE se determina por un ensayo cinético que mide el índice de aumento de la intensidad fluorescente generada por una disociación catalizada de TACE de un sustrato péptido internamente templado (SPDL-3). El dominio catalítico purificado de TACE humana recombinante (rhTACEc, Residuo 215 hasta 477 con dos mutaciones (S266A y N452Q) y una cola 6xHis) se utiliza en el ensayo. Se purifica a partir del sistema de expresión de células Hi5/baculovirus utilizando cromatografía de afinidad. El sustrato SPDL-3 es un péptido templado internamente (MCA-Pro-Leu-Ala-Gln-Ala-Val-Arg-Ser-Ser-Ser-Dpa-Arg-

NH₂), con su secuencia derivada del sitio de disociación pro-TNF α . MCA es (7-Metoxicumarin-4-il)acetilo. Dpa es N-3-(2,4-Dinitrofenil)-L-2,3-diaminopropionilo.

Una mezcla de ensayo de 50 μ l contiene HEPES 20 mM, pH 7,3, CaCl₂ 5 mM, 100 μ M de ZnCl₂, 2 % de DMSO, 0,04% de Metilcelulosa, 30 μ M de SPDL-3, 70 pM de rhTACEc y un compuesto de ensayo. RhTACEc se pre-incuba con un compuesto de ensayo durante 90 minutos a 25°C. La reacción comienza por el agregado del sustrato. La intensidad fluorescente (excitación a 320 nm, emisión a 405 nm) se midió cada 45 segundos durante 30 minutos utilizando un fluorescenciómetro (GEMINI XS, Molecular Devices). El índice de reacción enzimática se muestra como Unidades por segundo. El efecto de un compuesto de ensayo se muestra como % de actividad de TACE en ausencia del compuesto.

Los compuestos útiles para la actividad inhibitoria de TACE pueden exhibir valores de K_i inferiores a aproximadamente 1000 nM, preferentemente alrededor de 0,01 nM hasta alrededor de 1000 nM, con mayor preferencia alrededor de 0,1 nM hasta aproximadamente 100 nM, e incluso con mayor preferencia inferiores a aproximadamente 15 nM. La actividad inhibitoria de TACE (valores K_i) de algunos compuestos representativos de la presente invención se mencionan en la sección "EJEMPLOS" abajo mencionada.

Las composiciones farmacéuticas que contienen el ingrediente activo podrían presentarse en una forma adecuada para su utilización oral, por ejemplo, como comprimidos, grageas, suspensiones acuosas u oleosas, gránulos o polvos que se pueden dispersar, emulsiones, cápsulas duras o blandas, o jarabes o elixires. Las composiciones elaboradas para una utilización oral podrían prepararse de acuerdo con cualquier método conocido en la técnica de elaboración de composiciones farmacéuticas y tales composiciones podrían contener uno o más agentes seleccionados del grupo que consiste en agentes endulzantes, agentes saborizantes, agentes colorantes y agentes conservantes

con el objeto de proporcionar preparaciones farmacéuticamente elegantes y sabrosas. Los comprimidos contienen el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos que son adecuados para la elaboración de comprimidos. Estos excipientes podrían ser por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo, almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina o acacia, y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Los comprimidos pueden estar sin recubrir o cubiertos mediante técnicas conocidas para retrasar la desintegración y la absorción en el tracto gastrointestinal y por esa razón proporcionar una acción sostenida durante un período más prolongado. Por ejemplo, podría emplearse un material de retardo en el tiempo tal como monoestearato de glicerilo o diestearato de glicerilo. Podrían asimismo recubrirse mediante la técnica descrita en los Números de Patentes Estadounidenses 4.256.108; 4.166.452; y 4.265.874 para formar comprimidos terapéuticos osmóticos para liberación controlada.

El término composición farmacéutica pretende abarcar asimismo tanto la composición en masa como las unidades de dosificación individuales que comprenden más de un agente farmacéuticamente activo (por ejemplo, dos) tales como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de los agentes adicionales descritos en este trabajo, de manera conjunta con cualquier excipiente farmacéuticamente inactivo. La composición en masa y cada unidad de dosificación individual puede contener cantidades fijas de lo anteriormente mencionado "más de un agente farmacéuticamente activo". La composición en masa es material que todavía no se ha formado en unidades de dosificación individuales. Una unidad de dosificación ilustrativa es una unidad de dosificación oral tal como comprimidos,

píldoras, etcétera. Similarmente, el método descrito en este trabajo para tratar a un paciente mediante la administración de una composición farmacéutica de la presente invención pretende abarcar asimismo la administración de la composición en masa y las unidades de dosificación individuales anteriormente mencionadas.

Las formulaciones para utilización oral también pueden presentarse como cápsulas de gelatina dura en donde los ingredientes activos se mezclan con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o cápsulas de gelatina blanda en donde el ingrediente activo se mezcla con agua o un medio oleoso, por ejemplo aceite de maní, parafina líquida o aceite de oliva.

Las suspensiones acuosas contienen el material activo en mezcla con excipientes adecuados para la elaboración de suspensiones acuosas. Tales excipientes son agentes de suspensión, por ejemplo, carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetil-celulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma acacia; los agentes dispersantes o hidratantes podrían ser un fosfátido natural, por ejemplo, lecitina, o productos de condensación de un óxido alquileo con ácidos grasos, por ejemplo estearato de polioxietileno, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilen-oxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen-sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de polietilen-sorbitán. Las suspensiones acuosas podrían asimismo contener uno o más conservantes, por ejemplo, etilo o n-propilo, p-hidroxibenzoato, uno o más agentes colorantes, uno o más agentes saborizantes, y uno o más agentes endulzantes, tales como sacarosa, sacarina o aspartamo.

Las suspensiones oleosas podrían formularse mediante la suspensión del ingrediente activo en un aceite vegetal, por ejemplo, aceite de cacahuete, aceite de oliva, aceite de sésamo o aceite de coco, o en aceite mineral tal como parafina líquida. Las suspensiones oleosas podrían contener un agente espesante, por ejemplo, cera de abeja, parafina dura o alcohol cetílico. Los agentes endulzantes tales como aquellos mencionados anteriormente, y los agentes saborizantes podrían agregarse con el objeto de proporcionar una preparación oral sabrosa. Estas composiciones podrían preservarse mediante el agregado de un anti-oxidante tal como ácido ascórbico.

Los polvos y gránulos dispersables adecuados para la preparación de una suspensión acuosa mediante el agregado de agua proporcionan el ingrediente activo en mezcla con un agente dispersante o hidratante, un agente de suspensión y uno o más conservantes. Los agentes dispersantes o hidratantes y los agentes de suspensión adecuados están ilustrados por aquellos ya mencionados más arriba. Asimismo, pueden estar presentes excipientes adicionales, por ejemplo, agentes endulzantes, saborizantes y colorantes.

Las composiciones farmacéuticas de la invención podrían asimismo presentarse en la forma de una emulsión aceite-en-agua. La fase oleosa podría ser un aceite vegetal, por ejemplo, aceite de oliva o aceite de cacahuete, o un aceite mineral, por ejemplo, parafina líquida o mezclas de éstos. Los agentes emulsionantes adecuados podrían ser fosfátidos naturales, por ejemplo, porotos de soja, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo, monooleato de sorbitán, y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo, monooleato de polioxietilen-sorbitán. Las emulsiones podrían contener asimismo agentes endulzantes y saborizantes.

Los jarabes y elixires podrían formularse con agentes endulzantes, por ejemplo, glicerol, propilenglicol, sorbitol o sacarosa. Tales formulaciones podrían contener asimismo un emoliente, un conservante y agentes saborizantes y colorantes.

Las composiciones farmacéuticas podrían presentarse en la forma de una suspensión acuosa u oleaginosa estéril inyectable. Esta suspensión podría formularse de acuerdo con la técnica conocida utilizando aquellos agentes dispersantes o hidratantes adecuados y agentes de suspensión que se han mencionado anteriormente. La preparación inyectable estéril podría también ser una solución o suspensión inyectable estéril en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo, como una solución en 1,3-butanodiol. Entre los vehículos y solventes aceptables que podrían emplearse se encuentran agua, solución de Ringer y solución de cloruro de sodio isotónico. Además, los aceites fijos estériles se emplean convencionalmente como un solvente o un medio de suspensión. Con este propósito, cualquier aceite fijo blando podría emplearse, incluyendo mono- o diglicéridos sintéticos. Además, los ácidos grasos tales como ácido oleico encuentran su utilidad en la preparación de inyectables.

Los compuestos de la invención podrían también administrarse en la forma de supositorios para administración rectal del fármaco. Las composiciones pueden prepararse mezclando el fármaco con un excipiente no irritante adecuado que es sólido a temperaturas usuales pero líquido a temperatura rectal y por lo tanto se derretirá en el recto para liberar el fármaco. Tales materiales son manteca de cacao y polietilenglicoles.

Para utilizaciones tópicas, se emplean cremas, ungüentos, jaleas, soluciones o suspensiones, etcétera, que contienen los compuestos de la invención. (Para los propósitos de esta solicitud, la aplicación tópica incluye enjuagues bucales y gárgaras).

Los compuestos de la presente invención pueden administrarse en forma intranasal vía utilización tópica de vehículos intranasales adecuados, o vía rutas transdérmicas, utilizando aquellas formas de parches transdérmicos cutáneos bien conocidos por los expertos en la técnica. Con el propósito de suministrarse en la forma de un sistema de administración transdérmico, la administración de la dosis será, por supuesto, continua más que intermitente en todo el régimen de dosificación. Los compuestos de la presente invención podrían asimismo administrarse como un supositorio empleando bases tales como manteca de cacao, gelatina glicerinada, aceites vegetales hidrogenados, mezclas de polietilenglicoles de varios pesos moleculares y ésteres de ácidos grasos de polietilenglicol.

El régimen de dosificación que utiliza los compuestos de la presente invención se selecciona de acuerdo con una variedad de factores que incluyen tipo, especie, peso, sexo y condición médica del paciente; la gravedad de la afección a ser tratada; la ruta de administración; la función renal y hepática del paciente; y el compuesto particular empleado. Un médico o un veterinario con conocimientos usuales puede fácilmente determinar y prescribir la cantidad efectiva del fármaco requerido para prevenir, contrarrestar, detener o revertir el progreso de la afección. La precisión óptima para lograr la concentración del fármaco dentro del rango que produce eficacia sin toxicidad requiere un régimen basado en la cinética de la disponibilidad del fármaco a sitios objetivo. Esto implica una consideración de la distribución, el equilibrio, y la eliminación de un fármaco. Preferentemente, las dosis del compuesto de la Fórmula I útiles en el método de la presente invención oscilan entre 0,01 y 1000 mg por día. Más preferentemente, las dosificaciones oscilan entre 0,1 y 1000 mg/día. E incluso con mayor preferencia, las dosificaciones oscilan entre 0,1 y 500 mg/día. Para una administración oral, las composiciones se proporcionan preferentemente en forma

de comprimidos que contienen 0,01 hasta 1000 miligramos del ingrediente activo, particularmente 0,01, 0,05, 0,1, 0,5, 1,0, 2,5, 5,0, 10,0, 15,0, 25,0, 50,0, 100 y 500 miligramos del ingrediente activo para la adecuación sintomática de la dosificación para el paciente a ser tratado. Se suministra una cantidad efectiva del fármaco a un nivel de dosificación de desde aproximadamente 0,0002 mg/kg hasta aproximadamente 50 mg/kg de peso corporal por día. El rango es más particularmente desde aproximadamente 0,001 mg/kg hasta 1 mg/kg de peso corporal por día.

Favorablemente, el agente activo de la presente invención podría administrarse en una dosis simple diaria, o la dosificación diaria total podría administrarse en dosis divididas de dos, tres o cuatro veces por día.

La cantidad de ingrediente activo que podría combinarse con los materiales portadores para producir formas de dosificación unitarias variará dependiendo del paciente tratado y del modo particular de administración.

Se entiende, sin embargo, que el nivel de dosis específico para cualquier paciente en particular dependerá de una variedad de factores que incluyen la edad, el peso corporal, el estado de salud general, el sexo, la dieta, el tiempo de administración, la vía de administración, el índice de excreción, la combinación del fármaco y la gravedad de la enfermedad en particular que está sobrellevando la terapia.

Los compuestos de la invención podrían elaborarse mediante procesos conocidos por los expertos en la técnica y que se muestran en los siguientes esquemas de reacción y en las preparaciones y ejemplos descritos a continuación.

EJEMPLOS

Las siguientes abreviaturas se utilizan en los procedimientos y en los esquemas:

ACN	Acetonitrilo
AcOH	Ácido acético
Ac	Acuoso
BOC	ter-Butoxicarbonilo
BOC-ON	[2-(ter-butoxicarboniloxiimino)-2-fenilacetonitril]
BOC ₂ O	Anhídrido de BOC
C	grados Celsius
CBZCl	cloroformato de bencilo
DBU	1,8-Diazabicyclo[5.4.0]undec-7-eno
DCM	Diclorometano
DEAD	azodicarboxilato de dietilo
(DHQ)2PHAL	1,4-ftalazinadiil-diéter de Hidroquinina
DIAD	Diisopropilazodicarboxilato
DIPEA	Diisopropiletilamina
DMA	N,N-Dimetilacetamida
DMAP	4-Dimetilaminopiridina
DME	Dimetoxietano
DMF	Dimetilformamida
DMFDMA	N,N-Dimetilformamida dimetilacetal
DMPU	1,3-Dimetil-3,4,5,6-tetrahidro-2(1h)-pirimidinona
DMSO	Dimetilsulfóxido
EDCIClorhidrato	de 1-(3-Dimetilaminopropil)-3-etilcarbodiimida
EI	Ionización de electrones
Eq	Equivalentes
EtOAc	Acetato de etilo

312 319

EtOHEtanol

g gramos

h. horas

¹H protón

HATU hexafluorofosfato de N,N,N',N'-Tetrametil-O-(7-Azabenzotriazol-1-

il)Uronio

Hex hexanos

HOBT 1-Hidroxibenzotriazol

HPLC Cromatografía líquida de alta presión

LAH hidruro de litio aluminio

LDA diisopropilamida de litio

M Molar

mmol milimolar

mCPBA ácido *meta*-Cloroperoxibenzoico

Me Metilo

MeCN Acetonitrilo

MeOH Metanol

min Minutos

mg Miligramos

MHZ Megahertz

mL Mililitro

MPLC Cromatografía de líquidos de presión mediana

NMR Resonancia Magnética Nuclear

MS Espectroscopía de masa

NBS N-Bromosuccinimida

NMMN-Metilmorfolina

NMP 1-metil-2-pirrolidona

DN	durante toda la noche
PCC	clorocromato de piridinio
PTLC	Cromatografía de capa delgada preparativa
PyBrOP	hexafluorofosfato de bromo-tris-pirrolidino-fosfonio
Pyr	Piridina
TA	Temperatura ambiente
sgc	cromatografía sobre gel de sílice 60
tBOCter	Butoxicarbonilo
TACE	enzima conversora de TNF-alfa
TEA	Trietilamina
TFA	Ácido trifluoracético
THF	Tetrahidrofurano
TLC	Cromatografía de capa delgada

Los espectros de RMN se adquirieron en los siguientes instrumentos: 400 MHz RMN (Bruker), 500 MHz RMN (Bruker), 400 MHz RMN (Varian), 300 MHz RMN (Varian) utilizando CD₃OD, CDCl₃ o DMSO-d₆ como solventes. Los datos LC-MS se obtuvieron utilizando un espectrómetro de masa quadropole PESCiex API 150EX empleando ionización por electroscopía.

La purificación vía cromatografía de fase inversa (Gilson) se logró utilizando una columna de fase inversa C18 con un gradiente de (0,1 % de ácido fórmico) 5:95 hasta 90:10 acetonitrilo:agua, a un índice de flujo de 14 mL/min. Las muestras se recolectaron utilizando detección de UV. Alternativamente un ISCO Companion con (0,1% de ácido fórmico) 5:95 hasta 95:5 acetonitrilo:agua, a un índice de flujo = 10 - 55 mL/min.

La cromatografía sobre gel de sílice de fase normal se logró tanto en un instrumento Biotage utilizando cartuchos flash 60 Å 12/M, 25/M, ó 40/M, como en

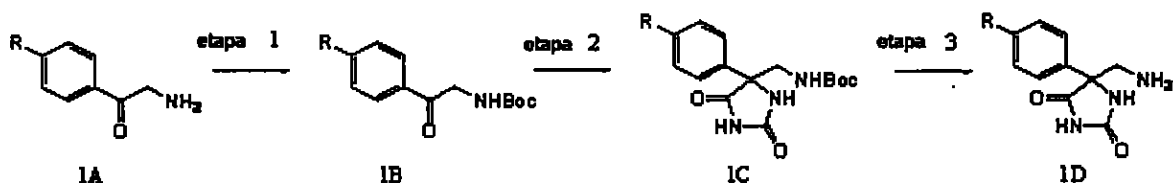
314 32X

un instrumento Jones Flash Master Personal utilizando cartuchos de Isolute flash
SI 5g, 10g, 20g, 50g, ó 70 g.

Los compuestos de la fórmula (I) podrían producirse mediante procesos conocidos por aquellos expertos en la técnica y según se detalla en los siguientes esquemas de reacción y en las preparaciones y ejemplos descritos a continuación. Estas preparaciones y ejemplos no deberían interpretarse con el fin de limitar el alcance de la descripción. Las rutas mecanísticas alternativas y las estructuras análogas podrían ser evidentes para aquellos expertos en la técnica. Algunos de los compuestos elaborados mediante estos procesos se enumeran en las tablas que aparecen a continuación. Todas las clases de formas isoméricas de los compuestos se consideran que están dentro del alcance de la invención.

RUTAS SINTÉTICAS Y EJEMPLOS

Ejemplo 1



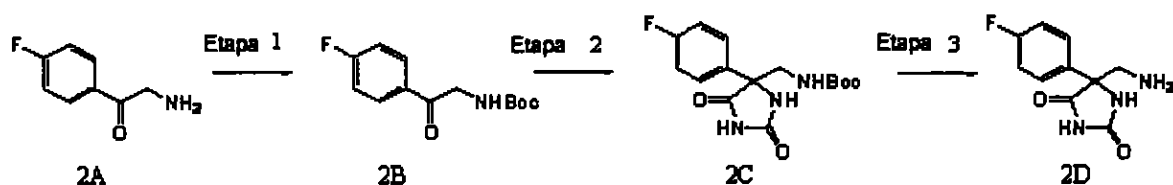
Procedimientos generales para el Ejemplo 1:

En la etapa 1, el Compuesto **1A** (disponible comercialmente, o preparado mediante un procedimiento similar a aquel descrito por Abdalla, G. M. y Sowell, J. W. *Journal of Heterocyclic Chemistry*, 1987, 24(2), 297-301) se trató con un equivalente de dicarbonato de Di-ter-butilo en solvente polar, tal como DMF, durante 30 minutos hasta 12 horas. El solvente fue removido y el compuesto **1B** podía utilizarse sin purificación ulterior o purificado mediante cromatografía sobre gel de sílice.

En la etapa 2, el compuesto **1B** se reaccionó con cianuro de potasio y carbonato de amonio en una solución apropiada de alcohol y agua, a 50°C hasta 90°C, durante 5 horas hasta 48 horas. Luego de enfriarse, se agregó agua y el compuesto **1C** podía recolectarse mediante filtración.

En la etapa 3, el compuesto **1C** se agitó con 2 hasta 20 equivalentes de cloruro de hidrógeno en metanol durante 5 hasta 48 horas. Después de agregarse éter etílico, el compuesto **1D** podía recolectarse mediante filtración.

Ejemplo 2



Etapa 1

El compuesto **2A** (Abdalla; G. M. y Sowell, J. W. *Journal of Heterocyclic Chemistry*, **1987**, *24*(2), 297-301) (Sal clorhidrato, 8,60g, 45,4 mmol), trietilamina (19,0 mL, 136 mmol), y dicarbonato de di-ter-butilo (11,9g, 54,4 mmol) se agitaron en cloruro de metileno (100 mL) a 25°C durante 16 horas. Se agregó NaHCO₃ (150 mL) acuoso saturado. La capa acuosa se extrajo con CH₂Cl₂ (100 mL) dos veces. La fase orgánica se lavó con salmuera (100 mL) y se secó sobre Na₂SO₄. El solvente se removió mediante evaporador giratorio para proporcionar el compuesto **2B** que se utilizó sin purificación ulterior.

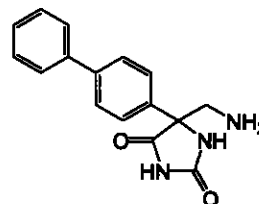
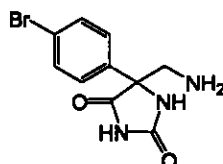
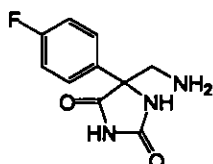
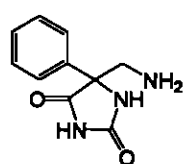
Etapa 2

El compuesto **2B** (9,06g, 35,8 mmol), KCN (3,49g, 53,7 mmol), y (NH₄)₂CO₃ (12,0 g, 125,2 mmol) se suspendieron en una mezcla de EtOH (35 mL) y agua (35 mL). La solución se agitó a 70°C durante tres días. Luego de enfriarse, se agregó agua (35 mL). El sólido se filtró y se lavó con agua tres veces. El sólido se secó bajo vacío a 40°C durante 16 horas para proporcionar el compuesto **2C** (7,9 g, 68%).

Etapa 3

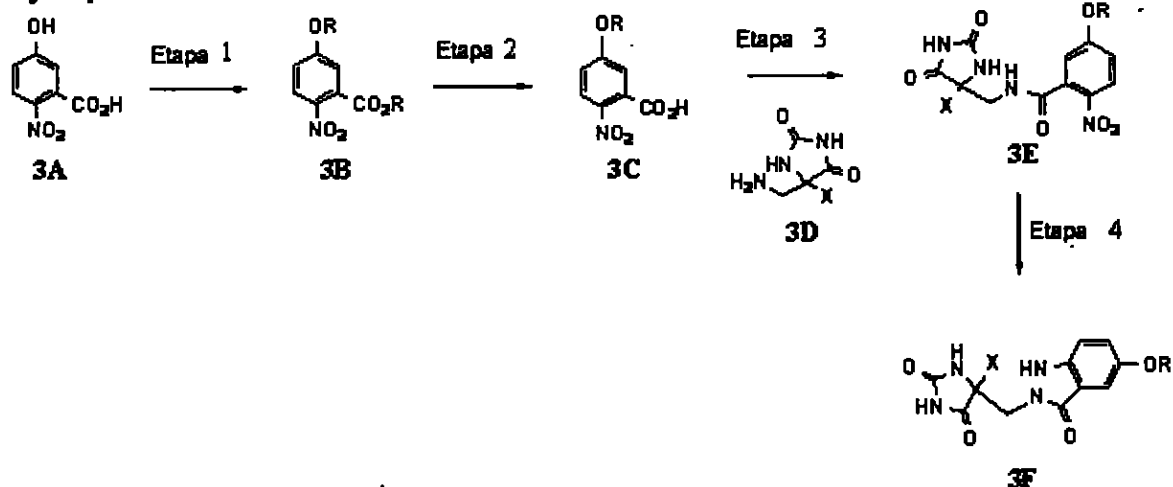
El compuesto **2C** (4,0 g) se suspendió en metanol (50 mL) y se agregó HCl (4M en dioxano, 20 mL). La solución se agitó a 25°C durante 3 horas. Se agregó éter etílico (50 ml). El sólido se filtró, se lavó con éter etílico dos veces, y se secó bajo vacío durante 12 horas para proporcionar el compuesto **2D** (2,7 g, 84%).

Los siguientes intermediarios se prepararon según se describe en los Ejemplos 1 y 2.



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Ejemplo 3



Procedimientos generales para el Ejemplo 3

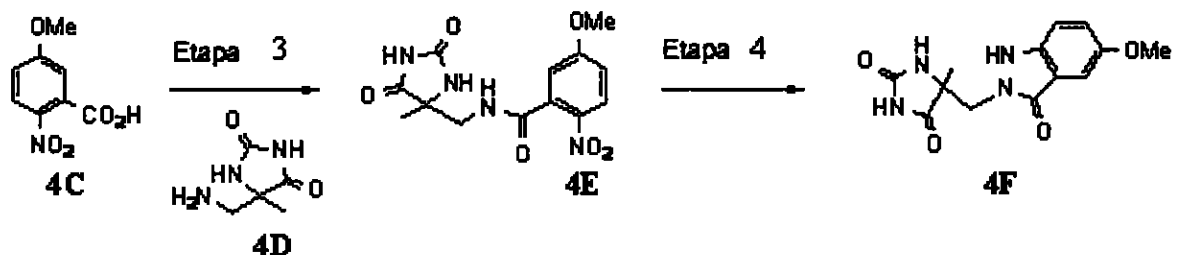
En la etapa 1, se disolvió ácido 5-hidroxi-2-nitro-benzoico (compuesto **3A**) en un solvente adecuado, tal como DMF, y reaccionó con un cloruro de alquilo o bromuro de alquilo en presencia de carbonato de cesio a temperatura ambiente durante 2 hasta 16 horas. Se agregaron agua y EtOAc. La fase orgánica se lavó con agua 1 hasta 5 veces para remover DMF. La fase orgánica se lavó con salmuera, se secó, se concentró para proporcionar el producto crudo (compuesto **3B**) el cual se utilizó sin purificación ulterior.

En la etapa 2, el compuesto **3B** se disolvió en dioxano/agua (3:1) y se trató con hidróxido de litio a temperatura ambiente durante 3 hasta 6 horas. La solución se acidificó mediante el agregado de una solución HCl 1N y se extrajo con EtOAc. Los productos (compuesto **3C**) se utilizaron sin purificación ulterior o se purificaron mediante cromatografía dependiendo del punto de ebullición de los productos secundarios del alcohol.

En la etapa 3, el compuesto **3C** se disolvió en un solvente adecuado, tal como DMF, y se acopló con el compuesto **3D** utilizando EDCI y HOBT a temperatura ambiente durante toda la noche. Luego de una elaboración acuosa/EtOAc, el producto (compuesto **3E**) se aisló mediante cromatografía.

En la etapa 4, el compuesto 3E se suspendió en MeOH/agua (1:1) bajo una atmósfera de N₂. Se agregaron NaOH y polvo de zinc y la mezcla de reacción se agitó a 70°C hasta 80°C durante 8 hasta 24 horas. Luego de enfriar a temperatura ambiente, la solución se reguló a pH=6~7 con solución HCl 1N. El producto (compuesto 3F) se extrajo con EtOAc y se purificó mediante HPLC de fase inversa.

Ejemplo 4



Etapa 3

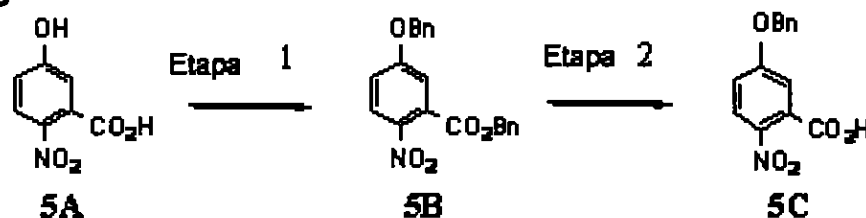
Un frasco de 25 mL se cargó con el compuesto 4C (331 mg, 1,68 mmol), compuesto 4D (Stratford, E. S. y Curley, R. W. Jr, *J. Med. Chem.* **1983**, 26, 1463-1469) (200 mg, 1,4 mmol), EDCI (403 mg, 2,1 mmol), HOBT (227 mg, 1,68 mmol), NMM (0,46 mL, 4.2 mmol), y DMF (7 mL). La solución se agitó a temperatura ambiente durante toda la noche. Se agregaron NaHCO₃ acuoso saturado (30 mL) y EtOAc (50 mL). La fase orgánica se separó y se lavó con agua (20 mL) y salmuera (20 mL), luego se secó sobre Na₂SO₄. El solvente se evaporó y el producto crudo se aisló mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₄OH 20:1:0,1 hasta 10:1:0,1) para proporcionar el compuesto 4E (201 mg, 45%).

Etapa 4

A un frasco de 10 mL se agregó el compuesto 4E (50 mg, 0,155 mmol), NaOH (25 mg, 0,62 mmol), polvo de zinc (62 mg, 0,47 mmol), MeOH (0,5 mL), y agua (0,5 mL). La solución se agitó a 75°C durante 16 horas. Luego de enfriarse a

temperatura ambiente, el sólido se removió mediante filtración. El filtrado se reguló a pH=5 mediante el agregado de HCl 2N. La fase acuosa se extrajo mediante EtOAc (10 mL). La solución orgánica se secó sobre Na₂SO₄ y se concentró. El producto se aisló mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₄OH, 40:1:0,1 hasta 20:1:0,1 hasta 10:1:0,1) para proporcionar el compuesto 4F 6,5 mg (14%).

Ejemplo 5



Etapa 1

El compuesto **5A** (1,33 g, 7,26 mmol), bromuro de bencilo (2,73 g, 16,0 mmol), y Cs₂CO₃ (7,1 g, 22,0 mmol) se mezclaron en DMF (30 mL) y se agitaron a temperatura ambiente durante toda la noche. Se agregó NaHCO₃ (100 mL) acuoso saturado y la fase acuosa se extrajo con EtOAc (100 mL) dos veces. Las fases orgánicas combinadas se lavaron con salmuera (50 mL), se secaron sobre Na₂SO₄, se filtraron, y se concentraron mediante evaporador giratorio. El producto se aisló mediante cromatografía sobre gel de sílice (Hexano/EtOAc: 10:1 hasta 5:1) para proporcionar el compuesto **5B** (2,25 g, 89%).

Etapa 2

El compuesto **5B** (2,25 g, 6,44 mmol) se disolvió en dioxano/agua (3:1, 35 mL) y se agregó LiOH (810 mg, 19,3 mmol). La solución se agitó a temperatura ambiente durante 3 horas. Se agregó agua (30 mL) seguido por el agregado de HCl 2N (30 mL). La fase acuosa se extrajo con EtOAc (50 mL) tres veces. La fase orgánica se lavó con salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró mediante evaporador giratorio. El producto crudo se purificó mediante

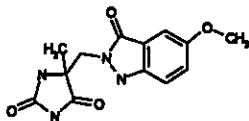
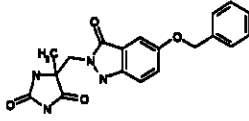
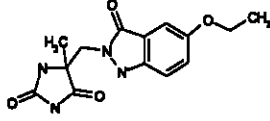
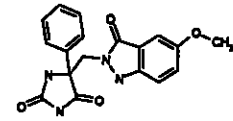
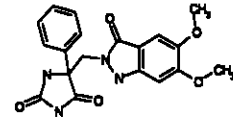
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cromatografía sobre gel de sílice ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{HCO}_2\text{H}$: 40:1:0,1 hasta 20:1:0,1) para proporcionar el compuesto **5C** (1,6 g, 91%).

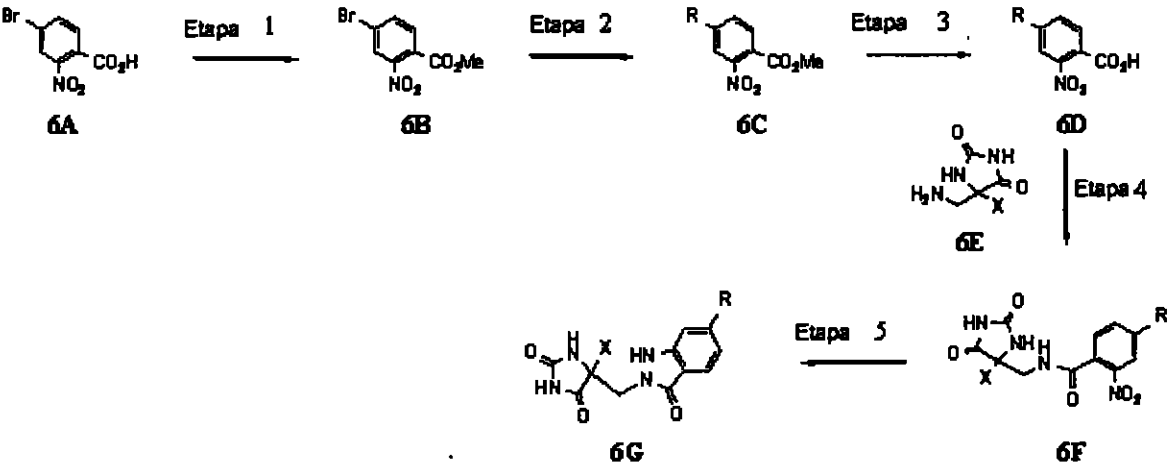
Los siguientes compuestos se prepararon según se describe en los Ejemplos 3-5.

En cada una de las Tablas a continuación, aquellos compuestos que poseen un valor K_i inferior a 10 nM (<10 nM) se designan con la letra "A"; aquellos con un valor K_i desde 10 hasta menos de 100 nM (10 - <100 nM) se designan con la letra "B"; aquellos con un valor K_i desde 100 hasta 1000 nM se designan con la letra "C"; y aquellos con un valor K_i superior a 1000 nM (>1000 nM) se designan con la letra "D".

Tabla 1

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
1		290,27	291,1 [M+H] ⁺	B
2		366,13	367,1 [M+H] ⁺	C
3		304,12	305,0 [M+H] ⁺	C
4		352,12	353,1 [M+H] ⁺	A
5		382,13	383,1 [M+H] ⁺	B

Ejemplo 6



Procedimientos generales para el Ejemplo 6

En la etapa 1, se disolvió ácido 4-bromo-2-nitro-benzoico (compuesto 6A) en un solvente adecuado, tal como DMF, y se reaccionó con yoduro de metilo en presencia de carbonato de cesio a temperatura ambiente durante 2-16 horas. Se agregaron agua y EtOAc y la fase orgánica se lavó con agua 1-5 veces para remover DMF. La fase orgánica se lavó con salmuera, se secó, se concentró, y se secó para proporcionar el producto crudo (compuesto 6B) que se utilizó sin purificación ulterior.

En la etapa 2, el éster metílico (compuesto 6B) se mezcló con $\text{Pd}(\text{OAc})_2$, Cs_2CO_3 , y un ligando apropiado, tal como 2-(Di-*t*-butilfosfino)-1,1'-binaftilo racémico. La mezcla se ubicó bajo vacío durante 1 hasta 10 minutos para remover el oxígeno, y se recargó con N_2 . Se agregaron un alcohol y tolueno y la solución se agitó a 50°C hasta temperatura de reflujo durante 12 hasta 72 horas. Luego de enfriar a temperatura ambiente, el sólido se removi6 mediante filtraci6n y el solvente se removi6. El producto pudo purificarse mediante cromatografía. Durante esta reacci6n, el éster metílico podria convertirse parcialmente en el éster del alcohol utilizado. Este producto secundario tambi6n se recolect6 y se hidroliz6 en la pr6xima etapa.

En la etapa 3, el compuesto 6C se disolvi6 en Dioxano/agua (3:1) y se trat6 con hidr6xido de litio a temperatura ambiente durante 3-6 horas. La soluci6n se acidific6 mediante el agregado de una soluci6n HCl 1N y se sometió a elaboraci6n acuosa/EtOAc. Los productos (compuesto 6D) se utilizaron sin purificaci6n ulterior o se purificaron mediante cromatografía dependiendo del punto de ebullici6n de los productos secundarios del alcohol.

En la etapa 4, el compuesto 6D se disolvi6 en un solvente adecuado, tal como DMF, y se acopl6 con el compuesto 6E bajo condiciones EDCI y HOBT a temperatura ambiente durante toda la noche. Luego de una elaboraci6n

acuosa/EtOAc, el producto (compuesto 6F) podía aislarse mediante cromatografía.

En la etapa 5, el compuesto 6F se suspendió en MeOH/agua (1:1) bajo atmósfera de N₂. Se agregaron NaOH y polvo de zinc y la mezcla de reacción se agitó a 70°C hasta 80°C durante 8 hasta 24 horas. Luego de enfriar a temperatura ambiente, la solución se reguló a pH=6~7 con una solución HCl 1N. El compuesto 6G se extrajo con EtOAc y se aisló mediante HPLC de fase reversa.

Ejemplo 7



Etapa 1

El compuesto 7A (10,0 g, 40,7 mmol) se disolvió en DMF (100 mL). Se agregaron Cs₂CO₃ (27,0g, 81,3 mmol) y yoduro de metilo (7,60 mL, 122,0 mmol). La solución se agitó a temperatura ambiente durante toda la noche. Se agregaron EtOAc (250 mL) y agua (100 mL). La fase orgánica se separó y se lavó con agua (100 mL) tres veces y salmuera (50 mL), luego se secó sobre Na₂SO₄, se filtró, y concentró utilizando evaporador giratorio. El producto se secó bajo vacío para proporcionar el compuesto 7B (10,3 g, 97%).

Etapa 2

Pd(OAc)₂ (43 mg, 0,19 mmol), 2-(di-*t*-butilfosfino)-1,1'-binaftilo racémico (92 mg, 0,23 mmol), y Cs₂CO₃ (1,88 g, 5,76 mmol) se ubicaron en un frasco de 50 mL. El frasco se colocó bajo vacío durante 2 minutos y se recargó con N₂. El compuesto 7B (1,00 g, 3,84 mmol) y MeOH (0,311 mL, 7,69 mmol) se disolvieron en tolueno (10 mL). La solución resultante se agregó al frasco anteriormente mencionado con una pipeta. La mezcla de reacción se agitó a 70°C de baño de aceite durante 48 horas. Luego de enfriar a temperatura ambiente, el sólido se

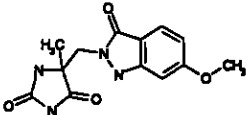
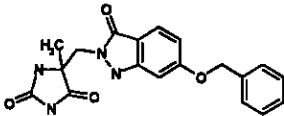
filtró y el solvente se removió utilizando un evaporador giratorio. El producto se aisló mediante cromatografía sobre gel de sílice (Hexano/EtOAc 20:1 hasta 10:1) para proporcionar el compuesto **7C** (380 mg, 47%).

Etapa 3

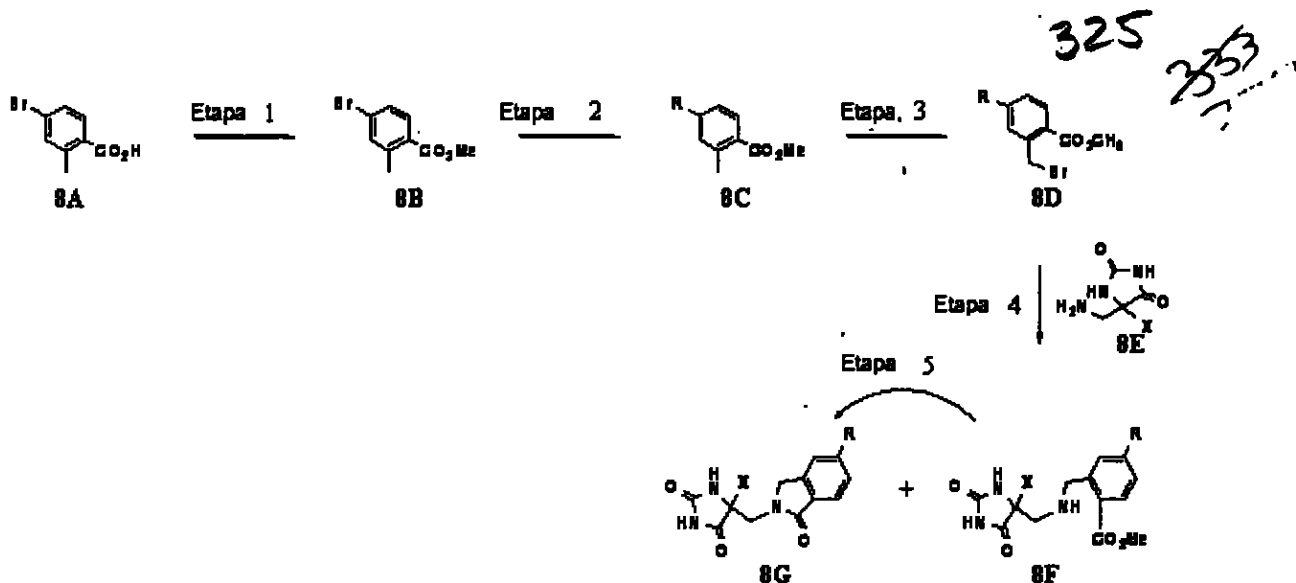
El compuesto **7C** (380 mg, 1,80 mmol) se disolvió en dioxano/agua (3:1, 8 mL) y se agregó LiOH (378 mg, 9,0 mmol). La solución se agitó a temperatura ambiente durante 3 horas. Se agregó agua (5 mL) seguido por el agregado de HCl 2N para regular el pH = 2~4. La fase acuosa se extrajo con EtOAc (10 mL) tres veces. La fase orgánica se lavó con salmuera, se secó sobre Na₂SO₄, se filtró, y se concentró. El producto crudo se secó bajo vacío para proporcionar el compuesto **7D** que se utilizó sin purificación ulterior.

Los siguientes compuestos se prepararon según se describe en los Ejemplos 6-7

Tabla 2

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
6		289,11	291,1 [M+H] ⁺	B
7		366,13	367,1 [M+H] ⁺	C

Ejemplo 8



Procedimiento general para el Ejemplo 8

En la etapa 1, el compuesto **8A** se disolvió en un solvente adecuado, tal como DMF, y se reaccionó con yoduro metílico en presencia de carbonato de cesio a temperatura ambiente durante 2-16 horas. Se agregaron agua y EtOAc y la fase orgánica se lavó con agua 1-5 veces para remover DMF. La fase orgánica se lavó con salmuera, se secó, se concentró, y se secó para proporcionar el producto crudo (compuesto **8B**) que se utilizó sin purificación ulterior.

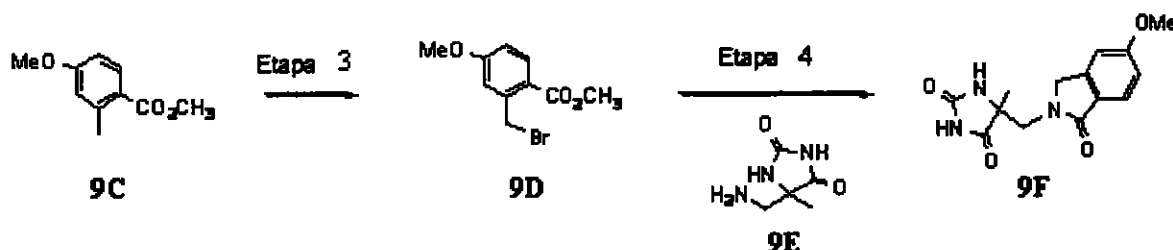
En la etapa 2, cuando se utilizó alcohol, la reacción se operó de manera similar a la etapa 2 en el ejemplo 6. Cuando se utilizó un estannano aromático o heterocíclico, la reacción se operó de la siguiente manera. El estannano aromático o heterocíclico se agregó a un frasco seco, seguido por el agregado de éster metílico del ácido 4-bromo-2-metil-benzoico (compuesto **8B**), una base, tal como Cs_2CO_3 , K_3PO_4 , y un catalizador de paladio, tal como $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$. El frasco se colocó bajo vacío durante 1 hasta 10 minutos para remover el oxígeno y se recargó con N_2 . Se agregó un solvente apropiado, tal como CH_3CN seco, y la solución se agitó a 60°C hasta temperatura de reflujo durante toda la noche hasta 3 días. El sólido se removió mediante filtración y el solvente se removió. El compuesto **8C** se aisló mediante cromatografía.

En la etapa 3, el compuesto **8C** se disolvió en un solvente inerte adecuado, tal como benceno, CCl_4 ó α,α,α -Trifluortolueno. Se agregaron NBS y peróxido de benzoílo y la solución se agitó a 50°C hasta 90°C durante 1 hasta 24 horas. El sólido se filtró y el solvente se removió. El residuo se disolvió en éter y se lavó con agua. El éter se removió para proporcionar el compuesto **8D** que se utilizó sin purificación ulterior.

En la etapa 4, el bromuro de bencilo (compuesto **8D**) se mezcló con metilamina de hidantoína **8E**, K_2CO_3 , y DMF. La solución se agitó a temperatura ambiente durante 12 hasta 24 horas. Luego el sólido se removió mediante filtración. El producto pudo purificarse mediante HPLC de fase inversa. Los compuestos **8F** y **8G** pudieron obtenerse en una relación variable.

La etapa 5 se utiliza cuando el compuesto **8F** se aisló en la etapa 4. El compuesto **8F** se disolvió en un solvente apropiado, tal como MeOH, y se agitó a 50°C hasta temperatura de reflujo durante 1 hasta 12 horas. El producto pudo obtenerse mediante la remoción del solvente mediante evaporador giratorio o purificándose vía cromatografía de fase inversa.

Ejemplo 9



Etapa 3

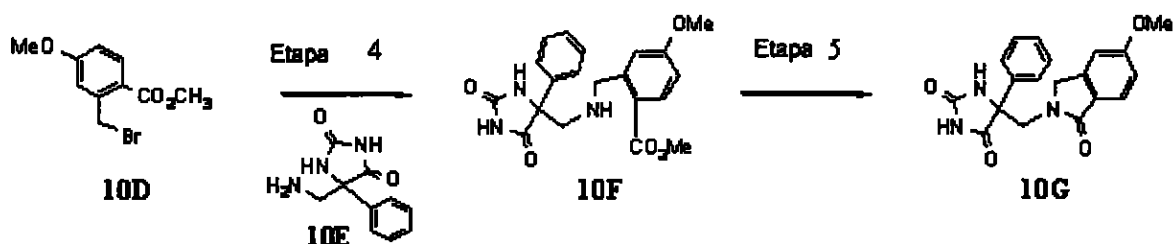
El compuesto **9C** (preparado de acuerdo con el procedimiento descrito por Wyrick, S. D. et al. *Journal of Medicinal Chemistry*, 1987, 30(10), 1798-806) (3,33 g, 18,5 mmol) se disolvió en benceno seco (40 mL). Se agregaron NBS (3,45 g, 19,4 mmol) y peróxido de benzoílo (134 mg, 0,55 mmol). La solución se agitó en

un baño de aceite a 75°C durante alrededor de 2 horas. Luego de enfriarse, el sólido se filtró y se lavó con Et₂O (150 mL). La solución orgánica luego se lavó con agua (50 mL) dos veces, se secó sobre Na₂SO₄ or MgSO₄, se filtró, y se concentró mediante evaporador giratorio. El producto crudo se secó bajo vacío para proporcionar el compuesto **9D** que se utilizó sin purificación ulterior. ¹H-RMN pareció indicar que aproximadamente 75% de este material era el compuesto **9D**.

Etapa 4

El compuesto **9D** (4,62 mmol), el compuesto **9E** (824 mg, 4,62 mmol), y K₂CO₃ (1,28 g, 9,24 mmol) se mezclaron en DMF (30 mL). La solución se agitó a temperatura ambiente durante 20 horas. Se agregó DMF (15 mL) y el sólido se filtró y se lavó con DMF. Toda la solución de DMF se combinó y se concentró a 25 mL. La solución resultante se aplicó a MPLC de fase inversa (CH₃CN/agua, 5% hasta 90%, conteniendo 0,1% HCO₂H) para proporcionar el compuesto **9F** (198 mg, 15%).

Ejemplo 10



Etapa 4

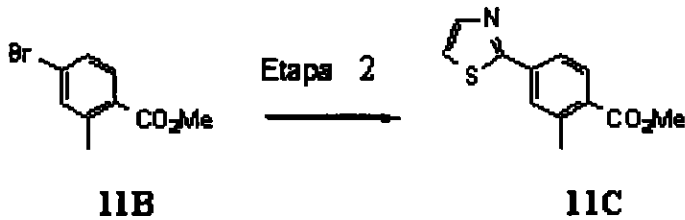
El compuesto **10D** (preparado en el ejemplo 9) (902 mg, 2,07 mmol, factor = 0,75), el compuesto **10E** (preparado según se describe en el Ejemplo 1, 500 mg, 2,07 mmol), y K₂CO₃ (629 mg, 4,56 mmol) se mezclaron en DMF (15 mL). La solución se agitó a temperatura ambiente durante 20 horas. Se agregó DMF (15 mL) y el sólido se filtró y se lavó con DMF. Toda la solución de DMF se combinó y

se concentró a 20 mL. Se aplicó a MPLC de fase inversa (CH₃CN/agua: 5% hasta 90%, conteniendo 0,1% HCO₂H) para proporcionar el compuesto **10F**.

Etapa 5

El compuesto **10F** (preparado en la etapa 4) se disolvió en MeOH (5 mL), se agitó a 65°C durante 5 horas, luego se concentró hasta secarse. El compuesto se suspendió en agua y se secó con liofilizador para proporcionar el compuesto **10G** (68,3 mg, 9,4%).

Ejemplo 11

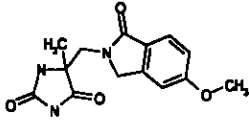


Etapa 2

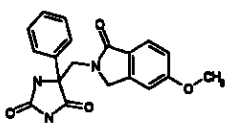
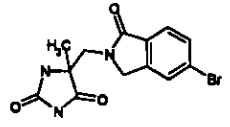
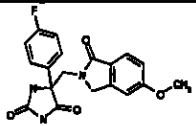
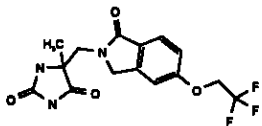
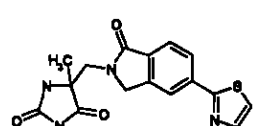
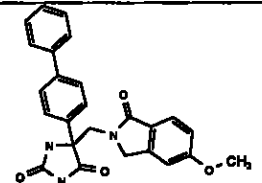
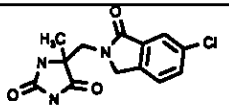
El compuesto **11B** (500 mg, 2,18 mmol), 2-tributylestaniltiazol (0,97 mL, 2,84 mmol), Pd(PPh₃)₂Cl₂, y CH₃CN seco se agitaron bajo nitrógeno a temperatura de reflujo durante toda la noche. Luego de enfriar a temperatura ambiente, el sólido se filtró. El producto se aisló mediante cromatografía sobre gel de sílice (Hexano/EtOAc: 20:1 hasta 10:1 hasta 5:1) para proporcionar el compuesto **11C** (480 mg, 94%).

Los siguientes compuestos se prepararon según se describe en los Ejemplos 8-11.

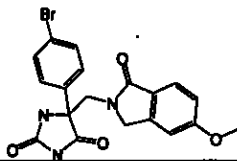
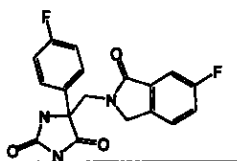
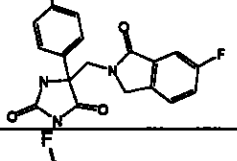
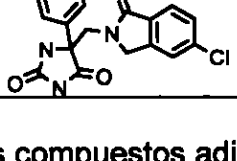
Tabla 3

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
8		289,11	290,1 [M+H] ⁺	B

329 237

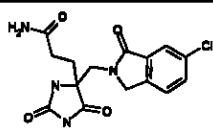
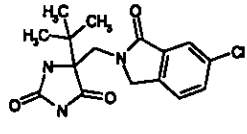
9		351,12	352,1 [M+H] ⁺	A
10		337,01	338 [M+H] ⁺ 340,1	C
11		369,11	370,1 [M+H] ⁺	A
12		357,09	358,1 [M+H] ⁺	B
13		342,08	343,1 [M+H] ⁺	C
14		427,2	428,2 [M+H] ⁺	A
15		293,06	294,1 [M+H] ⁺	B

330 330

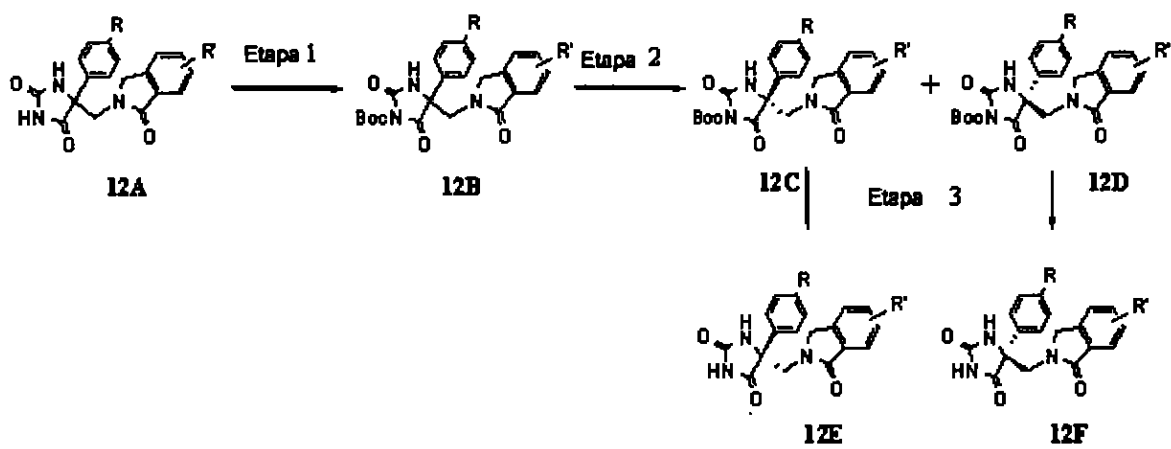
16		431,0	432,1 [M+H] ⁺	A
17		357,1	358,1 [M+H] ⁺	A
18		417,0	418,1 [M+H] ⁺	A
19		373,1	374,2 [M+H] ⁺	A

Los siguientes compuestos adicionales se prepararon según se describe en los Ejemplos 8 hasta 11.

Tabla 4

Compuesto #	Estructuras	Masa Exacta	Masa Observada	Ki (nM)
294		350,08	351,1[M+H] ⁺	B
295		335,10	336,1[M+H] ⁺	B

Ejemplo 12



Procedimientos generales para el Ejemplo 12:

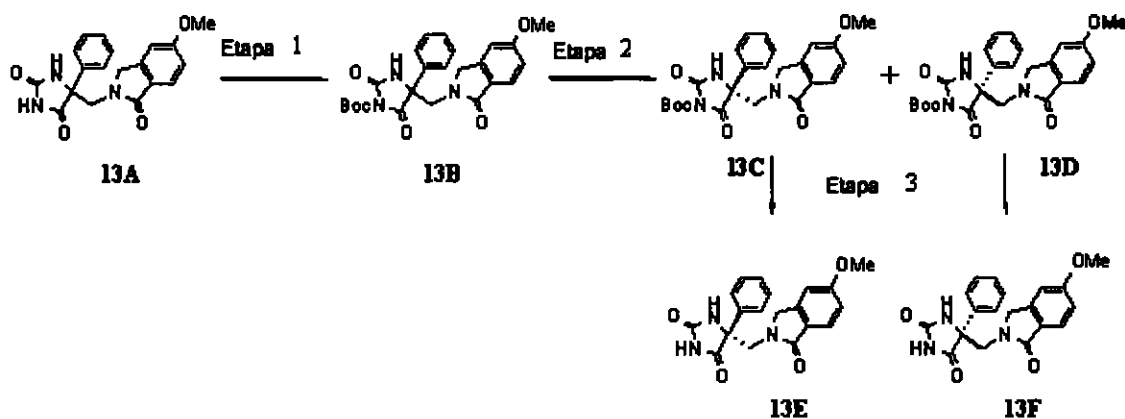
En la etapa 1, el compuesto racémico **12A** se trató con un equivalente de dicarbonato de di-ter-butilo y 4-N,N-dimetilaminopiridina en solvente polar, tal como DMF, durante 30 minutos hasta 12 horas. El solvente se removió y el producto (compuesto **12B**) se aisló mediante cromatografía sobre gel de sílice (pretratado con 1% trietilamina en Hexano).

En la etapa 2, el compuesto **12B** se disolvió en solventes adecuados concedidos por columna de HPLC, y se separó en partes constitutivas mediante HPLC utilizando una columna Chiralpak AD o Chiralcel OD preparativa para proporcionar los compuestos **12C** y **12D**.

En la etapa 3, el compuesto **12C** y **12D** se trataron con HCl excedente en metanol a 25°C hasta 60°C durante una hora hasta 12 horas. El solvente se concentró para proporcionar el compuesto **12E** y **12F**.

332
3800

Ejemplo 13



Etapa 1

El compuesto **13A** (810 mg, 2,07 mmol), dicarbonato de di-ter-butilo (429 mg, 1,97 mmol), y 4-dimetilaminopiridina (20 mg) se disolvieron en una mezcla de DMF (10 mL) y THF (20 mL). La solución se agitó a 25°C durante toda la noche. Los solventes se removieron mediante evaporador giratorio. El producto se aisló mediante cromatografía C18 (CH₃CN/agua; 5% hasta 90%) para proporcionar el producto **13B** (650 mg, 70%).

Etapa 2

El compuesto **13B** (600 mg) se disolvió en una mezcla de iso-propanol (6 mL) y CHCl₃ (4 mL). Se separó 2,5 mL vía HPLC con columna chiralcel OD preparativa (Fase móvil: iso-propanol/Hexano: 1:4). Las fracciones para cada pico se recolectaron y se concentraron mediante evaporador giratorio para proporcionar el compuesto **13C** (Primer pico, 197 mg) y el compuesto **13D** (segundo pico, 178 mg).

Etapa 3

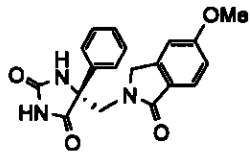
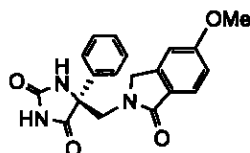
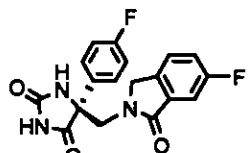
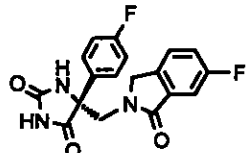
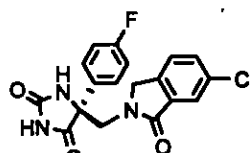
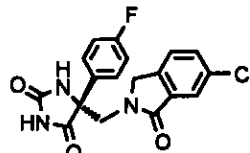
El compuesto **13C** (197 mg) se disolvió en metanol (3 mL). Se agregó HCl (4M en Dioxano, 0,5 mL). La solución se agitó en un baño de aceite a 60°C durante tres horas. El metanol se removió mediante evaporador giratorio para proporcionar el compuesto **13E**.

333 247

El compuesto 13F se preparó de la misma manera que el compuesto 13D (178 mg).

Los siguientes compuestos se prepararon según se describe en los

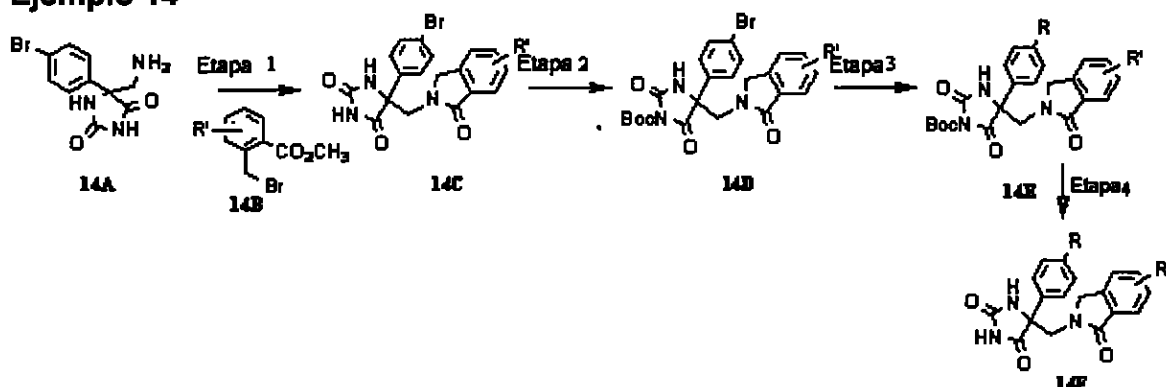
Ejemplos 12-13
Tabla 5

Compuesto #	Estructuras	Masa Exacta	Masa Observada	Ki (nM)
20	 Enantiómero A	351,1	352,2 [M+H] ⁺	A
21	 Enantiómero B	351,1	352,2 [M+H] ⁺	C
22	 Enantiómero A	357,1	358,1 [M+H] ⁺	C
23	 Enantiómero B	357,1	358,1 [M+H] ⁺	A
24	 Enantiómero A	373,06	374,2 [M+H]	C
25	 Enantiómero B	373,06	374,2 [M+H]	A

Datos Espectrales de RMN Protónica para los Compuestos seleccionados en la Tabla 5.

Compuesto 25. ^1H RMN (500 Hz, DMSO- d_6) δ 4,06 (d, J = 14Hz, 1H), 4,20 (d, J = 14 Hz, 1H), 4,32 (d, J = 18 Hz, 1H), 4,38 (d, J = 18 Hz, 1H), 7,19-7,39 (m, 2H), 7,55-7,80 (m, 5H), 8,93 (s, 1H), 10,96 (s, 1H).

Ejemplo 14



Procedimiento general para el Ejemplo 14

En la etapa 1, el compuesto 14A (preparado según se describe en el **Ejemplo 1**) se trató con un bromuro de bencilo (compuesto 14B) y una base DIPEA en DMF a 25°C hasta 60°C durante 12 hasta 24 horas. La solución de reacción se purificó vía cromatografía C18 de fase inversa para proporcionar el compuesto 14C.

En la etapa 2, el compuesto 14C se trató con un equivalente de dicarbonato de di-ter-butilo en solvente polar, tal como DMF, durante 30 minutos hasta 12 horas. El solvente se removió y el producto (compuesto 14D) se aisló mediante cromatografía sobre gel de sílice (pretratado con 1% trietilamina en Hexano).

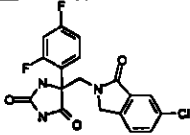
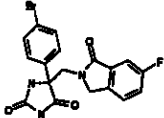
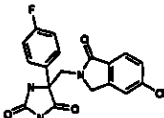
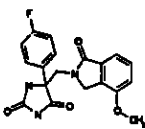
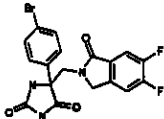
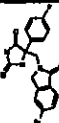
En la etapa 3, el compuesto 14D se sometió a una reacción catalizada con Pd con un ácido borónico heterocíclico o un estannano heterocíclico, o una reacción catalizada con cobre con una amina heterocíclica. La reacción se calentó en solventes apropiados, tales como DMF y acetonitrilo, a 60°C hasta 150°C,

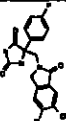
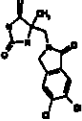
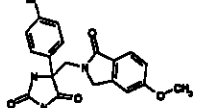
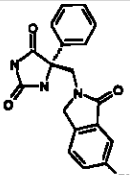
durante 5 minutos hasta 12 horas. En algunos casos, se empleó un reactor de microondas. El producto se purificó mediante cromatografía sobre gel de sílice para proporcionar el compuesto 14E o el compuesto 14F.

En la etapa 4, el compuesto 14E se disolvió en metanol y se agitó con HCl durante 1 hora hasta 12 horas a 25°C hasta 60°C. El solvente se removió para proporcionar el compuesto 14F.

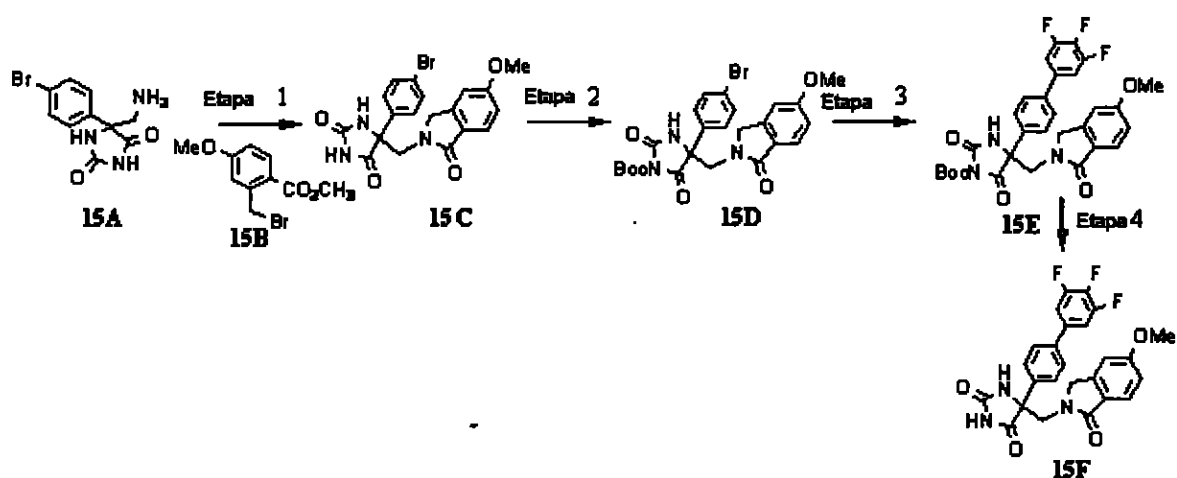
Los siguientes compuestos se prepararon según se describe en la etapa 1 del Ejemplo 14 de más arriba.

Tabla 6

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
100		391,05	392,07 [M+H] ⁺	n/a
101		417,01	418,1 [M+H] ⁺	A
102		373,06	374,2 [M+H] ⁺	A
103		369,11	370,1 [M+H] ⁺	D
104		435,00	436,1 [M+H] ⁺	B
105		417,01	418,420 [M+H] ⁺	B

106		407,0	408 [M+H] ⁺	A
107		327,0	328 [M+H] ⁺	B
108		429,03	430,432 [M+H] ⁺	B
109		355,07	378,2 [M+Na] ⁺	B

Ejemplo 15



Etapa 1

El compuesto **15A** (preparado según se describe en el **Ejemplo 1**, 1,0 g, 3,12 mmol), el compuesto **15B** (preparado en el **Ejemplo 9**, 1,06 g, 3,12 mmol, factor = 0,76), y base DIPEA (1,14 mL, 6,55 mmol) se mezclaron en DMF (22 mL). La solución se agitó a 55°C durante 20 horas. La solución de reacción se purificó vía MPLC C18 de fase inversa (columna de 130g, CH₃CN/agua/0,1% HCO₂H, 5% hasta 90%, dos separaciones) para proporcionar el compuesto **15C** (900 mg, 67%).

Etapa 2

El compuesto **15C** (2,7 g, 6,28 mmol) se suspendió en una mezcla de DMF (20 mL) y THF (40 mL). Se agregaron dicarbonato de di-ter-butilo (1,51 g, 6,91 mmol) y 4-dimetiaminopiridina (38 mg, 0,31 mmol). La solución se agitó a 25°C durante 16 horas. Los solventes se removieron mediante evaporador giratorio. El residuo se sometió a cromatografía sobre gel de sílice (Hexano/EtOAc: 2:1 hasta 1:1) para proporcionar el compuesto **15D** (2,36 g, 71%).

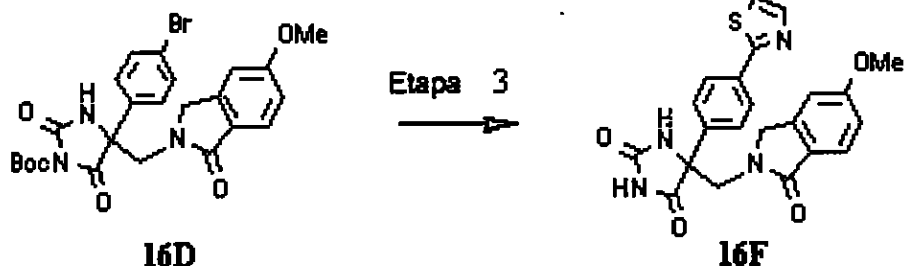
Etapa 3

El compuesto **15D** (100 mg, 0,19 mmol), ácido 3,4,5-trifluorfenilborónico (40 mg, 0,23 mmol), cloruro de 1,1'-bis(trifenilfosfino)ferroceno paladio (II) (15 mg, 0,02 mmol), carbonato de potasio (1M en agua, 1 mL) y acetonitrilo (1 mL) se agregaron a un tubo reactor de microondas. El tubo se selló y reaccionó en el reactor de microondas a 150°C durante 10 minutos. Luego de enfriarlo, la capa acuosa se removió y la capa orgánica se concentró. El producto crudo se purificó mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₃: 40:1:0.1) para proporcionar el compuesto **15E**.

Etapa 4

El compuesto **15E** obtenido de la etapa 3 se suspendió en MeOH. Se agregó HCl (2M en éter etílico, 0,5 mL). La mezcla de reacción se agitó a 50°C durante cinco horas. El solvente se removió. El producto se purificó vía cromatografía C18 de fase inversa (CH₃CN/agua/0,1% HCO₂H, 5% hasta 90%) para proporcionar el compuesto **15F** (8 mg, 8,8% del compuesto **15D**).

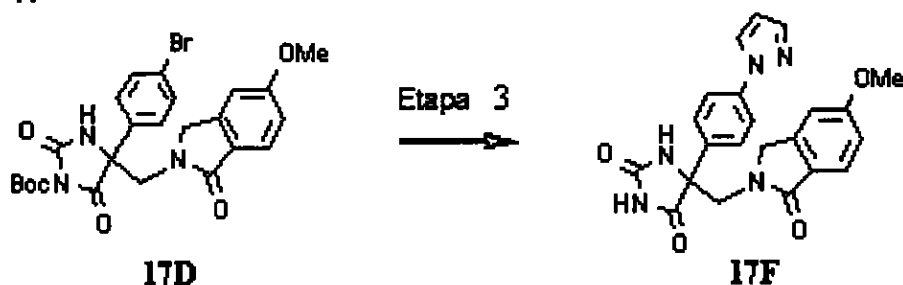
Ejemplo 16



Etapa 3

El compuesto **16D** (50 mg, 0,094 mmol, preparado en el ejemplo 13), 2-tributylestanniltiazol (53 mg, 0,14 mmol), diclorobis(trifenilfosfina) paladio (II) (7 mg, 0,01 mmol), y acetonitrilo (1 mL) se agregaron a un tubo reactor de microondas. El tubo se selló y reaccionó en un reactor de microondas a 150°C durante 10 minutos. El solvente se evaporó y el producto se purificó mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₃: 40:1:0,1 hasta 20:1:0,1) para proporcionar el compuesto **16F** (15 mg, 37%).

Ejemplo 17



Etapa 3

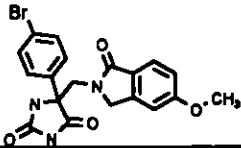
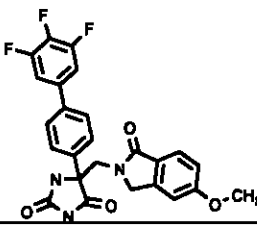
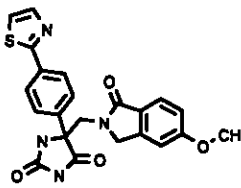
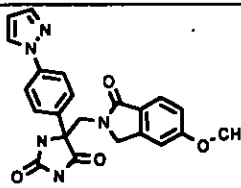
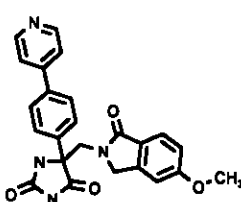
El compuesto **17D** (100 mg, 0,19 mmol, preparado en el ejemplo 13), pirazol (15,4 mg, 0,23 mmol), carbonato de cesio (124 mg, 0,38 mmol), yoduro de cobre (7,2 mg, 0,038 mmol), 1,10-fenantrolina (14 mg, 0,076 mmol), y N,N-dimetilacetamida (0,5 mL) se agregaron a un tubo de reacción seco y se llenaron con nitrógeno. El tubo de reacción se selló y se calentó en un baño de aceite a 120°C durante dos días. Luego de enfriarse, la solución de reacción se purificó mediante cromatografía C18 (CH₃CN/agua/0,1% HCO₂H, 5% hasta 90%) para proporcionar el compuesto **17F** (5 mg, 6,4%).

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211

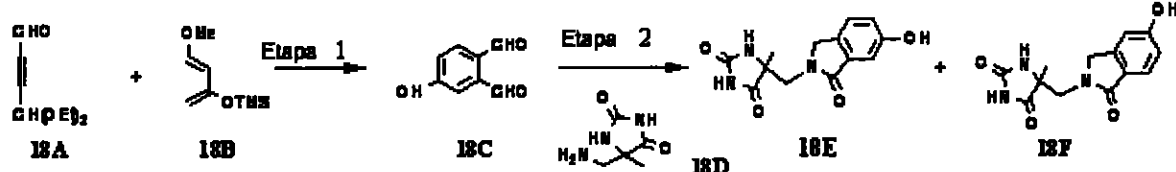
Los siguientes compuestos se prepararon según se describe en los

Ejemplos 14-17

Tabla 7.

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
26		429,0	430,1 [M+H] ⁺	A
27		481,1	482,3 [M+H] ⁺	B
28		434,1	435,1 [M+H] ⁺	A
29		417,1	418,2 [M+H] ⁺	A
30		428,2	429,1 [M+H] ⁺	A

Ejemplo 18



Etapa 1:

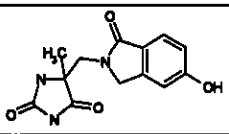
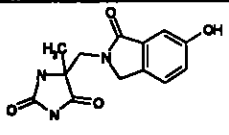
El compuesto **18A** (1,0 g, 6,4 mmol) y el compuesto **18B** (1,324 g, 7,68 mmol) se disolvieron en tolueno (4 mL) y se agitaron a 80°C durante 24 horas. Luego de enfriar a temperatura ambiente, el solvente se removió mediante evaporador giratorio. La mitad del producto crudo se disolvió en THF/ HCl 1N (1:1, 14 mL) y se agitó a temperatura ambiente durante 2 horas. Se agregaron EtOAc (15 mL) y agua (5 mL). La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (15 mL) dos veces. La fase orgánica combinada se secó sobre Na₂SO₄ y se concentró mediante evaporador giratorio para proporcionar el compuesto **18C** que se utilizó sin purificación ulterior.

Etapa 2

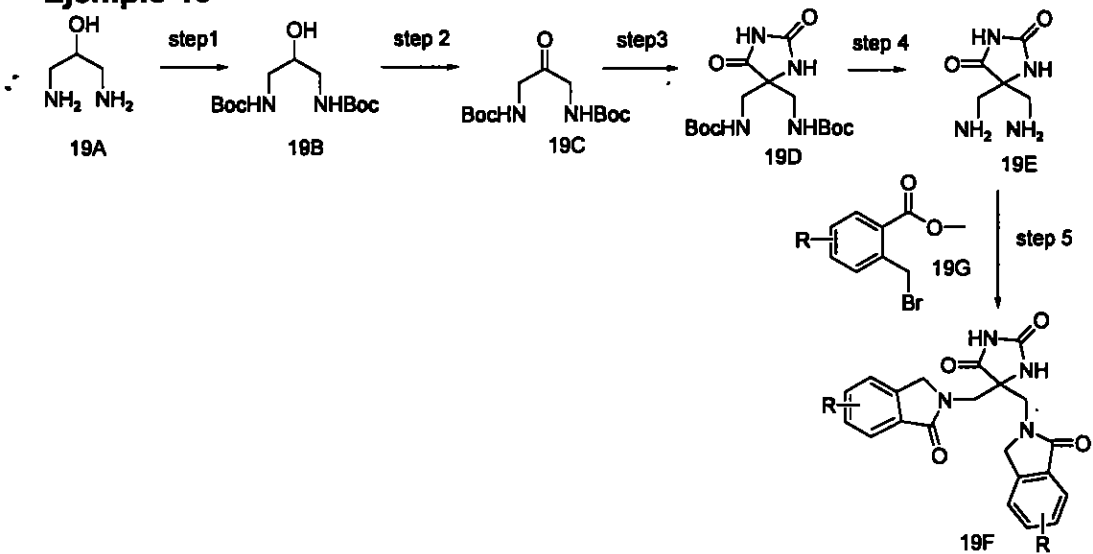
El compuesto **18C** (preparado en la etapa 1) se disolvió en DMF (15 mL) y se enfrió a 0°C en un baño de agua-hielo. Se agregó el compuesto **18D** (571 mg, 3,2 mmol) en una porción. La solución se dejó entibiar a temperatura ambiente por más de 2 horas, y se agitó a temperatura ambiente durante 3 días. Se agregó una solución HCl 2N (20 mL) y la fase acuosa se extrajo con EtOAc (50 mL) tres veces. Las fases orgánicas se combinaron, se secaron sobre Na₂SO₄, y se concentraron hasta secarse. El producto se aisló mediante LC de fase inversa (CH₃CN/agua/0,1% HCO₂H: 5% hasta 90%) para proporcionar el compuesto **18E** (65 mg, 7,4% de la etapa 1) y el compuesto **18F** (16 mg, 1,8% de la etapa 1).

Los siguientes compuestos se prepararon según se describe en el **Ejemplo 18**

Tabla 8

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
31		275,09	276,0 [M+H] ⁺	B
32		275,09	276,0 [M+H] ⁺	C

Ejemplo 19



Procedimientos generales para el **Ejemplo 19**:

En la etapa 1, el compuesto **19A** se trató con dos equivalentes de Boc₂O en un solvente adecuado, tal como diclorometano, durante 30 minutos hasta 12 horas. El solvente se removió y el compuesto **19B** pudo utilizarse sin purificación ulterior o purificarse mediante cromatografía sobre gel de sílice.

En la etapa 2, el compuesto **19B** se trató con PCC y celite en un solvente adecuado tal como diclorometano, durante 2 horas hasta 12 horas. El compuesto **19C** se purificó mediante cromatografía sobre gel de sílice.

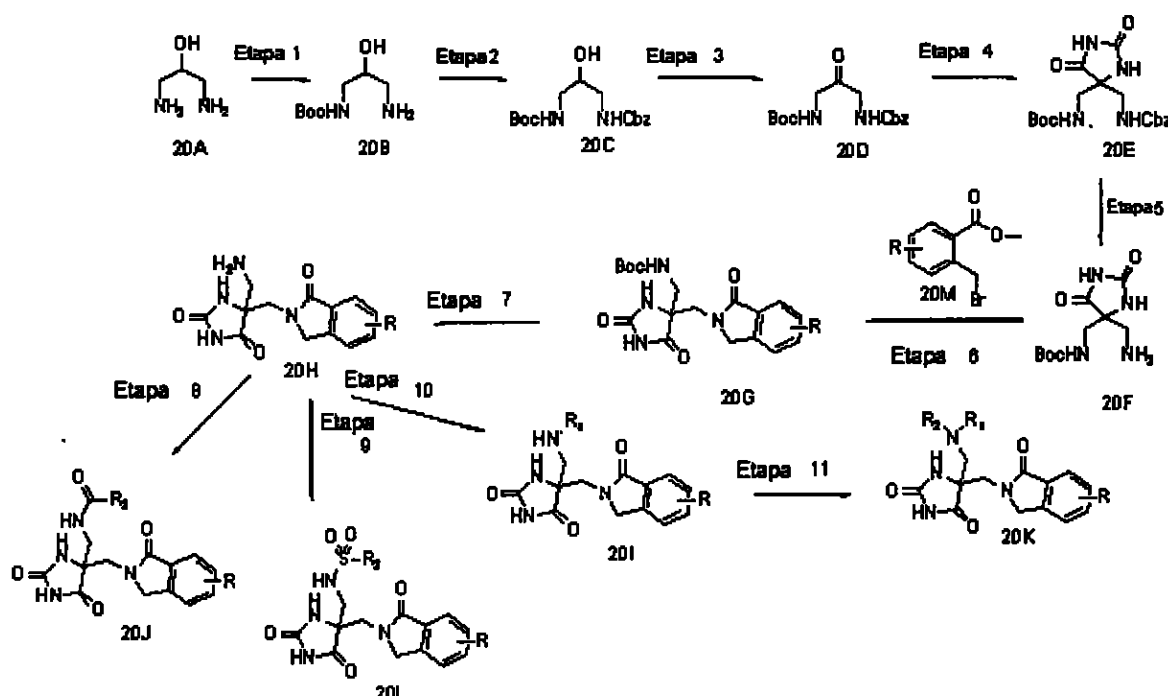
En la etapa 3, el compuesto **19C** se reaccionó con cianuro de potasio y carbonato de amonio en una solución apropiada de alcohol y agua, a 50°C hasta

90°C, durante 5 horas hasta 48 horas. Luego de enfriarse, se agregó agua y el compuesto **19D** pudo recolectarse mediante filtración.

En la etapa 4, el compuesto **19D** se agitó con 2 hasta 20 equivalentes de cloruro de hidrógeno en metanol durante 5 hasta 48 horas. El solvente se removió y el compuesto **19E** pudo utilizarse sin purificación ulterior.

En la etapa 5, el bromuro de bencilo (compuesto **19G**) se mezcló con metilamina de hidantoína **19E**, DIPEA, y DMF. La solución se agitó a temperatura ambiente durante 12 hasta 24 horas. El producto (**19F**) se removió mediante filtración o se purificó mediante cromatografía sobre gel de sílice.

Ejemplo 20.



Procedimientos generales para el Ejemplo 20:

En la etapa 1, el compuesto **20A** se trató con BOC-ON en un solvente adecuado tal como diclorometano, durante 2 horas hasta 12 horas. El compuesto **20B** se purificó mediante cromatografía sobre gel de sílice.

En la etapa 2, el compuesto **20B** se trató con CbzCl y una base tal como DIPEA, en un solvente adecuado, tal como diclorometano, durante 2 horas hasta 12 horas. El compuesto **20C** se purificó mediante cromatografía sobre gel de sílice.

En la etapa 3, el compuesto **20C** se trató con PCC y celite en un solvente adecuado tal como diclorometano, durante 2 horas hasta 12 horas. El compuesto **20D** se purificó mediante cromatografía sobre gel de sílice.

En la etapa 4, el compuesto **20D** se reaccionó con cianuro de potasio y carbonato de amonio en una solución apropiada de alcohol y agua, a 50°C hasta 90°C, durante 1 hora hasta 48 horas. Luego de enfriarse, se agregó agua y el compuesto **20E** podía recolectarse mediante filtración.

En la etapa 5, el compuesto **20E** se trató con Pd/C en un solvente adecuado tal como metanol, en un agitador Parr bajo una atmósfera de H₂. Luego de filtrar el catalizador y la concentración del solvente, el producto se utilizó sin purificación ulterior.

En la etapa 6, el bromuro de bencilo (compuesto **20M**) se mezcló con metilamina de hidantoína **20F**, DIPEA, y DMF. La solución se agitó a temperatura ambiente hasta 80°C durante 12 hasta 24 horas. El producto se removió mediante filtración o se purificó mediante cromatografía sobre gel de sílice.

En la etapa 7, el compuesto **20G** se agitó con 2 hasta 20 equivalentes de cloruro de hidrógeno en dioxano durante 1 hasta 12 horas. El solvente se removió y el compuesto **20H** se utilizó sin purificación ulterior.

En la etapa 8, el compuesto **20H** se acopló con el ácido carboxílico para proporcionar el compuesto **20J** que se purificó mediante cromatografía sobre gel de sílice.

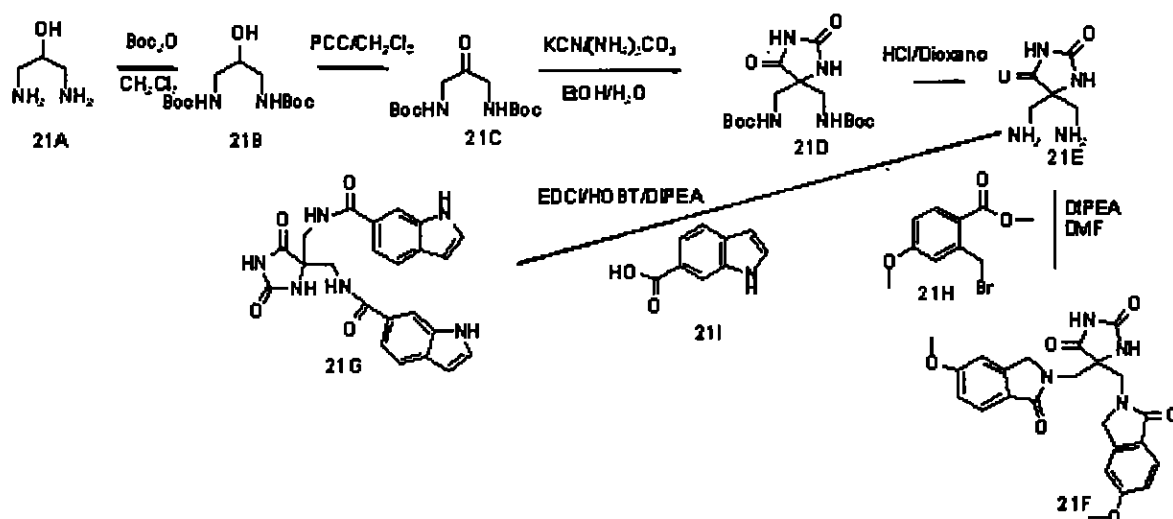
344 352

En la etapa 9, el compuesto **20H** se acopló con el compuesto de cloruro de sulfonilo para proporcionar el compuesto **20L** que se purificó mediante cromatografía sobre gel de sílice.

En la etapa 10, el compuesto **20H** se reaccionó con un compuesto de carbonilo bajo condición de aminación reductora para proporcionar el compuesto **20I**. Alternativamente, el compuesto **20H** se trató con un electrófilo adecuado y una base para proporcionar el producto **20I**, que se purificó mediante cromatografía sobre gel de sílice.

En la etapa 11, el compuesto **20I** se reaccionó con un compuesto de carbonilo bajo condición de aminación reductora para proporcionar el producto **20K**. Alternativamente, el compuesto **20I** se trató con un electrófilo adecuado y una base para proporcionar el producto **20K**, que se purificó mediante cromatografía sobre gel de sílice.

Ejemplo 21:



El compuesto **21B**: el compuesto **21A** (7 g, 77,7 mmol), y dicarbonato de di-ter-butilo (35,6 g, 163 mmol) se agitaron en cloruro de metileno (100 mL) a 25°C durante 2 horas. Se agregó NaCl (150 mL) acuoso saturado. La capa acuosa se extrajo con CH_2Cl_2 (100 mL) dos veces. La fase orgánica se lavó con

salmuera (100 mL), se secó sobre Na_2SO_4 . El solvente se removió mediante evaporador giratorio para proporcionar el compuesto **21B** (17g, 76%) que se utilizó sin purificación ulterior.

El compuesto **21C**: el compuesto **21B** (17 g, 58,6 mmol) se disolvió en cloruro de metileno (100 mL). Se agregaron PCC (25,2 g, 117 mmol) y celite (15 g) y la mezcla de reacción se agitó a 25°C durante toda la noche. El sólido se filtró y la solución resultante se concentró y se purificó vía cromatografía sobre gel de sílice (40% EtOAc/Hexanos) para proporcionar 3,62 g (22%) del compuesto **21C**.

El compuesto **21D**: el compuesto **21C** (3,62, 12,6 mmol), KCN (1,23g, 18,9 mmol), y $(\text{NH}_4)_2\text{CO}_3$ (3,62 g, 37,7 mmol) se suspendieron en una mezcla de EtOH (30 mL) y agua (30 mL). La solución se agitó a 80°C durante toda la noche. Luego de enfriarse, se agregó agua (35 mL). El sólido se filtró y se lavó con agua tres veces. El sólido se secó bajo vacío para proporcionar el compuesto **21D** (3 g, 67%).

El compuesto **21E**: el compuesto **21D** (3,0 g) se suspendió en metanol (50 mL) y se agregó HCl (4M en dioxano, 20 mL). La solución se agitó a 25°C durante 3 horas. Se agregó éter etílico (50 mL). El sólido se filtró, se lavó con éter etílico dos veces, y se secó bajo vacío el compuesto **21E** (1,34 g, 70%).

El compuesto **21F**: el compuesto **21E** (130 mg, 0,82 mmol), el compuesto **21H** (0,27 g, 1 mmol) y DIPEA (0,55 mL, 2 mmol) se mezclaron en DMF (5 mL). La solución se agitó a temperatura ambiente durante toda la noche. El solvente se removió y el material crudo se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3 \cdot \text{MeOH}/\text{CH}_2\text{Cl}_2$) para proporcionar 129 mg (35%) del compuesto **21E**.

Ejemplo 22:



El compuesto **22D**: el compuesto **22C** (2,78g, 8,57 mmol) se disolvió en cloruro de metileno (100 mL). Se agregaron PCC (4,62 g, 21,4 mmol) y celite (4,6 g) y la mezcla de reacción se agitó a 25°C durante toda la noche. Se agregaron otros 0,5 eq. de PCC (923 mg, 4,3 mmol) y se agitó durante 3 horas a

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temperatura ambiente. El sólido se filtró y la solución resultante se concentró y se purificó mediante cromatografía sobre gel de sílice (50% EtOAc/Hexanos) para proporcionar 1,86 g (73%) del compuesto **22D**.

El compuesto **22E**: el compuesto **22D** (1,86 g, 5,8 mmol), KCN (0,56 g, 8,65 mmol), y $(\text{NH}_4)_2\text{CO}_3$ (1,66 g, 17,3 mmol) se suspendieron en una mezcla de EtOH (20 mL) y agua (20 mL). La solución se agitó a 80°C durante toda la noche. Luego de enfriarse, se removió EtOH. El sólido se filtró y se lavó con agua tres veces. El sólido se secó bajo vacío para proporcionar el compuesto **22E** (1,45 g, 64%).

El compuesto **22F**: el compuesto **22E** (1,45 g, 3,68 mmol) se trató con Pd/C en metanol en un agitador Parr bajo una atmósfera de H_2 de 340 kPa (50 psi) durante 60 horas. Luego de filtrar el catalizador y la concentración del solvente, el compuesto **22E** (0,95 g, 99%) se utilizó sin purificación ulterior.

El compuesto **22G**: el compuesto **22F** (150 mg, 0,58 mmol), el compuesto **22M** (170 mg, 0,64 mmol) y DIPEA (0,22 mL, 1,28 mmol) se mezclaron en DMF (5 mL). La solución se agitó a 70°C durante toda la noche. El solvente se removió y el material se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 166 mg (71%) del compuesto **22G**.

El compuesto **22H**: el compuesto **22G** (166 mg) se suspendió en metanol (10 mL) y se agregó HCl (4M en dioxano, 4 mL). La solución se agitó a 25°C durante 2 horas. Se agregó éter etílico (50 mL). El solvente se removió y proporcionó el compuesto **22H** (0,14 g, 99%).

El compuesto **22I**: el compuesto **22H** (42 mg, 0,12 mmol) y el compuesto **22J** (26 mg, 0,16 mmol) se disolvieron en DMF (20 mL). Se agregaron EDCI (30 mg, 0,16 mmol), HOBT (21 mg, 0,16 mmol) y DIPEA (0,05 mL, 0,28 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 2 horas. El solvente se removió y el material crudo se concentró y se purificó mediante cromatografía

sobre gel sílice (10% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 7 mg (13%) del compuesto 22I.

El compuesto 22L: el compuesto 22H (25 mg, 0,073 mmol) y ciclopentanona (7,5 mg, 0,088 mmol) se agitaron en cloruro de metileno (5 mL). Se agregó tetraisopropóxido de titanio (0,043 mL, 0,15 mmol) seguido por el agregado de DIPEA (0,015 mL, 0,088 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. Luego, se agregó $\text{Na}(\text{OAc})_3\text{BH}$ (31 mg, 0,15 mmol) y la mezcla se agitó a temperatura ambiente durante toda la noche. Se agregó K_2CO_3 ac. (20 mL) saturado, y la mezcla se agitó a temperatura ambiente brevemente. El sólido se filtró a través de una almohadilla de celite. El filtrado se diluyó con cloruro de metileno (30 mL), y se extrajo con salmuera. La capa orgánica se secó y se concentró hasta sequedad. El material crudo se purificó mediante PTLC (10% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 7 mg (26%) del compuesto 22L.

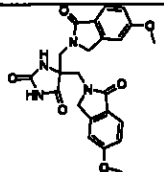
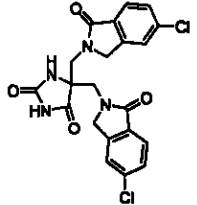
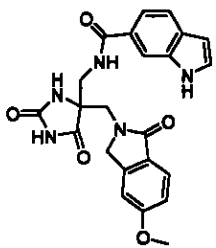
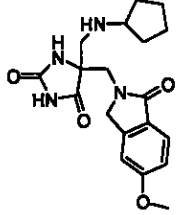
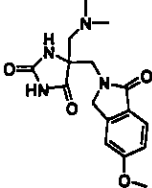
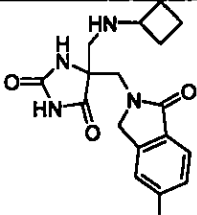
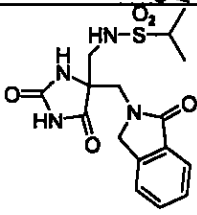
El compuesto 22K: el compuesto 22H (20 mg, 0,06 mmol) e isopropilsulfonilo (27 mg, 0,18 mmol) se disolvieron en cloruro de metileno (10 mL). Se agregó DIPEA (0,04 mL, 0,26 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante 48 horas. El solvente se removió y el material crudo se purificó mediante cromatografía – sobre gel de sílice (10% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 2 mg (8%) del compuesto 22K.

Los siguientes compuestos se prepararon según se describe en los Ejemplos 19-22.

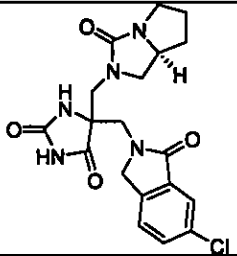
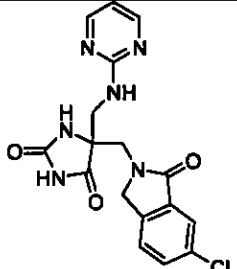
Tabla 9

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
33		450,15	451,1 [M+H] ⁺	B

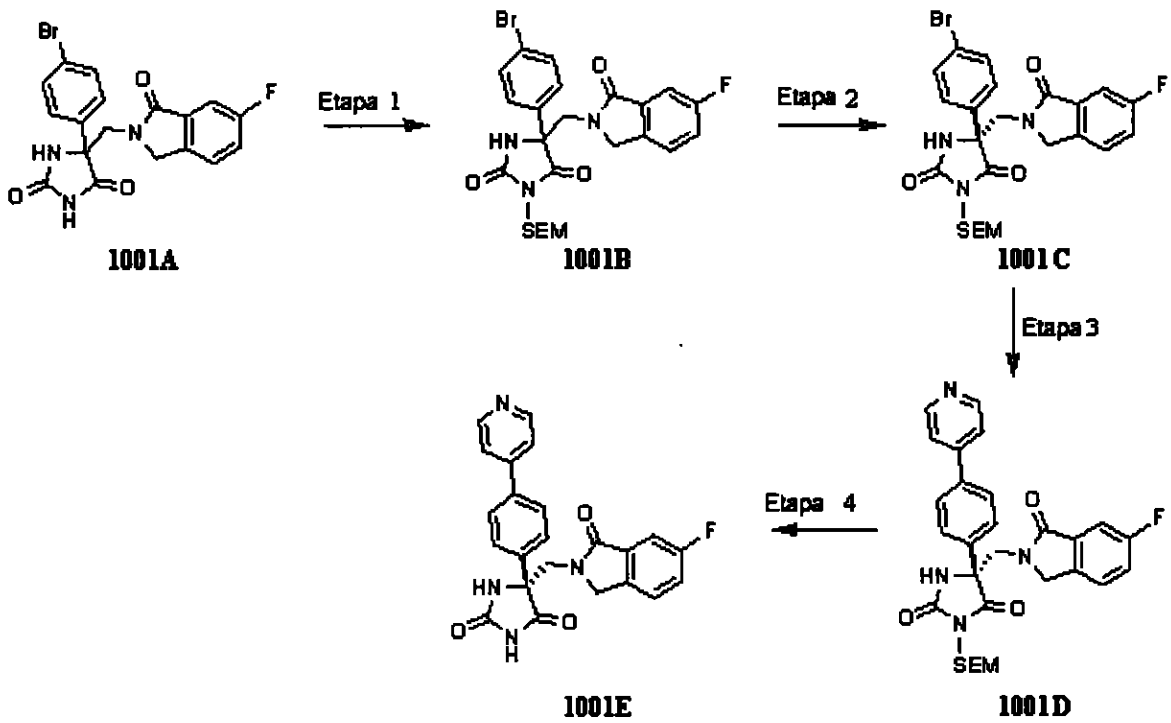
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51

				
34		458,05	459,3 [M+H] ⁺	B
35		447,15	448,2 [M+H] ⁺	A
36		372,18	373,2 [M+H] ⁺	B
37		332,15	333,1 [M+H] ⁺	C
38		358,16	359,2 [M+H] ⁺	B
39		380,12	381,2 [M+H] ⁺	C

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350

40		417,12	418,1 [M+H] ⁺	D
41		386,09	387,2 [M+H] ⁺	C

Ejemplo 1001:



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Etapa 1

A una solución del compuesto **1001A** (1,65 g, 3,95 mmol) en DMF anhidro (35 mL) se agregó cloruro de 2-(trimetilsilil)etoximetilo (SEMCl, 0,93 mL, 4,73 mmol) y DIPEA (0,9 mL, 5,14 mmol). La solución se agitó a 25°C durante toda la noche. DMF se removió bajo vacío. El producto **1001B** se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 2:1. Rendimiento: 1,6 g, 74%).

Etapa 2

El compuesto **1001B** se resolvió mediante columna Chiralcel OD (Fase móvil: Hexano/2-propanol 3:1). El primer pico se recolectó y se concentró para proporcionar el compuesto **1001C**.

Etapa 3

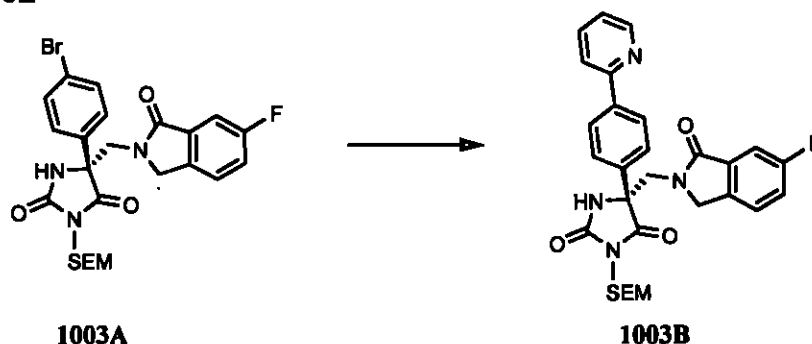
Se agregó a un frasco seco el compuesto **1001C** (1,5 g, 2,73 mmol) y ácido 4-piridilborónico (670 mg, 5,50 mmol). El frasco se sometió a vacío y se rellenoó con nitrógeno tres veces. Se agregó Pd(dppf)Cl₂ (220 mg, 0,30 mmol) seguido por el agregado de CH₃CN (20 mL) y K₂CO₃ acuoso (1 M, 15 mL). La solución se agitó a 80°C (baño de aceite) durante 16 horas. Luego de enfriarse, se agregó CH₃CN (100 mL) y el sólido se removió mediante filtración. La capa acuosa se separó y se extrajo con EtOAc (20 mL) una vez. La solución orgánica se combinó y se concentró. El producto se purificó mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₄OH: 20:1:0.1) para proporcionar el compuesto **1001D**.

Etapa 4

El compuesto **1001D** se disolvió en una mezcla de metanol y HCl (4M en dioxano) (2:1, 30 mL) y se agitó durante toda la noche en un frasco sellado a presión a 90°C (baño de aceite). Luego de enfriarse la solución, ésta se transfirió a un frasco de fondo redondo de 250 mL. Se concentró y se secó bajo vacío. La mezcla cruda se disolvió en metanol (50 mL) y se agregó Et₃N (0,5 mL) y se agitó

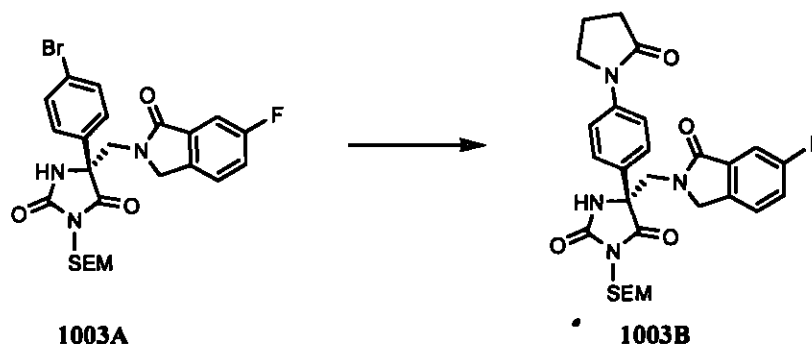
durante toda la noche a 25°C. El solvente luego se removió y el producto se purificó mediante cromatografía C18 de fase inversa (CH₃CN/agua 5% hasta 90%, con el agregado de 0,1% HCO₂H) para proporcionar el compuesto **1001E** (815g, 71% del compuesto **1001C**).

Ejemplo 1002



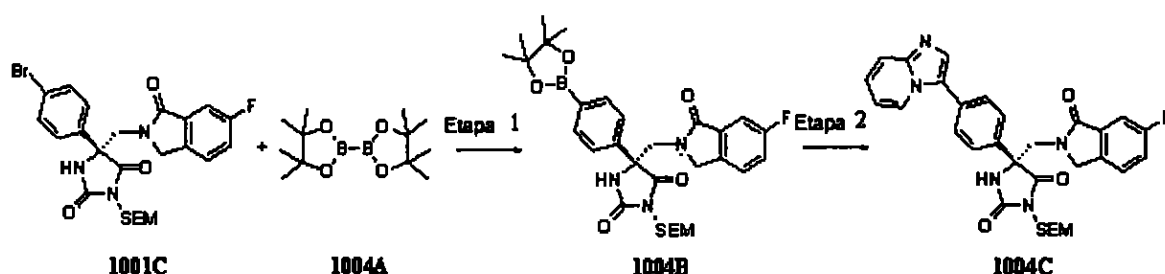
A un frasco secado con fuego se agregó el compuesto **1003A** (100 mg, 0,182 mmol), dicloruro de [1,4-bis(difenilfosfino)butano] paladio(II) [Pd(dppb)Cl₂, 12 mg, 0,02 mmol], y óxido de cobre (II) (15 mg, 0,18 mmol). El frasco se sometió a vacío y se rellenó con nitrógeno. Se agregaron 2-tri-n-butilestannilpiridina (0,076 mL, 0,237 mmol) y DMF (1 mL). La solución se agitó en un baño de aceite a 100°C durante 5 horas. Luego de enfriarse, el DMF se removió mediante evaporador giratorio. El producto se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc 2:1) para proporcionar **1003B** (84 mg, 84%).

Ejemplo 1003



A un tubo de presión seca se agregó el compuesto **1003A** (50 mg, 0,091 mmol), bis(dibencilidenacetona) paladio [$\text{Pd}(\text{dba})_2$, 1,6 mg, 0,0018 mmol], 9,9-dimetil-4,5-bis(difenilfosfino)xanteno (Xantphos, 3,0 mg, 0,0055 mmol), y Cs_2CO_3 (60 mg, 0,182 mmol). El tubo de presión se sometió a vacío y se rellenó con nitrógeno. Se agregaron pirrolidinona (14 mg, 0,16 mmol) y dioxano (0,5 mL). El tubo se selló y se agitó durante toda la noche a 100°C (baño de aceite). Luego de enfriarse, se agregó dioxano (2 mL) y el sólido se removió mediante filtración. La solución se concentró y se purificó mediante cromatografía sobre gel de sílice ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 40:1) para proporcionar el compuesto **1003B** (27 mg).

Ejemplo 1004:



Etapa 1

El compuesto **1001C** se preparó según se describe en el Ejemplo 1001.

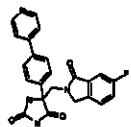
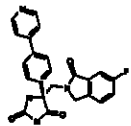
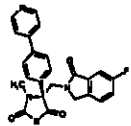
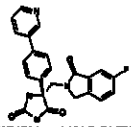
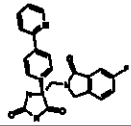
Una mezcla del compuesto **1001C** (0,3 g, 0,55 mmol), bis(pinacolato)diboro (**1004A**; 170 mg, 0,65 mmol), acetato de potasio (170 mg, 1,70 mmol), y $[\text{PdCl}_2(\text{dppf})]\text{CH}_2\text{Cl}_2$ (50 mg, 0,05 mmol) en 1,4-dioxano (10 mL) se sometió a vacío y rellenó con argón tres veces. La mezcla de reacción se agitó a 100°C (baño de aceite) durante 1,5 horas. Luego de enfriarse, la mezcla se diluyó en EtOAc (50 mL) y se filtró a través de una almohadilla de celite. El filtrado se concentró in vacuo y el material residual se purificó mediante cromatografía en columna sobre gel de sílice (2% MeOH en CH_2Cl_2) para otorgar el compuesto **1004B** (300 mg, 91% de rendimiento).

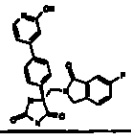
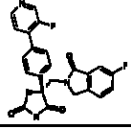
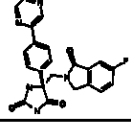
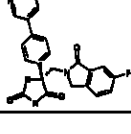
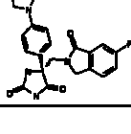
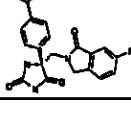
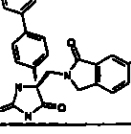
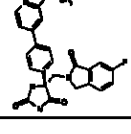
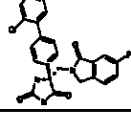
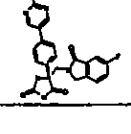
Etapa 2

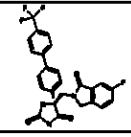
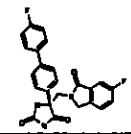
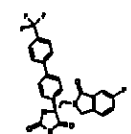
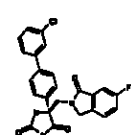
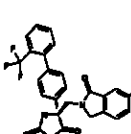
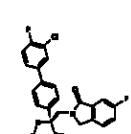
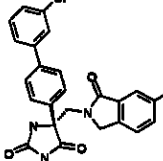
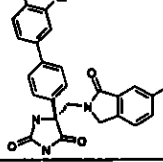
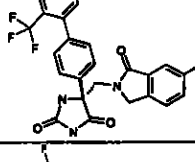
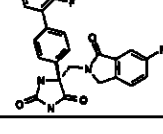
Una solución del compuesto **1004B** (60 mg, 0,10 mmol), 3-bromoimidazo[1,2-a]piridina (30 mg, 0,15 mmol), y [PdCl₂(dppf)]CH₂Cl₂ (8,2 mg, 0,01 mmol) en CH₃CN (3 mL) se trató con carbonato de potasio (0,6 mL, 0,6 mmol, 1M en H₂O). La mezcla se sometió a vacío y rellenó con argón tres veces. La mezcla de reacción se agitó a 90°C. (baño de aceite) durante 17 horas. Luego de enfriarse, la mezcla se diluyó en EtOAc (20 mL) y se filtró a través de una almohadilla de celite. El filtrado se concentró in vacuo y el material residual se purificó mediante TLC preparativa (10% MeOH en CH₂Cl₂) para proporcionar el compuesto **1004C** (42 mg, 71% de rendimiento).

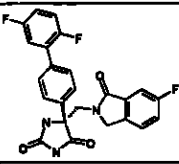
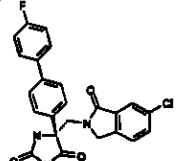
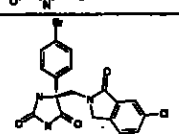
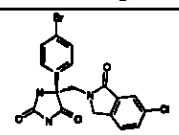
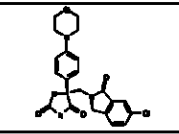
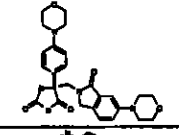
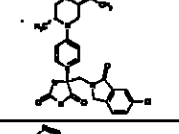
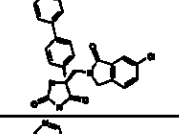
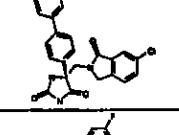
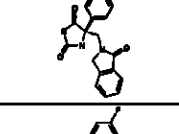
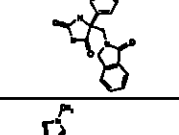
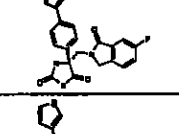
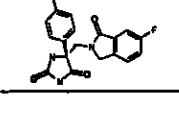
Los siguientes compuestos se prepararon según se describe en los **Ejemplos 1001, 1002, 1003, ó 1004.**

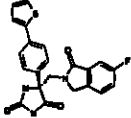
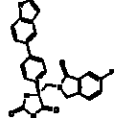
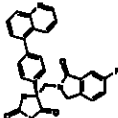
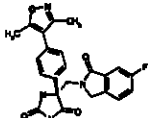
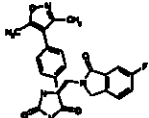
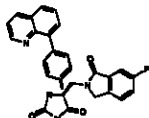
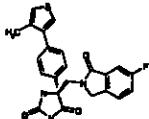
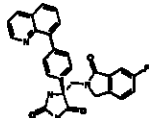
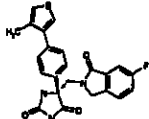
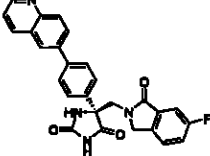
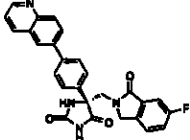
Tabla 1000

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
110		416,13	417,1 [M+H] ⁺	A
111		416,13	417,1 [M+H] ⁺	A
112		430,14	431,1 [M+H] ⁺	B
113		416,13	417,1 [M+H] ⁺	A
114		416,13	417,1 [M+H] ⁺	A

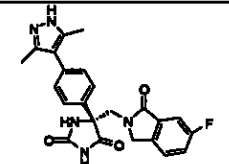
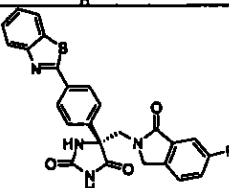
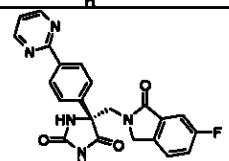
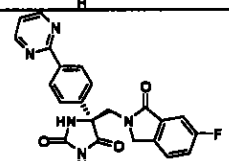
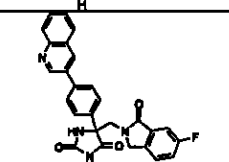
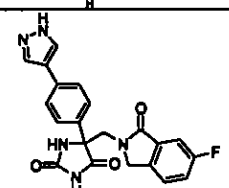
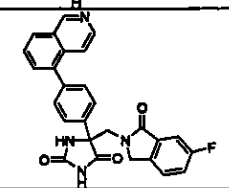
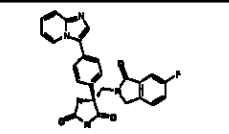
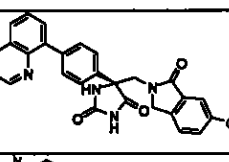
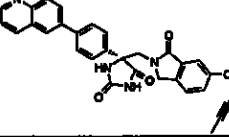
115		432,12	433,2 [M+H] ⁺	A
116		434,12	435,2 [M+H] ⁺	A
117		417,12	418,1 [M+H] ⁺	A
118		417,12	418,1 [M+H] ⁺	A
119		422,14	423,2 [M+H] ⁺	A
120		422,08	423,1 [M+H] ⁺	A
121		450,09	451,1 [M+H] ⁺	D
122		446,14	447,2 [M+H] ⁺	A
123		466,08	467,3 [M+H] ⁺	A
124		447,13	448,2 [M+H] ⁺	A
125		483,12	484,3 [M+H] ⁺	D

				
126		433,12	434,2 [M+H] ⁺	A
127		483,12	484,3 [M+H] ⁺	B
128		449,09	450,2 [M+H] ⁺	A
129		483,12	484,3 [M+H] ⁺	C
130		467,08	468,3 [M+H] ⁺	C
131		449,09	450,2 [M+H] ⁺	A
132		467,08	468,3 [M+H] ⁺	A
133		483,12	484,3 [M+H] ⁺	A
134		451,11	452,2 [M+H] ⁺	A

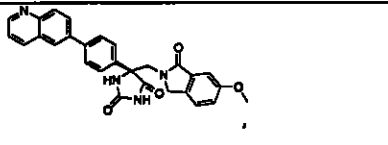
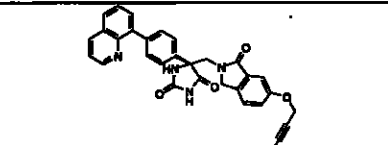
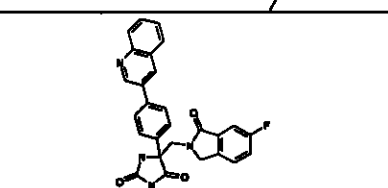
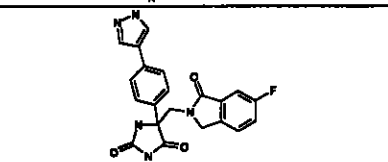
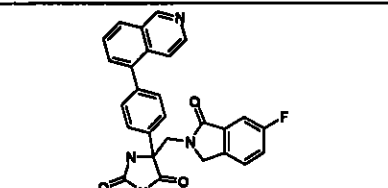
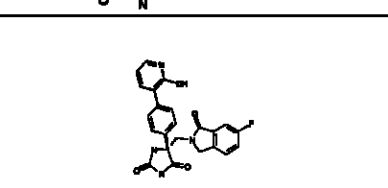
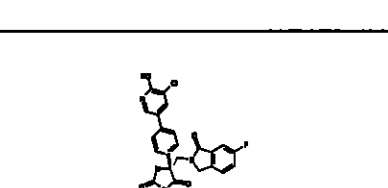
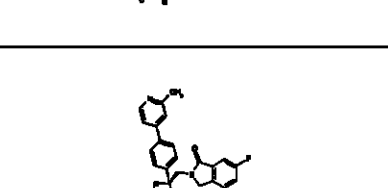
135		451,11	452,2 [M+H] ⁺	A
136		449,09	450,1 [M+H] ⁺	n/a
137		432,98	434,1 [M+H] ⁺	C
138		432,98	434,1 [M+H] ⁺	A
139		440,13	441,1 [M+H] ⁺	A
140		491,2	492,3 [M+H] ⁺	C
141		481,2	482,1 [M+H] ⁺	A
141		432,1	433,2 [M+H] ⁺	D
143		432,1	433,2 [M+H] ⁺	A
144		339,1	340 [M+H] ⁺	C
145		339,1	340 [M+H] ⁺	A
146		419,4	420,2 [M+H] ⁺	A
147		421,44	422,2 [M+H] ⁺	A

148		421,44	422,2 [M+H] ⁺	A
149		454,45	455,3 [M+H] ⁺	A
150		466,46	467,3 [M+H] ⁺	A
151		434,14	435,2[M+H] ⁺	A
152		434,14	435,1[M+H] ⁺	C
153		466,14	467,3[M+H] ⁺	C
154		435,11	436,2[M+H] ⁺	C
155		466,14	467,3[M+H] ⁺	A
156		435,11	436,1[M+H] ⁺	A
157		466,14	467,3[M+H] ⁺	C
158		466,14	467,3[M+H] ⁺	A

359 367

159		433,16	434,2[M+H] ⁺	A
160		472,10	473,3[M+H] ⁺	A
161		417,12	418,2[M+H] ⁺	A
162		417,12	440,2[M+Na] ⁺	C
163		466,14	467,3[M+H] ⁺	B
164		405,12	406,2[M+H] ⁺	A
165		466,14	467,3[M+H] ⁺	A
166		455,44	456,3 [M+H] ⁺	n/a
167		464,15	465,3 [M+H] ⁺	A
168		516,18	517,1 [M+H] ⁺	C

360 360

169		478,16	479,3 [M+H] ⁺	A
170		516,18	517,3 [M+H] ⁺	n/a
171		466,46	467,3 [M+H] ⁺	B
172		405,38	406,2 [M+H] ⁺	A
173		466,46	467,3 [M+H] ⁺	A
174		432,12	433,1 [M+H] ⁺	A
175		466,08	467,1 [M+H] ⁺	A
176		430,14	431,2 [M+H] ⁺	D

Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1000.

Compuesto 111. ¹H-RMN (500 MHz, DMSO-d₆) δ 9,0 (s, 1H), 8,7 9(d, J = 6,0 Hz, 2H), 7,92 (d, J = 8,7 Hz, 2H), 7,79 (d, J = 8,7 Hz, 2H), 7,76 (d, J = 6,0 Hz, 2H),

361 268

7,65 (m, 1H), 7,48 (m, 2H), 4,40 (d, J = 17,3 Hz, 1H), 4,31 (d, J = 17,3 Hz, 1H), 4,27 (d, J = 14,2 Hz, 1H), 4,14 (d, J = 14,2 Hz, 1H).

Compuesto 120. ^1H -RMN (500 MHz, DMSO- d_6) δ 8,99 (s, 1H), 8,03 (d, J = 8,8 Hz, 2H), 7,96 (d, J = 3,3 Hz, 1H), 7,84 (d, J = 3,3 Hz, 1H), 7,77 (d, J = 8,8 Hz, 2H), 7,65 (s, 1H), 7,47 (m, 2H), 4,38 (d, J = 17,6 Hz, 1H), 4,28 (d, J = 17,6 Hz, 1H), 4,27 (d, J = 14,3 Hz, 1H), 4,13 (d, J = 14,3 Hz, 1H).

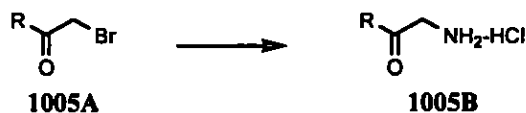
Compuesto 123. ^1H -RMN (500 MHz, DMSO- d_6) δ 8,99 (s, 1H), 7,84 (s, 1H), 7,74 (d, J = 8,4 Hz, 2H), 7,66 (dd, J = 8,5, 4,6 Hz, 1H), 7,54 (d, J = 8,4 Hz, 2H), 7,49 (m, 2H), 6,65 (s, 1H), 4,40 (d, J = 17,5 Hz, 1H), 4,31 (d, J = 17,5 Hz, 1H), 4,29 (d, J = 14,2 Hz, 1H), 4,10 (d, J = 14,2 Hz, 1H).

Compuesto 139. ^1H NMR (500 MHz, CD_3OD) δ 3,17-3,21 (m, 4H), 3,83-3,88 (m, 4H), 4,14-4,52 (m, 4H), 7,01 (d, J = 8,8 Hz, 2H), 7,47 (d, J = 8 Hz, 1H), 7,46-7,48 (m, 3H), 7,75 (s, 1H).

Compuesto 143. ^1H NMR (400 MHz, CDCl_3) δ 4,21-4,50 (m, 4H), 7,498 (d, J = 0,8 Hz, 1H), 7,52 (d, J = 0,4 Hz, 1H), 7,73-7,76 (m, 3H), 7,76-7,87 (m, 4H), 8,60 (d, J = 6 Hz, 2H).

Compuesto 155. ^1H NMR (500 MHz, CD_3OD) δ 8,84 (dd, J = 1,89, 4,1 Hz, 1H); 8,43 (dd, J = 1,58, 8,2 Hz, 1H); 7,99 (dd, J = 1,58, 8,2 Hz, 1H); 7,85 (m, 3H); 7,8 (dd, J = 1,26 Hz, 6,94 Hz, 1H); 7,75 (m, 3H), 7,70 (dd, J = 7,25 Hz, 0,95 Hz, 1H); 7,59 (dd, J = 4,73 Hz, 7,57 Hz, 1H); 7,58 (dd, J = 4,4 Hz, 8,2 Hz, 1H); 7,51 (dd, J = 2,5 Hz, 7,8 Hz, 1H); 7,40 (m, 1H); 4,54 (d, J = 17,0 Hz, 1H); 4,48 (d, J = 17,0 Hz, 1H); 4,48 (d, J = 14,5 Hz, 1H); 4,32 (1H, d, J = 14,5 Hz, 1H).

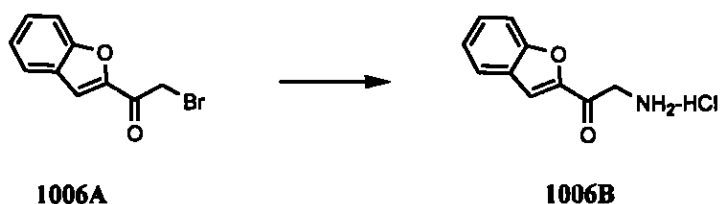
Ejemplo 1005:



Procedimiento general para el ejemplo 1005

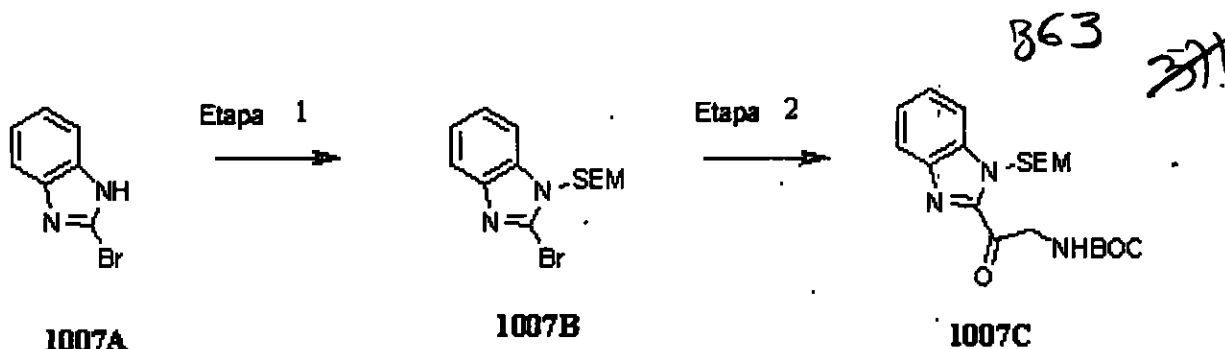
El Compuesto **1005A** se trató con un equivalente de hexameten tetraamina en cloroformo u otro solvente adecuado durante aproximadamente 5 horas. El producto se recogió mediante filtración y luego se trató con HCl en etanol durante un día a tres días. Luego, el sólido se recogió mediante filtración para dar el compuesto **1005B**.

Ejemplo 1006



1-Benzofuran-2-il-2-bromo-etanona (**1006A**, 3,0g, 12,55 mmol), hexametilentetraamina (1,94 g, 13,80 mmol), y NaI (350 mg) se agitaron en CHCl_3 (40 mL) durante cinco horas. El sólido se recogió mediante filtración y se secó bajo vacío. Luego el sólido se suspendió en etanol (30 mL) y se agregó HCl (conc., 36% en agua, 10 mL). La solución se agitó a 25°C durante 4 d. El sólido se recogió mediante filtración y se lavó con etanol, se secó bajo vacío para dar el compuesto **1006B** (3,05 g, contenía NH_4Cl).

Ejemplo 1007



Etapa 1

A un frasco secado a la llama se agregó 2-bromo-1H-benzimidazol (**1007A**, 2,94 g, 14,92 mmol), THF anhidro (75 mL), y NaH (95%, 490 mg, 19,4 mmol). La solución se agitó a 25°C durante 45 minutos; Se agregó SEMCl (3,17 mL, 17,9 mmol). La solución se agitó a 25°C durante 2,5 horas. Se agregaron agua (50 mL) y EtOAc (100 mL). La capa acuosa se separó y se extrajo con EtOAc (100 mL) una vez. Las capas orgánicas se combinaron y se concentraron bajo vacío. el producto se purificó mediante SGC (Hexano/EtOAc: 3:1) para dar el compuesto **1007B** (3,6 g, 74%).

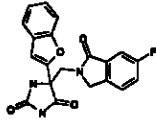
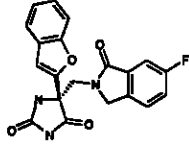
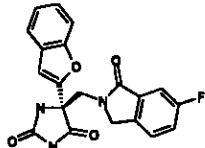
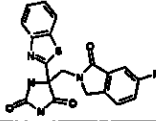
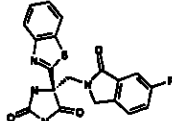
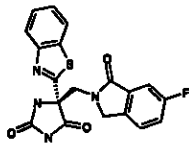
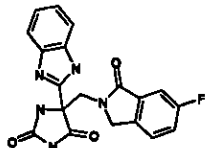
Etapa 2

A un frasco secado a la llama se agregó el compuesto **1007B** (1,427 g, 4,35 mmol) y éter etílico anhidro /THF (2:1, 15 mL). La solución se enfrió hasta -78°C. Se agregó n-butilitio (1,6 M, 0,46 mL, 0,73 mmol) y se agitó a -78 °C durante 30 minutos. En otro frasco con forma de pera secado a la llama se agregó N-(ter-butoxicarbonil)glicina-N'-metoxi-N'-metilamida (949 mg, 4,35 mmol) y THF anhidro (2 mL). Se agregó a 0°C cloruro de Isopropilmagnesio (2 M, 2,5 mL, 5,0 mmol). La solución se agitó a 0°C durante 5 minutos y se agregó en la solución de compuesto **1003C** por medio de cánula a -78 °C. Luego, la solución se calentó gradualmente hasta -20°C y se agitó entre -20°C y 10°C durante 4 horas. Se agregó solución de NH₄Cl saturada y la solución acuosa se extrajo con EtOAc (50 mL) tres veces. Las fases orgánicas se combinaron y se concentraron. El producto se purificó mediante SGC (cromatografía sobre gel de sílice) (Hexano/EtOAc: 3:1) para dar el compuesto **1007C** (1,0 g, 57%).

364 372

Los siguientes compuestos se prepararon según lo descrito en el **Ejemplo 1, 14, 1005, 1006, y/o 1007.**

Tabla 1001

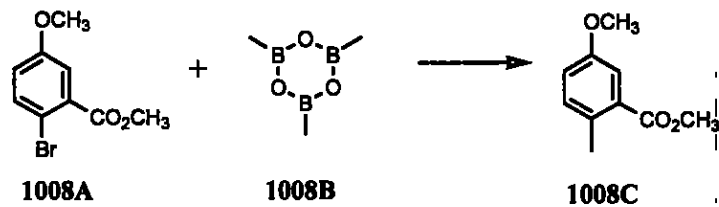
Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
177		379,10	380,1 [M+H] ⁺	A
178		379,10	380,1 [M+H] ⁺	A
179		379,10	380,1 [M+H] ⁺	D
180		396,07	397,1 [M+H] ⁺	B
181		396,07	397,1 [M+H] ⁺	A
182		396,07	397,1 [M+H] ⁺	B
183		379,11	380,1 [M+H] ⁺	A

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Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1003.

Compuesto 181. ¹H-RMN (500 MHz, DMSO-d₆) δ 11,3 (s, 1H), 9,34 (s, 1H), 8,18 (d, J = 8,5 Hz, 1H), 8,12 (d, J = 7,6 Hz, 1H), 7,67 (m, 1H), 7,61 (m, 1H), 7,50 (m, 3H), 4,65 (d, J = 14,3 Hz, 1H), 4,44 (d, J = 17,3 Hz, 1H), 4,38 (d, J = 17,3 Hz, 1H), 4,34 (d, J = 14,3 Hz, 1H).

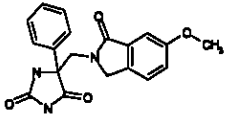
Ejemplo 1008

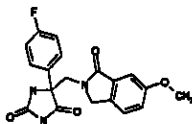
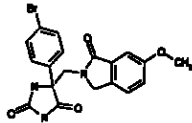


El compuesto **1008A** (20 g, 81,61 mmol), **1008B** (13,36 mL, 97,93 mmol), Pd(dppf)Cl₂ (1,0g, 1,36 mmol), dioxano (350 mL), agua (50 mL), y Cs₂CO₃ (22,5g, 163 mmol) se agitaron a 110 °C (baño de aceite) bajo nitrógeno durante 16 horas. Después del enfriamiento, el sólido se retiró mediante filtración. La solución se concentró y se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc, 10:1) para dar **1008C** (12,1g, 80%).

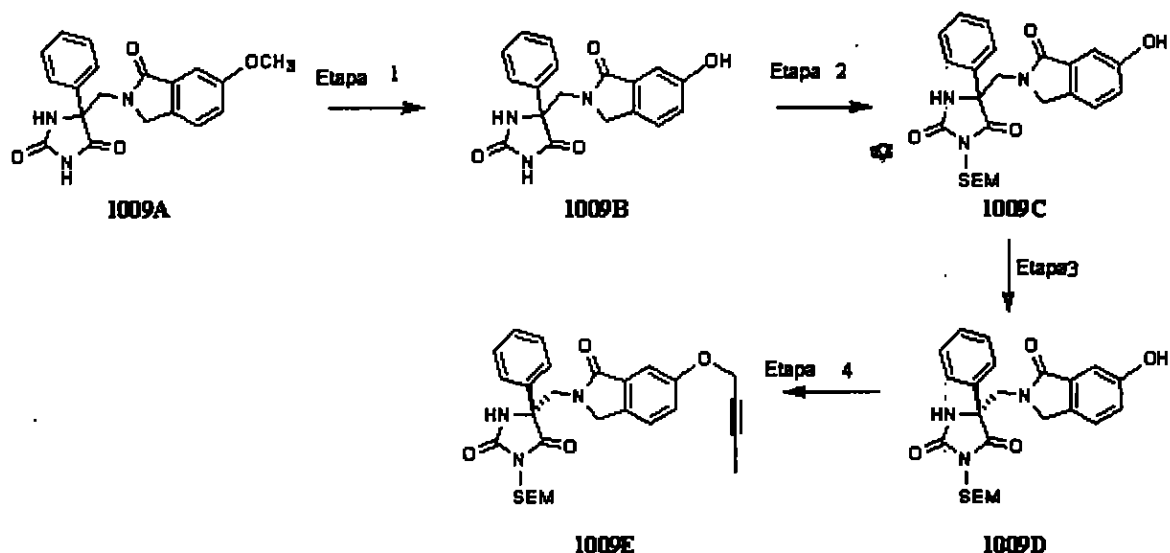
Los siguientes compuestos se prepararon según lo descrito en los **Ejemplos 14 y 1008.**

Tabla 1002

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
184		351,12	352,1 [M+H] ⁺	A

185		369,11	370,1 [M+H] ⁺	A
186		429,03	430,2 [M+H] ⁺ 432,2 [M+Na] ⁺	A

Ejemplo 1009



Etapa 1

El Compuesto **1009A** (1,18g, 3,36mmol) y clorhidrato de piridina (2,33g, 20,17 mmol) se agregaron en un tubo de reactor de microondas de 20 mL y se reaccionó a 200°C durante 1 hora. Después de enfriamiento, el sólido se disolvió en DMF y se purificó mediante cromatografía C18 (CH₃CN/agua 5% hasta 90%, con 0,1% HCO₂H) para dar el compuesto **1009B** (0,87 g, 77%).

Etapa 2

El Compuesto **1009B** (0,75 g, 2,22 mmol) se disolvió en DMF (12 mL). Se agregaron SEMCl (0,48 mL, 2,44 mmol) y DIPEA (0,775 mL, 4,44 mmol) y la solución se agitó a 25°C durante 4 horas. Se eliminó la DMF bajo vacío y el

producto se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc: 3:1 hasta 1:1) para dar el compuesto **1009C** (0,81 g, 78%).

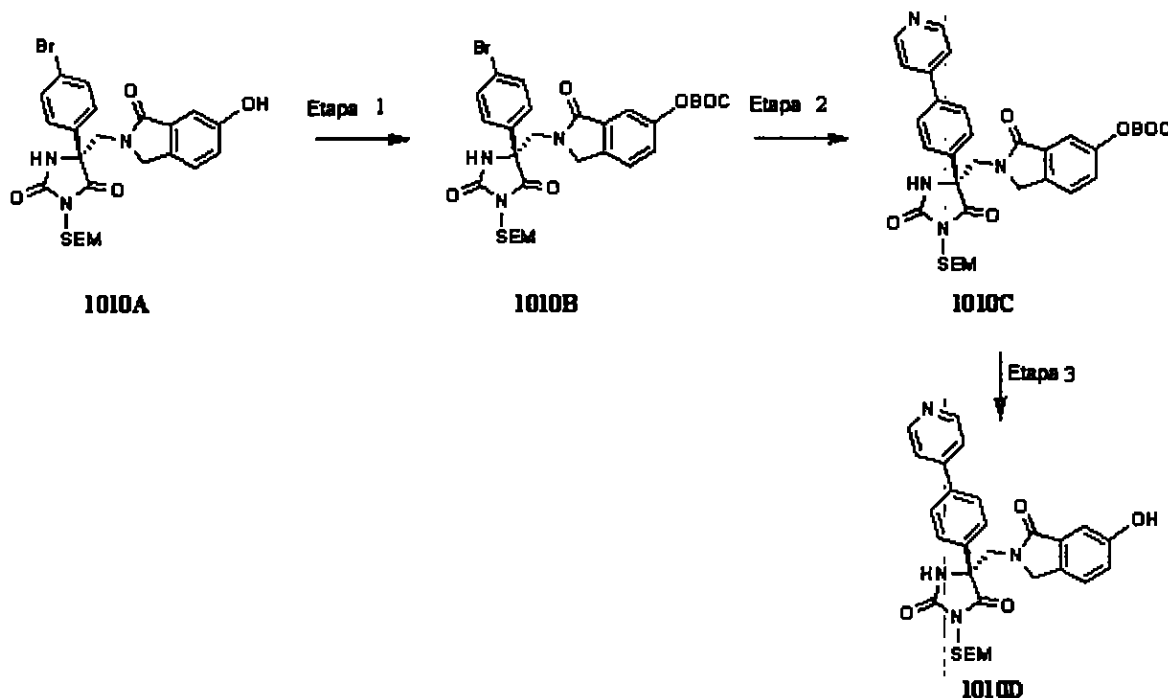
Etapa 3

Se resolvió el Compuesto **1009C** en una columna Chiralcel OD utilizando Hexano y 2-propanol como fase móvil. El primer pico se recogió y se concentró para dar el compuesto **1009D**.

Etapa 4

El Compuesto **1009D** (100mg, 0,214 mmol), 1-bromo-2-butino (34 mg, 0,257 mmol), y Cs_2CO_3 (140 mg, 0,428 mmol) se agitaron en DMF (2 mL) a 0°C durante 2 horas, luego a 25°C durante toda la noche. Se agregó agua (5 mL) y la solución acuosa se extrajo con EtOAc (10 mL) tres veces. Las fases orgánicas se combinaron y se concentraron. El producto se purificó mediante cromatografía sobre gel de sílice (Hexano/EtOAc: 3:1) para dar el compuesto **1009E** (81 mg).

Ejemplo 1010



Etapa 1

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El Compuesto **1010A** (1,03g, 1,88 mmol), (BOC)₂O (493 mg, 2,26 mmol), y Cs₂CO₃ (741 mg, 2,26 mmol) se agitaron durante la noche en CHCl₃ (20 mL). Se agregó agua. La capa acuosa se extrajo con EtOAc (3×50 mL). Las capas orgánicas combinadas se concentraron y se purificaron mediante cromatografía sobre gel de sílice (Hexano/EtOAc 5% hasta 90%) para dar el compuesto **1010B** (1,01 g, 83%).

Etapa 2

A un frasco seco se agregó el compuesto **1010B** (500 mg, 0,77 mmol) y ácido 4-piridilborónico (190 mg, 1,55 mmol). El frasco se sometió a vacío y se recargó con nitrógeno tres veces. Se agregó Pd(dppf)Cl₂ (28 mg, 0,04 mmol) y seguido mediante adición de CH₃CN (5 mL) y K₂CO₃ (1M, 4 mL). La solución se agitó a 80 °C (baño de aceite) durante 16 horas. Después de enfriamiento, se agregó CH₃CN (100 mL) y el sólido se eliminó por filtración. La capa acuosa se separó y se extrajo una vez con EtOAc (20 mL). La solución orgánica se combinó y se concentró. El producto se purificó mediante cromatografía sobre gel de sílice (CH₂Cl₂/MeOH/NH₄OH: 20:1:0,1) para dar el compuesto **1010C**.

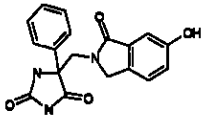
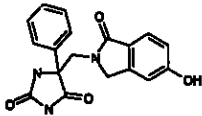
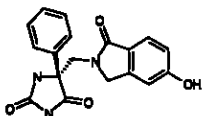
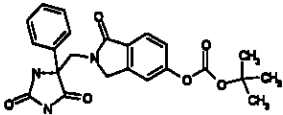
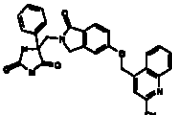
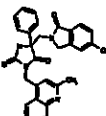
Etapa 3

El Compuesto **1010C** obtenido en la etapa 2 se disolvió en MeOH (10 mL) y se agregó HCl (4M en dioxano, 3 mL) y se agitó durante la noche a 25°C. Luego se eliminó MeOH y el producto se secó bajo vacío para dar el compuesto **1010D** (315 mg, 75% del compuesto **1010B**).

Los siguientes compuestos se prepararon según lo descrito en los **Ejemplos 14 y 1009 o 1010.**

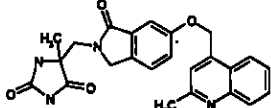
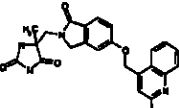
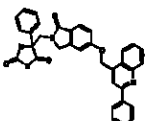
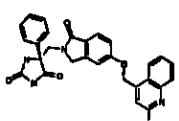
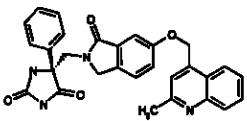
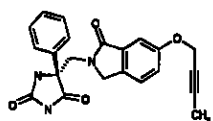
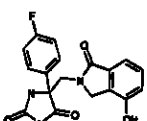
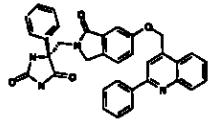
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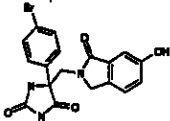
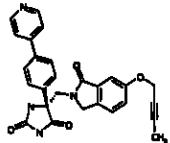
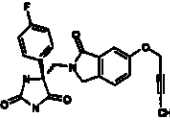
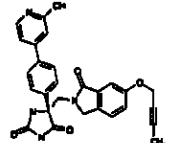
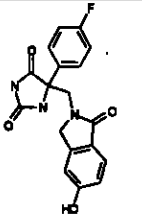
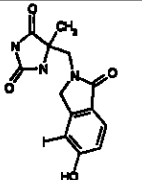
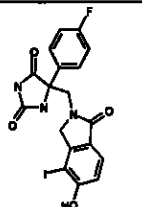
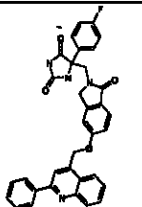
Tabla 1003

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
187		337,11	338,1 [M+H] ⁺	B
188		337,11	338,1 [M+H] ⁺ 360,1 [M+Na] ⁺	A
189		337,11	338,2 [M+H] ⁺ 360,2 [M+Na] ⁺	A
190		437,16	438,2 [M+H] ⁺	A
191		492,18	493,3 [M+H] ⁺	A
192		492,18	493,3 [M+H] ⁺	C

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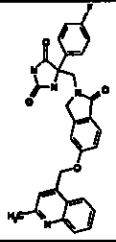
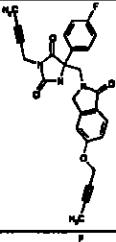
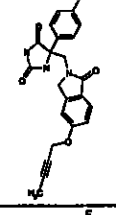
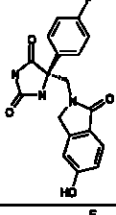
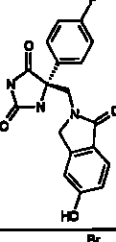
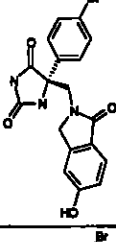
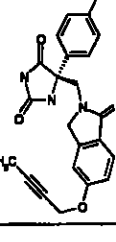
378

193		430,16	431,1 [M+H] ⁺	A
194		430,16	431,1 [M+H] ⁺	A
195		554,20	555,1 [M+H] ⁺	B
196		492,16	493,1 [M+H] ⁺	A
197		492,16	493,1 [M+H] ⁺	A
198		389,14	390,1 [M+H] ⁺	A
199		355,10	356,1 [M+H] ⁺	C
200		554,20	555,1 [M+H] ⁺	B

201		415,02	416,2 [M+H] ⁺	B
202		466,16	467,1 [M+H] ⁺	A
203		407,13	408,2 [M+H] ⁺	A
204		482,16	483,3 [M+H] ⁺	A
205		355,1	356 [M+H] ⁺	A
206		400,99	402 [M+H] ⁺	C
207		480,99	482 [M+H] ⁺	D
208		572,19	573 [M+H] ⁺	B

372

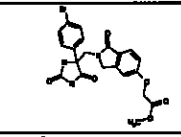
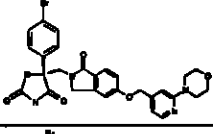
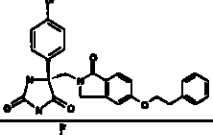
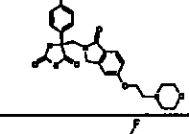
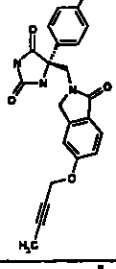
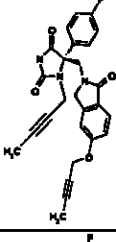
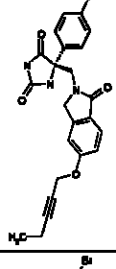
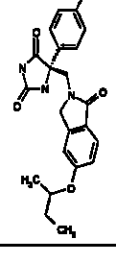
380

209		510,17	511 [M+H] ⁺	A
210		459,16	460 [M+H] ⁺	D
211		407,13	408 [M+H] ⁺	A
212		355,1	356 [M+H] ⁺	C
213		355,1	356 [M+H] ⁺	A
214		415,02	416,418 [M+H] ⁺	A
215		467,05	468,470 [M+H] ⁺	A

216		518,2	519 [M+H] ⁺	C
217		480,1	481 [M+H] ⁺	A
218		452,1	453 [M+H] ⁺	B
219		409,14	410 [M+H] ⁺	A
220		411,16	412 [M+H] ⁺	A
221		531,19	532 [M+H] ⁺	B
222		485,1	486,488 [M+H] ⁺	A
223		446,14	447 [M+H] ⁺	A
224		465,21	466 [M+H] ⁺	C
225		558,09	559,561 [M+H] ⁺	A

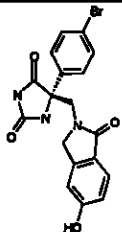
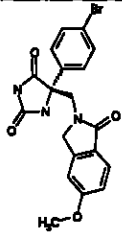
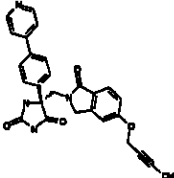
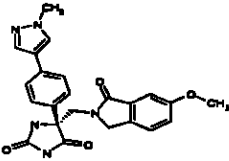
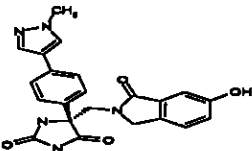
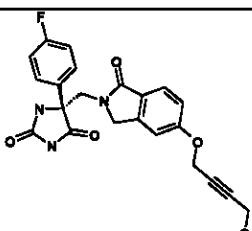
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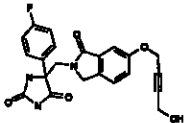
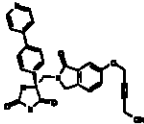
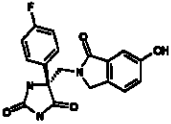
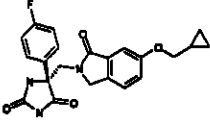
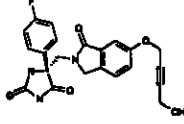
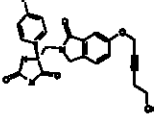
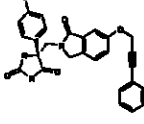
382

226		487,04	488,490 [M+H] ⁺	A
227		591,11	592,1 [M+H] ⁺	B
228		519,1	520,1 [M+H] ⁺	C
229		528,1	529,4 [M+H] ⁺	B
230		407,13	408 [M+H] ⁺	A
231		459,16	460 [M+H] ⁺	C
232		421,14	422 [M+H] ⁺	A
233		471,08	472,474 [M+H] ⁺	C

375

383

234		415,02	416,418 [M+H] ⁺	A
235		429,03	430,432 [M+H] ⁺	A
236		466,16	467 [M+H] ⁺	A
237		431,44	432,2 [M+H] ⁺	A
238		417,41	418,2 [M+H] ⁺	n/a
239		423,12	424,2 [M+H] ⁺	A

240		423,12	424,2 [M+H] ⁺	A
241		482,16	483,3 [M+H] ⁺	A
242		355,10	356,2 [M+H] ⁺	A
243		409,14	410,2 [M+H] ⁺	A
244		423,12	424,1 [M+H] ⁺	n/a
245		435,16	436,2 [M+H] ⁺	n/a
246		469,14	470,3 [M+H] ⁺	n/a

Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1003.

Compuesto 198. ^1H -RMN (400 MHz, DMSO- d_6) δ 9,22 (s, 1H), 7,64 (m, 2H), 7,43 (m, 4H), 7,22 (t, $J = 2,2$ Hz, 1H), 7,16 (dd, $J = 9,6, 1,2$ Hz, 1H), 4,82 (d, $J = 2,0$ Hz, 2H), 4,16 (m, 4H), 3,33 (s, 3H).

Compuesto 203. ^1H -RMN (400 MHz, DMSO- d_6) δ 7,63 (dd, $J = 8,8, 5,6$ Hz, 2H), 7,43 (d, $J = 8,4$ Hz, 1H), 7,13 (m, 4H), 4,80 (d, $J = 0,8$ Hz, 1H), 4,39 (d, $J = 17,6$ Hz, 1H), 4,17 (d, $J = 17,6$ Hz, 1H), 4,13 (d, $J = 13,6$ Hz, 1H), 3,71 (d, $J = 13,6$ Hz, 1H) 3,34 (s, 3H).

Compuesto 213. ^1H RMN (500 Hz, CD_3OD) δ 4,11 (d, $J = 15$ Hz, 1H), 4,27 (d, $J = 15$ Hz, 1H), 4,29 (d, $J = 17$ Hz, 1H), 4,38 (d, $J = 17$ Hz, 1H), 6,84-6,89 (m, 2H), 7,16-7,21 (m, 2H), 7,56-7,60 (m, 1H), 7,71-7,76 (m, 2H)

Compuesto 219. ^1H RMN (500 Hz, CD_3OD) δ 0,36-0,40 (m, 2H), 0,61-0,68 (m, 2H), 1,25-1,35 (m, 1H), 3,91 (d, $J = 7$ Hz, 2H), 4,14 (d, $J = 15$ Hz, 1H), 4,30 (d, $J = 15$ Hz, 1H), 4,34 (d, $J = 17$ Hz, 1H), 4,43 (d, $J = 17$ Hz, 1H), 7,01-7,05 (m, 2H), 7,17-7,23 (m, 2H), 7,65-7,69 (m, 1H), 7,72-7,77 (m, 2H)

Compuesto 232 ^1H RMN (500 Hz, CD_3OD) δ 1,13 (t, $J = 8$ Hz, 3H), 2,21-2,27 (m, 2H), 4,15 (d, $J = 14$ Hz, 1H), 4,31 (d, $J = 14$ Hz, 1H), 4,36 (d, $J = 17$ Hz, 1H), 4,45 (d, $J = 17$ Hz, 1H), 4,79 (t, $J = 2$ Hz, 2H), 7,04-7,14 (m, 2H), 7,16-7,25 (m, 2H), 7,64-7,79 (m, 3H).

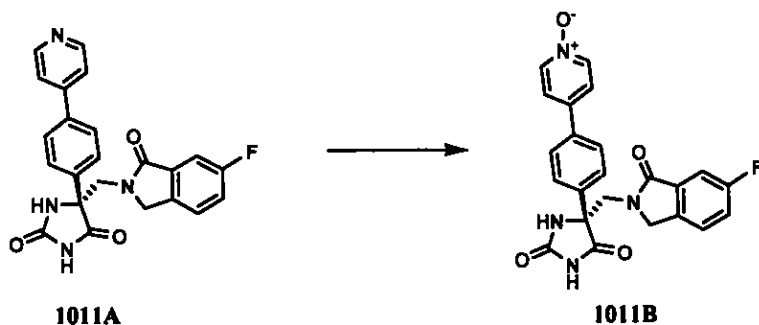
Compuesto 233. ^1H RMN (500 Hz, CD_3OD) δ 7,678 (d, $J = 8,5$ Hz, 1H); 7,455 (d, $J = 4,1$ Hz, 1H), 7,817 (d, $J = 4,1$ Hz, 1H); 7,099 (s, 1H); 7,052 (dd, $J = 2,207, 6,305$ Hz, 1H); 4,515 (d, $J = 17,3$ Hz, 1H), 4,450 (d, $J = 17,3$ Hz, 1H); 4,065 (d, $J = 14,5$ Hz, 1H); 3,89 (s, 3H); 3,87 (d, $J = 14,5$ Hz, 1H); 3,85 (m, 1H); 2,46 (m, 2H); 2,09 (m, 1H) 1,89 (m, 1H); 1,76 (m, 1H); 1,67 (m, 1H); 1,54 (m, 1H); 1,32 (m, 1H).

Compuesto 239. ^1H RMN (500 Hz, DMSO- d_6) δ 4,11 (d, $J = 15$ Hz, 1H), 4,27 (d, $J = 15$ Hz, 1H), 4,29 (d, $J = 17$ Hz, 1H), 4,38 (d, $J = 17$ Hz, 1H), 6,84-6,89 (m, 2H), 7,16-7,21 (m, 2H), 7,56-7,60 (m, 1H), 7,71-7,76 (m, 2H)

378 386

Compuesto 243. ^1H -RMN (500 MHz, CD_3OD) δ 8,53 (s, 1H), 7,67 (dd, $J = 8,5$, 5 Hz, 2H), 7,46 (d, $J = 8$ Hz, 1H), 7,27 (t, $J = 8,5$ Hz, 2H), 7,15 (m, 2H), 4,31 9d, $J = 17,0$ Hz, 1H), 4,22 (d, $J = 17$ Hz, 1H), 4,13 (d, $J = 14,2$ Hz, 1H), 4,06 (d, $J = 14,2$ Hz, 1H), 3,88 9d, $J = 6,5$ Hz, 2H), 3,35 9m, 2H), 1,22 (m, 1H), 0,57 (d, $J = 8$ Hz, 1H), 0,33 (d, $J = 5$ Hz, 1H).

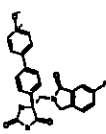
Ejemplo 1011



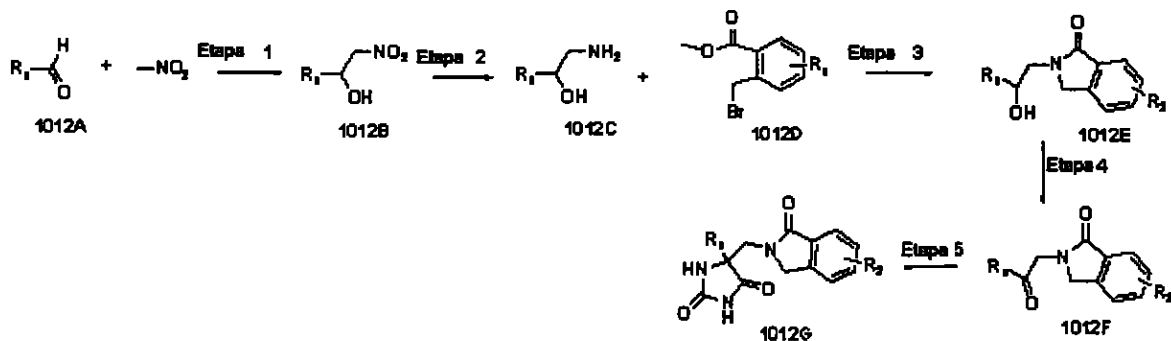
A una solución del compuesto **1011A** (100mg) en DMF (5 mL) se agregó peróxido de m-clorobenzoílo (MCPBA, 100mg). La solución se agitó durante toda la noche a 25°C. El producto se purificó mediante cromatografía en fase inversa C18 (CH_3CN /agua 5% hasta 90%, con 0,1% HCO_2H) para dar el compuesto **1011B** (73 mg).

Los siguientes compuestos se prepararon según lo descrito en los **Ejemplos 1010 y 1011.**

Tabla 1004

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
247		432,12	433,1 [M+H] ⁺	A

Ejemplo 1012.



En la etapa 1, el Compuesto 1012A se trató con nitrometano y KO^tBu en una mezcla de THF y *t*-BuOH durante 2 hasta 12 h. Alternativamente, el compuesto 1012A se trató con nitrometano y TBAF en un solvente adecuado tal como THF durante 2 hasta 12 h. El Compuesto 1012B se purificó mediante cromatografía sobre gel de sílice.

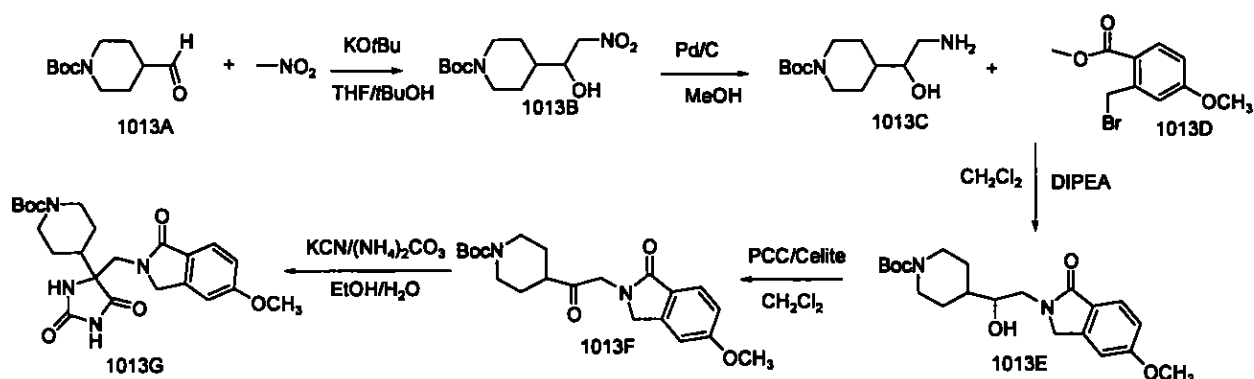
En la etapa 2, se trató el Compuesto 1012B con Pd/C en un solvente adecuado tal como metanol, en un agitador Parr bajo atmósfera de H₂. Después de separación por filtración del catalizador y concentración del solvente, el producto se utilizó sin más purificación.

En la etapa 3, se mezcló bromuro de bencilo (compuesto 1012D) con el compuesto 1012C, DIPEA, y DMF. La solución se agitó a 0°C hasta temperatura ambiente durante 12 hasta 24 horas. El producto se eliminó mediante filtración o se purificó mediante cromatografía sobre gel de sílice.

En la etapa 4, se trató el compuesto **1012E** con PCC y Celite en un solvente adecuado tal como diclorometano durante 2 hasta 12 h. El compuesto **1012F** se purificó mediante cromatografía sobre gel de sílice.

En la etapa 5, el compuesto **1012F** se hizo reaccionar con cianuro de potasio y carbonato de amonio en una solución apropiada de alcohol y agua, a 50 °C hasta 90°C, durante 5 hasta 48 horas. Después del enfriamiento, se agregó agua y el compuesto **1012G** se recogió mediante filtración.

Ejemplo 1013.



Compuesto 1013B: A una solución de THF (15 mL) y t-BuOH (15 mL) se agregó el compuesto **1013A** (1,2 g, 5,6 mmol) y nitrometano (0,61 mL, 11,2 mmol) seguido por la adición de KO^tBu (0,63 g, 5,6 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se ajustó a pH 6 utilizando HOAc. La mezcla de reacción se diluyó con EtOAc (30 mL), y se extrajo con salmuera. La capa acuosa se extrajo con EtOAc (30 mL × 2). Las capas orgánicas combinadas se lavaron con salmuera, se secaron y se concentraron hasta sequedad. El material crudo se purificó mediante PTLC (25% EtOAc/Hexanos) para dar 1,24 g (81%) del compuesto **1013B**.

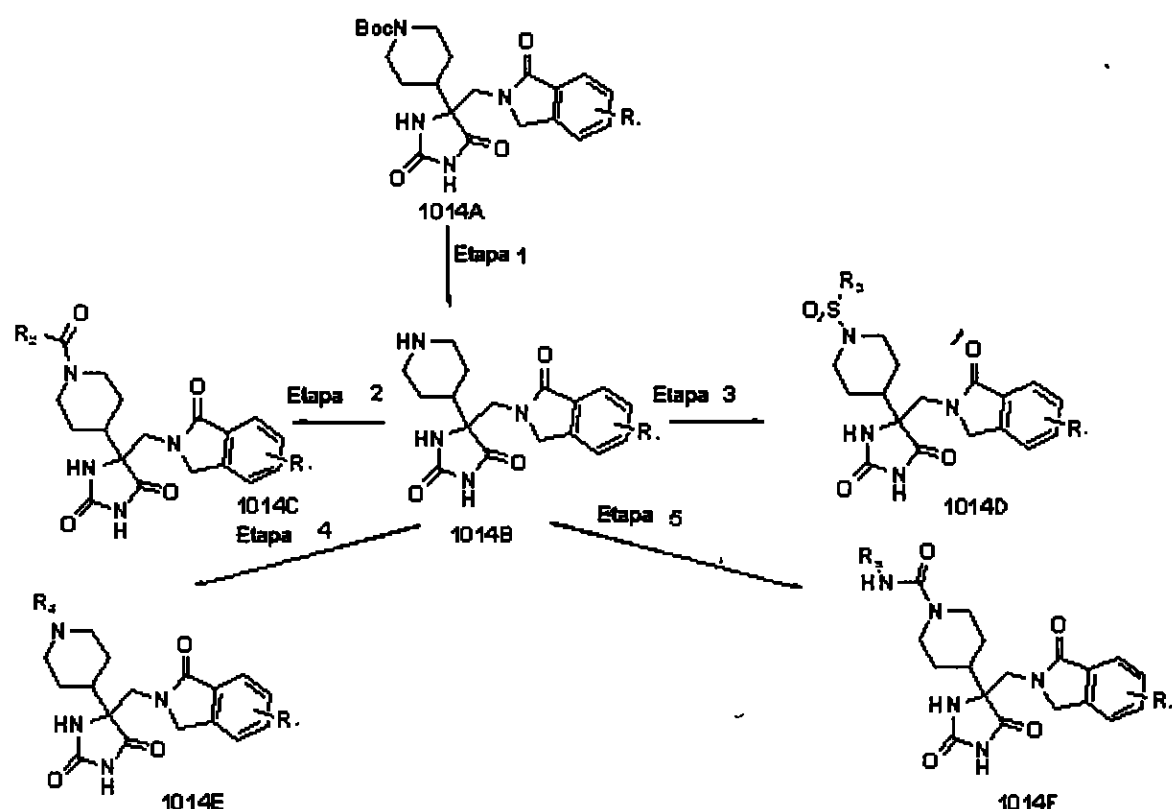
Compuesto **1013C**: el compuesto **1013B** (1,24 g, 4,5 mmol) se trató con Pd/C en metanol en un agitador Parr bajo atmósfera de H₂ (340 kPa (50 psi)) durante toda la noche. Después de la separación por filtración del catalizador y la concentración del solvente, el compuesto **1013C** (1,1 g, 99%) se utilizó sin más purificación.

El compuesto **1013E**: el compuesto **1013C** (1,02 g, 4,2 mmol) se disolvió en diclorometano (30 mL) a 0°C. El compuesto **1013D** (1,13 g, 4,2 mmol) y DIPEA (0,73 mL, 4,2 mmol) se agregaron y la reacción se agitó a 0°C y se calentó lentamente hasta ta durante toda la noche. La mezcla de reacción se lavó con HCl (1N, 50 mL) y salmuera (50 mL). La capa orgánica se secó y se concentró hasta sequedad. El material crudo se purificó mediante PTLC (50% EtOAc/Hexanos) para dar 0,88 g (54%) del compuesto **1013E**.

El compuesto **1013F**: el compuesto **1013E** (0,88 g, 2,25 mmol) se disolvió en cloruro de metileno (30 mL). Se agregaron PCC (1,22 g, 5,63 mmol) y Celite (1,22 g) y la mezcla de reacción se agitó a 25°C durante toda la noche. El sólido se separó por filtración y la solución resultante se concentró y se purificó mediante cromatografía sobre gel de sílice (90% EtOAc/Hexanos) para proporcionar 0,62 g (71%) del compuesto **1013F**.

El compuesto **1013G**: el compuesto **1013F** (1,01 g, 2,6 mmol), KCN (0,25 g, 3,9 mmol), y (NH₄)₂CO₃ (0,75 g, 7,8 mmol) se suspendieron en una mezcla de NH₃ en Metanol (7 N, 10 mL) y agua (10 mL). La solución se agitó a 90°C durante toda la noche. Después de enfriamiento, se agregó agua (20 mL). El sólido se filtró y se lavó con agua tres veces. El sólido se secó bajo vacío para dar el compuesto **1013G** (0,86 g, 72%).

Ejemplo 1014.



Etapa 1.

Se agitó el compuesto **1014A** con 2 a 20 equivalentes de cloruro de hidrógeno en metanol durante 5 a 48 horas. El solvente se eliminó y el compuesto **1014B** pudo utilizarse sin más purificación.

Etapa 2.

El Compuesto **1014B** se trató con anhídrido carboxílico y DIPEA para dar el compuesto **1014C** el cual se purificó mediante cromatografía sobre gel de sílice.

Etapa 3.

El compuesto **1014B** se acopló con el compuesto de cloruro de sulfonilo para dar el compuesto **1014D**, el cual se purificó mediante cromatografía sobre gel de sílice.

Etapa 4.

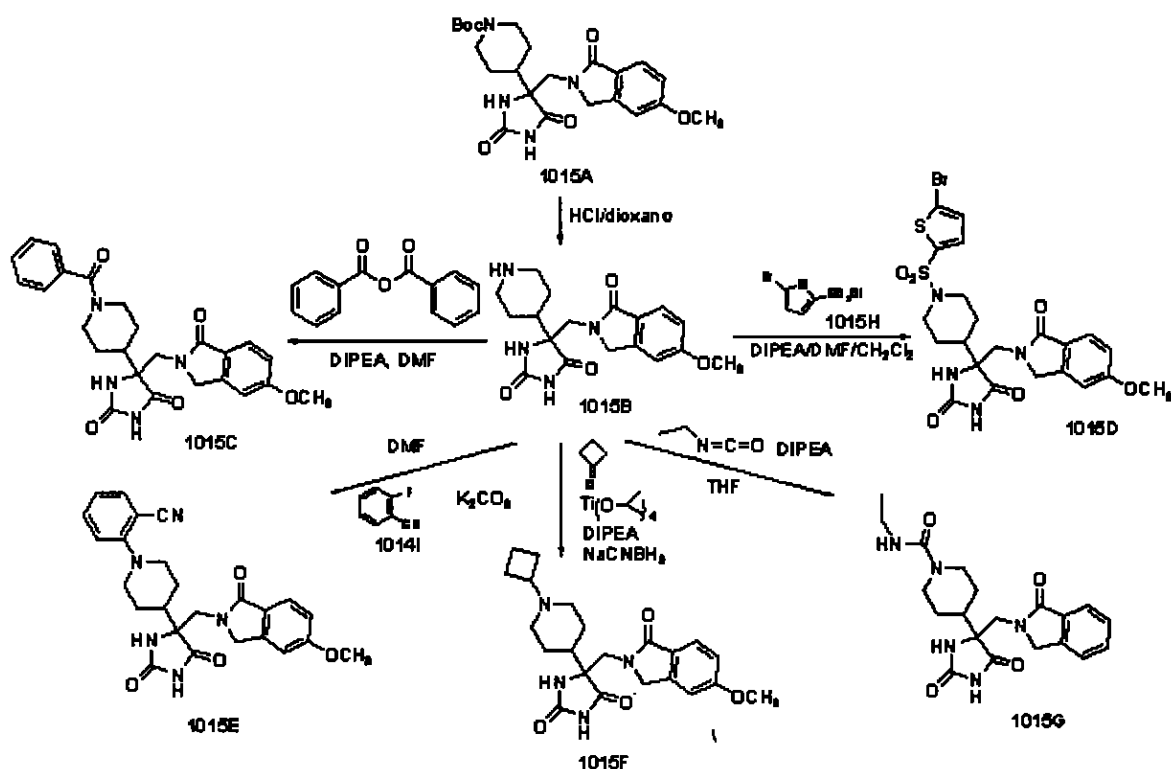
El compuesto **1014B** se hizo reaccionar con compuesto de carbonilo bajo condiciones de aminación reductiva para dar el compuesto **1014E**. Alternativamente, el compuesto **1014B** se trató con un electrófilo adecuado y una base para dar el compuesto **1014E**, el cual se purificó mediante cromatografía sobre gel de sílice.

Etapa 5.

Se hizo reaccionar el compuesto **1014B** con compuesto de isocianato y DIPEA para dar el compuesto **1014F**, el cual se purificó mediante cromatografía sobre gel de sílice.

Ejemplo 1015.

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Compuesto 1015B: Se suspendió el compuesto **1015A** (0,86 g) en metanol (10 mL) y se agregó HCl (4M en dioxano, 10 mL). La solución se agitó a 25°C durante 3 horas. El solvente se eliminó y el material se secó bajo vacío para dar el compuesto **1015B** (0,74 g, 99%).

Compuesto 1015C: el compuesto **1015B** (40 mg, 0,11 mmol) y anhídrido del ácido benzoico (25 mg, 0,11 mmol) se disolvieron en DMF (1 mL). Se agregó DIPEA (0,06 mL, 0,33 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3 \cdot \text{MeOH/CH}_2\text{Cl}_2$) para proporcionar 3,7 mg (7%) del compuesto **1015C**.

Compuesto 1015D: el compuesto **1015B** (40 mg, 0,11 mmol) y el compuesto **1015H** (30 mg, 0,11 mmol) se disolvieron en DMF (1 mL). Se agregó

DIPEA (0,25 mL, 1,4 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 2,2 mg (3%) del compuesto **1015D**.

Compuesto 1015E: Compuesto **1015B** (40 mg, 0,11 mmol) y el compuesto **1015I** (0,024 mL, 0,22 mmol) se disolvieron en DMF (1 mL). Se agregó K_2CO_3 (46 mg, 0,33 mmol) y la mezcla de reacción se agitó a 90°C durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 2,6 mg (5%) del compuesto **1015E**.

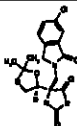
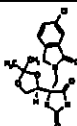
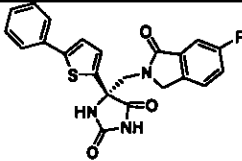
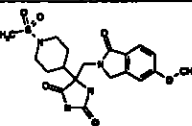
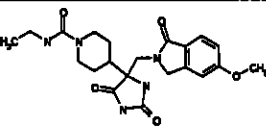
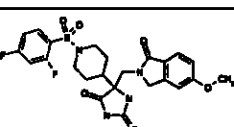
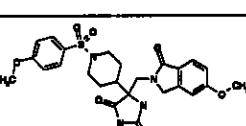
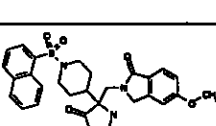
Compuesto 1015F: Compuesto **1015B** (46 mg, 0,13 mmol) y ciclobutanona (0,2 mL) se agitaron en cloruro de metileno (1 mL). Se agregó tetraisopropóxido de titanio (0,045 mL, 0,15 mmol) seguido por la adición de DIPEA (0,027 mL, 0,16 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h. Luego, se agregó NaCNBH_3 (41 mg, 0,65 mmol) y la mezcla se agitó a ta durante toda la noche. El solvente se eliminó. El material crudo se purificó mediante PTLC (10% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 3,1 mg (6%) del compuesto **1015F**.

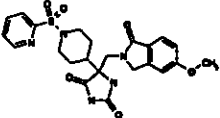
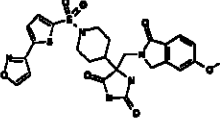
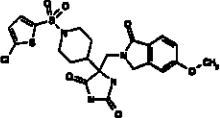
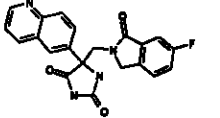
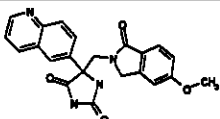
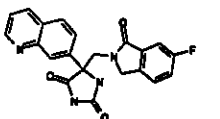
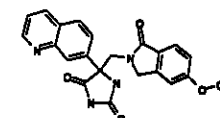
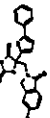
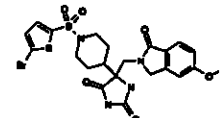
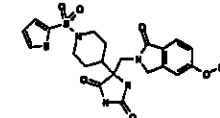
Compuesto 1015G: Se disolvieron el compuesto **1015B** (80 mg, 0,24 mmol) e isocianato de etilo (0,018 mL, 0,24 mmol) en DMF (1 mL). Se agregó DIPEA (0,17 mL, 0,97 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (9% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 11 mg (11%) del compuesto **1015G**.

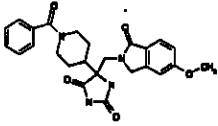
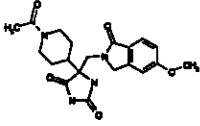
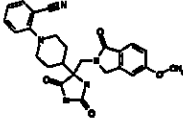
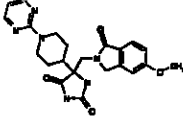
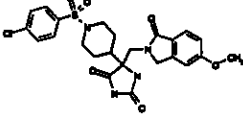
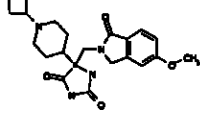
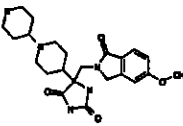
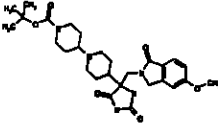
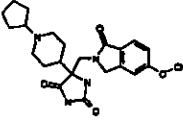
Los siguientes compuestos se prepararon según lo descrito en los Ejemplos 1012 a 1015.

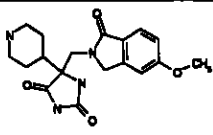
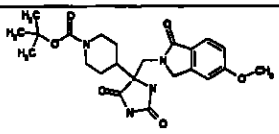
Tabla 1005

386 394

Compuesto #	Estructura	Masa Exacta	Masa Observada	Ki (nM)
248		379,09	380,1[M+H] ⁺	C
249		379,09	380,1[M+H] ⁺	C
250		421,09	422,1[M+H] ⁺	B
251		421,09	422,1[M+H] ⁺	A
252		436,14	437,1[M+H] ⁺	B
253		429,2	430,1[M+H] ⁺	B
254		534,14	535,1[M+H] ⁺	B
255		528,17	529,3[M+H] ⁺	B
256		548,17	549,3[M+H] ⁺	A

257		499,15	500,3[M+H] ⁺	B
258		571,12	572,1[M+H] ⁺	A
259		538,07	539,1[M+H] ⁺	A
260		390,11	391,1[M+H] ⁺	A
261		402,13	403,2[M+H] ⁺	A
262		390,11	391,1[M+H] ⁺	A
263		402,13	403,1[M+H] ⁺	A
264		433,11	434,1[M+H] ⁺	A
265		582,02	585,1[M+H] ⁺	A
266		504,11	505,1[M+H] ⁺	A

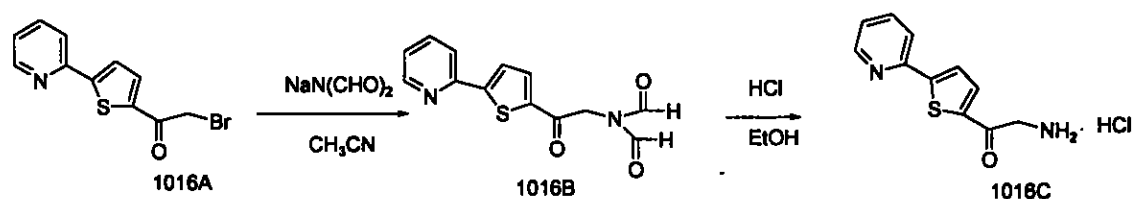
267		462,19	463,1[M+H] ⁺	B
268		400,17	401,1[M+H] ⁺	A
269		459,19	460,1[M+H] ⁺	B
270		436,19	437,2[M+H] ⁺	B
271		532,12	533,3[M+H] ⁺	B
272		412,21	413,2[M+H] ⁺	C
273		441,24	442,1[M+H] ⁺	C
274		541,29	542,3[M+H] ⁺	C
275		426,23	427,2[M+H] ⁺	C

276		358,16	359,1[M+H] ⁺	C
277		458,22	459,1[M+H] ⁺	B

Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1005.

Compuesto 262. ¹H RMN (500 Hz, CD₃OD) δ 8,921 (m, 1H); 8,433 (d, J = 8,6 Hz, 1H); 8,357 (s, 1H); 8,072 (m, 4H); 7,622 (m, 1H); 7,545 (m, 1H); 7,476 (m, 1H); 7,369 (m, 1H); 4,522 (d, J = 17 Hz, 1H); 4,510 (d, J = 14,5 Hz, 1H); 4,425 (d, J = 17 Hz, 1H), 4,350 (d, J = 14,5 Hz, 1H).

Ejemplo 1016.



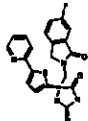
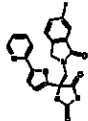
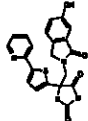
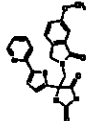
Compuesto 1016B: el compuesto **1016A** (500 mg, 1,77 mmol) se suspendió en CH₃CN (5 mL) seguido por la adición de NaN(CHO)₂ (202 mg, 2,12 mmol). La mezcla de reacción se agitó a ta durante 30 min antes de calentarse hasta 70°C y se agitó durante 2 h. El sólido se recogió mediante filtración por succión y se lavó con acetonitrilo para proporcionar **1016B** (380 mg, 78%) en forma de un sólido marrón.

390 398

Compuesto **1016C**: el compuesto **1016B** (380 mg, 1,38 mmol) se agitó con HCl (36% ac., 1 mL) y EtOH (10 mL) a ta durante 2 días. Luego, se calentó hasta 60°C durante 2 hr. El solvente se eliminó y se secó bajo vacío para proporcionar **1016C** (345 mg, 98%). El material se utilizó sin más purificación.

Los siguientes compuestos se prepararon según lo descrito en el **Ejemplo 1016**, **Ejemplo 2** y **Ejemplo 8**.

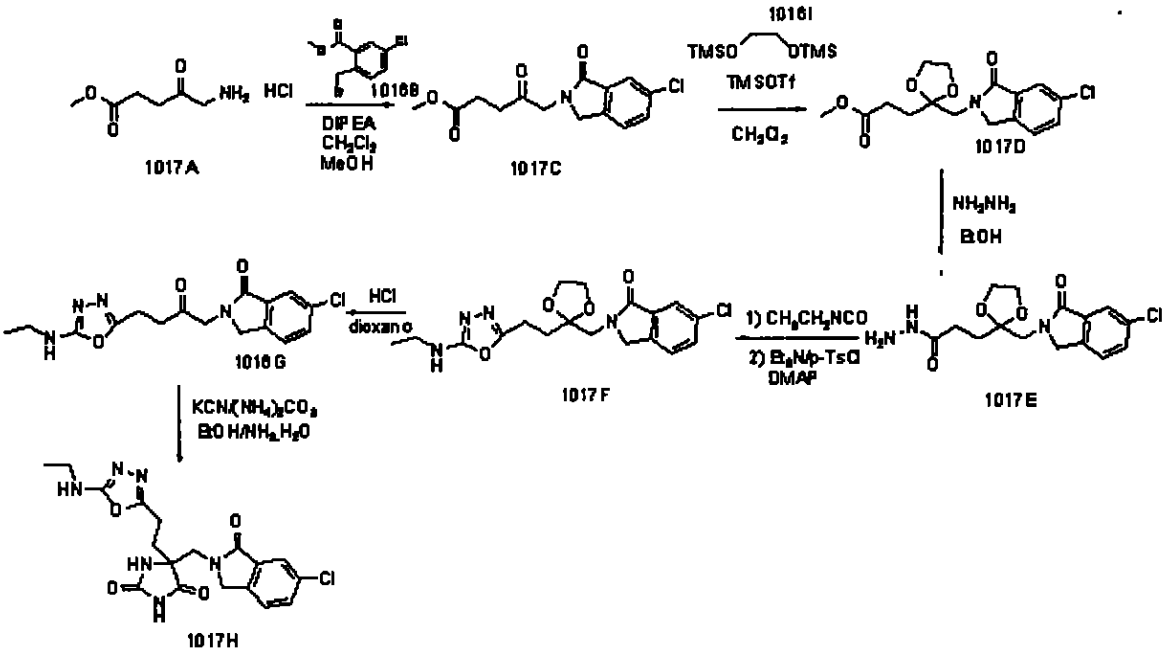
Tabla 1006

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
278		422,08	423,1[M+H] ⁺	A
279		422,08	423,1[M+H] ⁺	C
280		420,9	421,1[M+H] ⁺	A
281		434,1	435,2[M+H] ⁺	A

Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1006.

Compuesto 278. ¹H RMN (500 Hz, CD₃OD) δ 8,503 (d, J = 4,73 Hz, 1H); 7,84 (m, 2H); 7,67 (d, J = 3,8 Hz, 1H); 7,56 (dd, J = 4,4 Hz, 8,5 Hz, 1H); 7,50 (dd, J = 2,5 Hz, 7,8 Hz, 1H); 7,38 (m, 1H); 7,33 (d, J = 4,1 Hz, 2H); 7,3 (m, 1H); 4,52 (d, J = 17 Hz, 1H); 4,45 (d, J = 17 Hz, 1H); 4,43 (d, J = 14,2 Hz, 1H); 4,28 (d, J = 14,2 Hz, 1H).

Ejemplo 1017.



Compuesto 1017C: Se disolvió el compuesto **1017A** (1,5 g, 8,26 mmol) en diclorometano (20 mL) y metanol (10 mL) a 0°C. Se agregaron el compuesto **1017B** (2,64 g, 10 mmol) y DIPEA (2.9 mL, 16.5 mmol) y la reacción se agitó a 0°C y se calentó lentamente hasta ta durante toda la noche. Luego, la mezcla de reacción se calentó hasta 50°C y se agitó durante 2 h. La mezcla de reacción se lavó con salmuera (50 mL). La capa orgánica se secó y se concentró hasta sequedad. El material crudo se purificó mediante PTLC (50% EtOAc/hexanos) para proporcionar 0,7g (29%) del compuesto **1017C**.

Compuesto 1017D: El compuesto **1017C** (200 mg, 0,68 mmol) se agitó en CH₂Cl₂ (15 mL) a 0°C seguido por la adición del compuesto **1017I** (0,5 mL, 2,04 mmol) y TMS-OTf (13 µL, 0,07 mmol). La mezcla de reacción se agitó a 0°C hasta 5°C durante 6 hr antes de calentarse hasta ta y se agitó durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante PTLC (EtOAc) para proporcionar 0,21g (91%) del compuesto **1017D**.

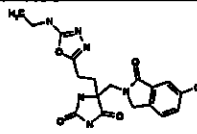
Compuesto **1017E**: Se calentó el compuesto **1017D** (210 mg, 0,62 mmol) en un tubo sellado con NH_2NH_2 (0,2 mL, 6,2 mmol) y EtOH (2 mL) a 60°C durante toda la noche. El solvente se eliminó y dio el material crudo **1017E** (210 mg, 99%) el cual se utilizó sin más purificación.

Compuesto **1017F**: Se disolvieron el compuesto **1017E** (210 mg, 0,62 mmol) e isocianato de etilo (59 μL , 0,74 mmol) en CH_2Cl_2 (10 mL). La mezcla de reacción se agitó a temperatura ambiente durante toda la noche. A esta mezcla se agregó Et_3N (0,43 mL, 3,1 mmol), DMAP (15 mg, cat.) y *p*-TsCl (141 mg, 0,74 mmol). La reacción se agitó a ta durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (10% $\text{NH}_3\cdot\text{MeOH}/\text{CH}_2\text{Cl}_2$) para proporcionar 60 mg (25%) del compuesto **1017F**.

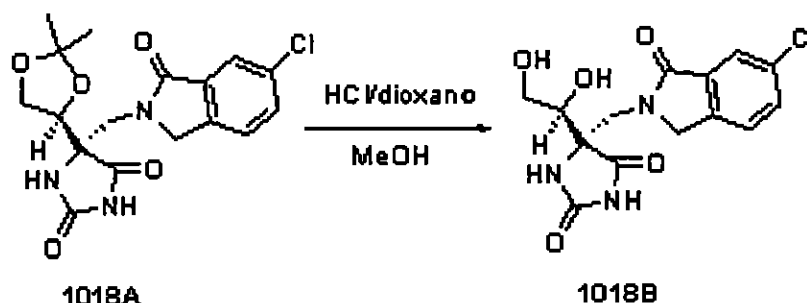
Compuesto **1017G**: se calentó el compuesto **1017F** (60 mg, 0,15 mmol) en un tubo sellado con HCl (3 mL, 4N en dioxano) a 65°C durante 48 hr. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (5% $\text{NH}_3\cdot\text{MeOH}/\text{CH}_2\text{Cl}_2$) para proporcionar 35 mg (66%) del compuesto **1017G**.

Compuesto **1017H**: Se suspendieron el compuesto **1017G** (34 mg, 0,1 mmol), KCN (10 mg, 0,15 mmol), y $(\text{NH}_4)_2\text{CO}_3$ (30 mg, 0,3 mmol) en una mezcla de $\text{NH}_3\cdot\text{H}_2\text{O}$ (1 mL) y etanol (1mL). La solución se agitó a 90°C durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante cromatografía sobre gel de sílice (10% $\text{NH}_3\cdot\text{MeOH}/\text{CH}_2\text{Cl}_2$) para proporcionar 6 mg (15%) del compuesto **1017H**.

Los siguientes compuestos se prepararon según lo descrito en el **Ejemplo 1017**

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
282		418,12	419,1[M+H] ⁺	B

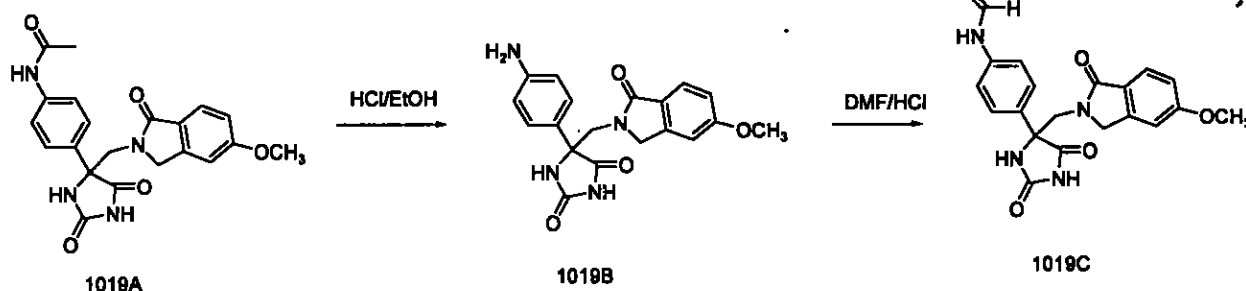
Ejemplo 1018.



Compuesto **1018A**: Se sintetizó el compuesto **1018A** siguiendo los procedimientos del **Ejemplo 1012**.

Compuesto **1018B**: Se agitó el compuesto **1018A** (180 mg, 047 mmol) en MeOH (1 mL) a ta. Se agregó HCl (3 mL, 4N en dioxano) y la mezcla de reacción se calentó hasta 70°C durante toda la noche. El solvente se evaporó. El material crudo se absorbió en agua y el sólido se recogió por filtración con succión para proporcionar **1018B** (115 mg, 71%).

Ejemplo 1019.



Compuesto 1019A: Se sintetizó el compuesto **1019A** siguiendo los procedimientos descritos en el Ejemplo **1012**.

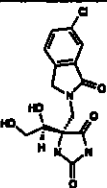
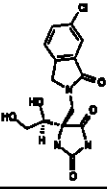
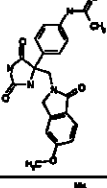
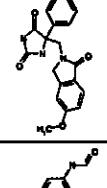
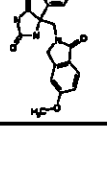
Compuesto 1019B: Se disolvió el compuesto **1019A** (74 mg, 0,18 mmol) en EtOH (2 mL) y se agregó HCl (0,4 mL, ac. 36%) y la mezcla de reacción se calentó hasta 70°C durante toda la noche. El solvente se eliminó y proporcionó **1019B** en forma de un sólido amarillo claro (74 mg, 99%).

Compuesto 1019C: Se agitó el compuesto **1019B** (20 mg, 0,05 mmol) en DMF (1 mL) y HCl (cat., 4 N en dioxano) a 120°C durante toda la noche. El solvente se eliminó y el material crudo se purificó mediante PTLC (9% $\text{NH}_3 \cdot \text{MeOH} / \text{CH}_2\text{Cl}_2$) para proporcionar 8 mg (37%) del compuesto **1019C**.

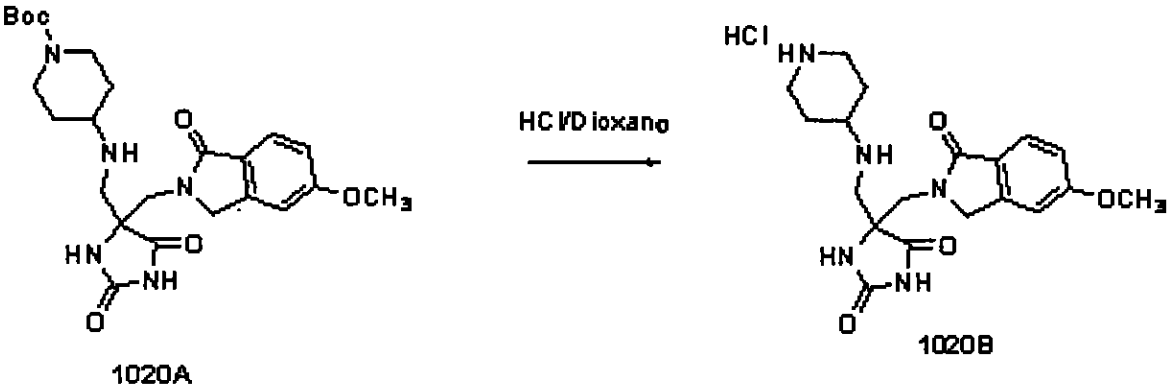
Los siguientes compuestos se prepararon según lo descrito en el Ejemplo **1012**, **1018** y **1019**.

Tabla 1008

395 ~~403~~

Compuesto #	Estructura	Masa Exacta	Masa Obs.	Ki (nM)
283		339,06	340,2[M+H] ⁺	B
284		339,06	340,2[M+H] ⁺	D
285		408,14	409,2[M+H] ⁺	A
286		366,13	367,1[M+H] ⁺	A
287		394,13	395,2[M+H] ⁺	B

Ejemplo 1020.



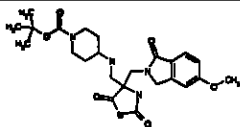
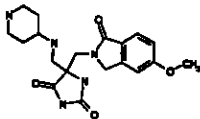
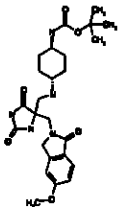
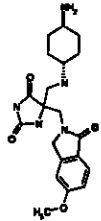
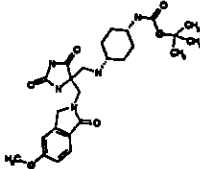
Compuesto 1020A: Se sintetizó el compuesto 1020A siguiendo los procedimientos descritos en el Ejemplo 22.

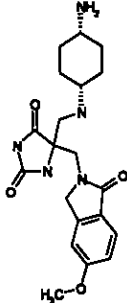
396 ~~404~~

Compuesto **1020B**: Se agitó el compuesto **1020A** (855 mg, 1,86 mmol) en MeOH (10 mL) y HCl (10 mL, 4N en dioxano) a ta durante 2 hr. El solvente se eliminó y el material se secó para proporcionar **1020B** (735 mg, 99%).

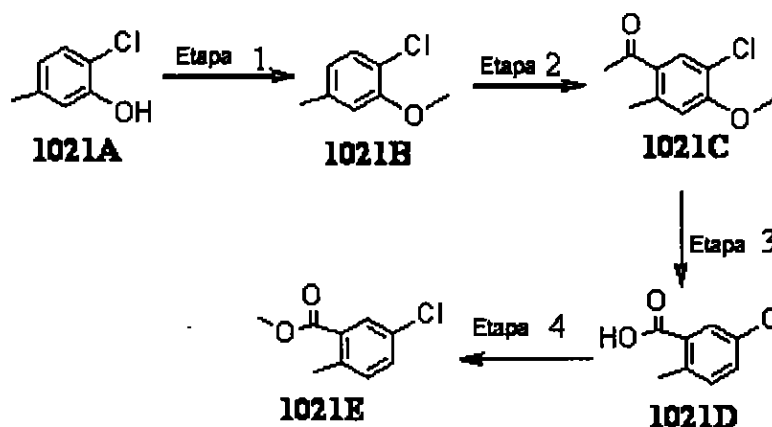
Los siguientes compuestos se prepararon según lo descrito en el **Ejemplo 22** y en el **Ejemplo 1020**.

Tabla 1009

Compuesto #	Estructura	Masa exacta	Masa obs.	Ki (nM)
288		487,24	488,3[M+H] ⁺	B
289		387,19	388,1[M+H] ⁺	C
290		501,26	502,3[M+H] ⁺	B
291		401,21	402,2[M+H] ⁺	C
292		501,26	502,3[M+H] ⁺	B

293		401,21	402,1[M+H] ⁺	B
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Ejemplo 1021



Etapa 1

Se agregaron al frasco DMF (100 mL), carbonato de cesio (41,13 g, 126 mmol), y 2-cloro-5-metilfenol (**1021A**) (15,0 g, 105 mmol). Se agregó por goteo yoduro de metilo (17,92 g, 126 mmol) por medio de un embudo de adición. La mezcla de reacción se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción se diluyó con EtOAc, se lavó con agua y salmuera, y se secó con Na₂SO₄. El material resultante se filtró, y se concentró hasta sequedad. El producto crudo se purificó mediante cromatografía sobre gel de sílice flash utilizando 1:4 EtOAc:hexanos como la fase móvil para proporcionar 15,93 g de **1021B**.

Etapa 2

Un frasco que contenía AlCl_3 (2,55 g, 19,1 mmol), y LiCl (0,41 g, 9,6 mmol) se colocó en un baño frío a -30°C . Se agregó por goteo una solución de **1021B** (1,0 g, 6,38 mmol) y cloruro de acetilo (0,75 g, 9,5 mmol) en 20 mL de CH_2Cl_2 . La mezcla de reacción se agitó durante 1 h a -30°C , luego se dejó calentar hasta ta y se agitó durante toda la noche a ta . La mezcla de reacción se volcó en una mezcla de hielo y EtOAc . La capa orgánica se lavó con agua, NaHCO_3 ac. saturado y agua, luego se secó con Na_2SO_4 , y se concentró hasta sequedad para proporcionar 1,18 g del compuesto **1021C**.

Etapas 3

Se disolvió hidróxido de sodio (58 g, 1,45 mol) en agua (260 mL) y el frasco se enfrió en un baño de agua helada. Se agregó por goteo bromo (19 mL) al frasco con agitación. La mezcla de reacción se agitó durante 0,5 h después de completarse la adición. La solución resultante se agregó por goteo a un frasco enfriado con agua helada que contenía el compuesto **1021C** (18,5 g, 93,1 mmol). Después de completarse la adición, la mezcla de reacción se dejó calentar hasta ta y se dejó agitando durante toda la noche. La mezcla de reacción se calentó a 40°C durante 2 h. Se agregó NaHSO_3 (55 g). La mezcla de reacción se agitó durante 1 h. El material resultante se diluyó con NaOH ac. al 10% y se extrajo con EtOAc para eliminar el material de partida. La capa acuosa se ajustó a pH 1 y se extrajo con EtOAc adicional. La capa orgánica se secó con Na_2SO_4 , se filtró y se concentró hasta sequedad para proporcionar 12,31 g de **1021D**.

Etapas 4

Se agregaron a un frasco DMF (10 mL), Compuesto **1021D** (0,50 g, 2,49 mmol), y K_2CO_3 (0,41 g, 2,96 mmol). Se agregó por goteo yoduro de metilo (0,42 g, 2,96 mmol). La mezcla de reacción se agitó durante toda la noche a temperatura ambiente. La mezcla de reacción se concentró hasta sequedad para proporcionar 0,52 g de **1021E**.

Los siguientes compuestos se prepararon según lo descrito en la etapa 1 en el Ejemplo 14 y el Ejemplo 1021.

Tabla 1010

Compuesto #	Estructura	Masa exacta	Masa obs.	Ki (nM)
296		403,07	404,2 [M+H] ⁺	A
297		389,06	390,2 [M+H] ⁺	A
298		403,07	404,1 [M+H] ⁺	n/a

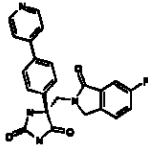
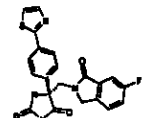
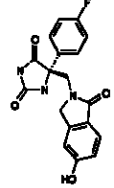
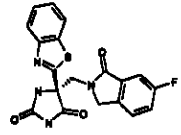
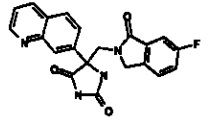
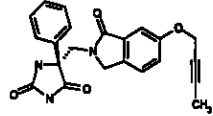
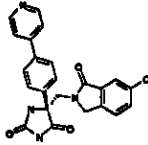
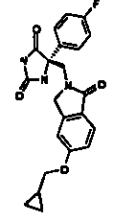
Datos Espectrales de RMN protónica para Compuestos Seleccionados en la Tabla 1010.

Compuesto 296. ¹H RMN (500 Hz, DMSO-d₆) δ 3,93 (s, 3H), 4,00 (d, J = 14 Hz, 1H), 4,19 (d, J = 14 Hz, 1H), 4,23 (d, J = 18 Hz, 1H), 4,34 (d, J = 18 Hz, 1H), 7,24-7,34 (m, 2H), 7,42 (s, 1H), 7,62-7,73 (m, 3H), 8,92 (s, 1H), 10,95 (s, 1H).

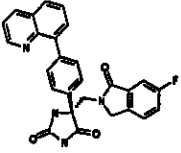
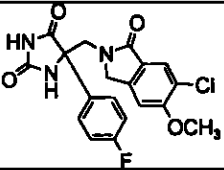
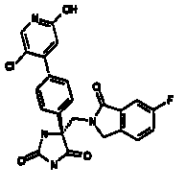
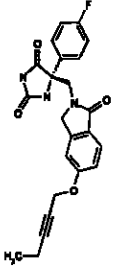
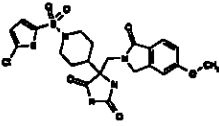
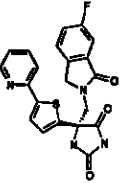
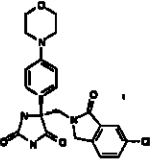
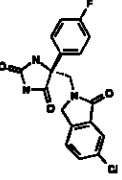
La actividad inhibitoria de TACE específica (valores Ki) de algunos compuestos representativos de la presente invención se expone a continuación.

Tabla 1011

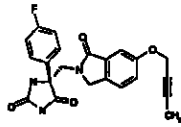
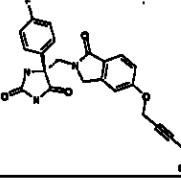
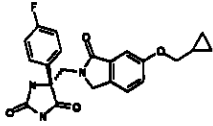
400 404

Compuesto #	Estructura	Ki (nM)
111		0,48
120		4
213		0,8
181		3,17
262		4,91
198		1,29
143		1,87
219		2,4

401
~~402~~

155		1,05
296		1,01
123		1,2
232		1,0
233		2,35
278		2,2
139		2,8
25		0,43

402
411
1

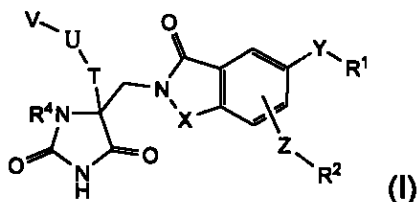
203		0,23
239		0,11
243		3,00

Los expertos en la técnica apreciarán que podrían efectuarse cambios en las realizaciones antes descritas sin apartarse de su amplio concepto inventivo. Por lo tanto, se entiende que esta invención no se encuentra limitada a las realizaciones en particular descritas, sino que tiene el propósito de abarcar las modificaciones que están dentro del espíritu y alcance de la invención, según lo definido por las reivindicaciones adjuntas.

REIVINDICACIONES

403
A12

1. Un compuesto representado por la Fórmula (I):



o su sal, solvato o isómero farmacéuticamente aceptable, en donde:

X se selecciona del grupo formado por $-S-$, $-C(R^4)_2-$ o $-N(R^4)-$;

T se selecciona del grupo formado por H (estando U y V ausentes), alquilo, alquenilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo, y arilalquilo, estando dicho arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo opcionalmente fusionado con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en donde cada uno de cualquiera de los grupos alquilo, alquenilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo antes mencionados de T está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} es independientemente seleccionada del grupo de porciones R^{10} que aparecen más adelante;

U está ausente o presente, y si está presente U se selecciona del grupo formado por un enlace covalente, $-N(R^4)-$, $-N(R^4)C(R^4)_2-$, $-N(R^4)C(O)-$, $-O-$, $-N(R^4)S(O)_2-$, $-N(R^4)C(O)N(R^4)-$, y $-N(R^4)C(S)N(R^4)-$;

V está ausente o presente, y si está presente V se selecciona del grupo formado por alquilo, arilo, heteroarilo, heterociclilo y cicloalquilo, dicho arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo están opcionalmente fusionados con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en donde cada uno de cualquiera de los antes mencionados alquilo, arilo, heteroarilo, heterociclilo y

cicloalquilo está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente del grupo de porciones R^{10} que aparecen más adelante;

Y está ausente o presente, y si está presente Y se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, y $-S(O)_2-$;

Z está ausente o presente, y si está presente Z se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-N(R^4)-$, $-C(O)N(R^4)-$, $-N(R^4)C(O)-$, $-N(R^4)C(O)N(R^4)-$, $-S(O)_2N(R^4)-$, $-N(R^4)-S(O)_2-$, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, y $-S(O)_2-$;

n es 1 a 3;

R^1 se selecciona del grupo formado por H, $-OR^4$, halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo de R^1 está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} que aparecen más adelante, con la condición de que cuando Y está presente e Y es N, S o O, entonces R^1 no es halógeno;

R^2 se selecciona del grupo formado por H, $-OR^4$, halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, alquilarilo, alquilheteroarilo y arilalquilo de R^2 está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} que aparecen más adelante, con

la condición de que cuando Z está presente y Z es N, S o O, entonces R² no es halógeno;

cada R⁴ es igual o diferente y se selecciona independientemente del grupo formado por H y alquilo;

R¹⁰ se selecciona del grupo formado por -OR⁴, -N(R⁴)₂, -S(O)-, -S(O)₂-, -N(R⁴)S(O)₂-, -S(O)₂N(R⁴)-, -O(fluoralquilo), halógeno, alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo, en donde cada uno de los grupos alquilo, fluoralquilo, arilo, heteroarilo, heterociclilo, cicloalquilo, alquilarilo y arilalquilo de R¹⁰ está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R³⁰ las cuales pueden ser iguales o diferentes, cada porción R³⁰ se selecciona independientemente del grupo de porciones R³⁰ que aparecen más adelante;

R²⁰ se selecciona del grupo formado por halógeno, alquilo, fluoralquilo; y

R³⁰ se selecciona del grupo formado por halógeno, alquilo, y fluoralquilo.

2. El compuesto de acuerdo con la reivindicación 1, en donde dicho isómero es un estereoisómero.

3. El compuesto de acuerdo con la reivindicación 1 en donde T es alquilo o arilo; X es -C(R⁴)₂-; Y está ausente; Z está ausente o presente; R² se selecciona del grupo formado por H, halógeno y alquilo; y si Z está presente Z es -O-.

4. El compuesto de acuerdo con la reivindicación 1 en donde T es alquilo o arilo; X es -C(R⁴)₂-; Y está ausente; Z está ausente o presente, y si está presente Z es -O-; y R² se selecciona del grupo formado por alquilarilo y alquilheteroarilo.

5. El compuesto de acuerdo con la reivindicación 1 en donde T es alquilo o arilo; X es -N(R⁴)-; Y está ausente; Z está ausente o presente; R² se selecciona del grupo formado por H, halógeno y alquilo; y si Z está presente Z es -O-.

6. El compuesto de acuerdo con la reivindicación 1 en donde X es $-\text{CH}_2-$ o $-\text{N}(\text{R}^4)-$.
7. El compuesto de acuerdo con la reivindicación 6 en donde X es $-\text{CH}_2-$.
8. El compuesto de acuerdo con la reivindicación 6 en donde X es $-\text{N}(\text{R}^4)-$.
9. El compuesto de acuerdo con la reivindicación 8 en donde R^4 es H.
10. El compuesto de acuerdo con la reivindicación 1 en donde T es alquilo.
11. El compuesto de acuerdo con la reivindicación 10 en donde T es $-\text{CH}_3$.
12. El compuesto de acuerdo con la reivindicación 1 en donde T es arilo y dicho arilo está no sustituido u opcional e independientemente sustituido con una a cinco porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente del grupo de porciones R^{10} .
13. El compuesto de acuerdo con la reivindicación 12 en donde R^{10} es halógeno.
14. El compuesto de acuerdo con la reivindicación 12 en donde R^{10} es heteroarilo.
15. El compuesto de acuerdo con la reivindicación 12 en donde R^{10} es arilo.
16. El compuesto de acuerdo con la reivindicación 1 en donde U se selecciona del grupo formado por un enlace covalente, $-\text{N}(\text{R}^4)-$, $-\text{N}(\text{R}^4)\text{C}(\text{O})-$, y $-\text{N}(\text{R}^4)\text{S}(\text{O})_2-$.
17. El compuesto de acuerdo con la reivindicación 16 en donde U es un enlace covalente.
18. El compuesto de acuerdo con la reivindicación 16 en donde U es $-\text{N}(\text{R}^4)-$.
19. El compuesto de acuerdo con la reivindicación 16 en donde U es $-\text{N}(\text{R}^4)\text{C}(\text{O})-$.

20. El compuesto de acuerdo con la reivindicación 1 en donde V se selecciona del grupo formado por arilo, heteroarilo, heterociclilo y cicloalquilo, dicho arilo, heteroarilo, heterociclilo, y cicloalquilo está opcionalmente fusionado con una o más porciones seleccionadas del grupo formado por arilo, heteroarilo, heterociclilo, o cicloalquilo, en donde cada uno de cualquiera de dicho arilo, heteroarilo, heterociclilo y cicloalquilo está no sustituido u opcional e independientemente sustituido con una a cuatro porciones R^{10} las cuales pueden ser iguales o diferentes, cada porción R^{10} se selecciona independientemente entre el grupo de porciones R^{10} .

21. El compuesto de acuerdo con la reivindicación 1 en donde Y se selecciona del grupo formado por un enlace covalente, $-(C(R^4)_2)_n-$, $-C(O)-$ y $-O-$.

22. El compuesto de acuerdo con la reivindicación 21 en donde Y es $-O-$.

23. El compuesto de acuerdo con la reivindicación 21 en donde Y es $-(C(R^4)_2)_n-$.

24. El compuesto de acuerdo con la reivindicación 21 en donde Y es $-C(O)-$.

25. El compuesto de acuerdo con la reivindicación 21 en donde Y es un enlace covalente.

26. El compuesto de acuerdo con la reivindicación 1 en donde R^1 se selecciona del grupo formado por $-OR^4$, H, alquilo, fluoralquilo, alquilarilo, halógeno y heteroarilo.

27. El compuesto de acuerdo con la reivindicación 26 en donde R^1 es H.

28. El compuesto de acuerdo con la reivindicación 26 en donde R^1 es alquilarilo.

29. El compuesto de acuerdo con la reivindicación 26 en donde R^1 es alquilo.

30. El compuesto de acuerdo con la reivindicación 26 en donde R¹ es fluoralquilo.

31. El compuesto de acuerdo con la reivindicación 26 en donde R¹ es halógeno.

32. El compuesto de acuerdo con la reivindicación 26 en donde R¹ es -OR⁴.

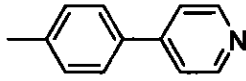
33. El compuesto de acuerdo con la reivindicación 32 en donde R⁴ es -CH₂C≡CCH₃.

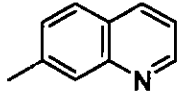
34. El compuesto de acuerdo con la reivindicación 32 en donde R⁴ es -CH₂C≡CCH₂OH.

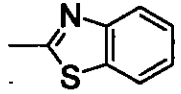
35. El compuesto de acuerdo con la reivindicación 32 en donde R⁴ es -CH₂-.

36. El compuesto de acuerdo con la reivindicación 29 en donde dicho alquilo es -CH₃.

37. El compuesto de acuerdo con la reivindicación 29 en donde dicho alquilo es -CH₂CH₃.

38. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en conjunto forman  y R¹ se selecciona del grupo formado por F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, y -CH₂-.

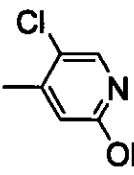
39. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R¹ se selecciona del grupo formado por F, Cl, OH, -OCH₂C≡CCH₃, -OCH₂C≡CCH₂OH, -OCH₃, y -OCH₂-.

40. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R¹ se selecciona del

209 2. 3. 4. 5. 6. 7. 8. 9. 10. 11. 12. 13. 14. 15. 16. 17. 18. 19. 20. 21. 22. 23. 24. 25. 26. 27. 28. 29. 30. 31. 32. 33. 34. 35. 36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49. 50. 51. 52. 53. 54. 55. 56. 57. 58. 59. 60. 61. 62. 63. 64. 65. 66. 67. 68. 69. 70. 71. 72. 73. 74. 75. 76. 77. 78. 79. 80. 81. 82. 83. 84. 85. 86. 87. 88. 89. 90. 91. 92. 93. 94. 95. 96. 97. 98. 99. 100.

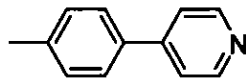
grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

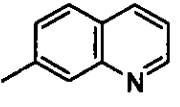
41. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman

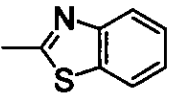


OH y R¹ se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

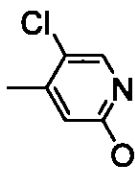
42. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R¹ se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

43. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R² se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

44. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R² se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

45. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman  y R² se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

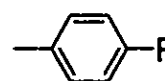
46. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V cuando se toman en forma conjunta forman



OH y R^2 se selecciona del grupo formado por F, Cl, OH,

$-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

47. El compuesto de acuerdo con la reivindicación 1 en donde T, U, y V

cuando se toman en forma conjunta forman  y R^2 se selecciona del grupo formado por F, Cl, OH, $-OCH_2C\equiv CCH_3$, $-OCH_2C\equiv CCH_2OH$, $-OCH_3$, y $-OCH_2$ -.

48. El compuesto de acuerdo con la reivindicación 30 en donde dicho fluoralquilo es $-CH_2CF_3$.

49. El compuesto de acuerdo con la reivindicación 31 en donde dicho halógeno se selecciona del grupo formado por $-Br$, $-Cl$ y $-F$.

50. El compuesto de acuerdo con la reivindicación 32 en donde R^4 es $-CH_3$.

51. El compuesto de acuerdo con la reivindicación 29 en donde dicho alquilo está sustituido con una a cuatro porciones R^{20} las cuales pueden ser iguales o diferentes, cada porción R^{20} se selecciona independientemente del grupo de porciones R^{20} .

52. El compuesto de acuerdo con la reivindicación 51 en donde R^{20} es arilo.

53. El compuesto de acuerdo con la reivindicación 1 en donde Z se selecciona del grupo formado por un enlace covalente, $-N(R^4)-$, $-(C(R^4)_2)_n-$, $-C(O)-$ y $-O-$.

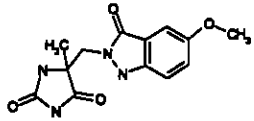
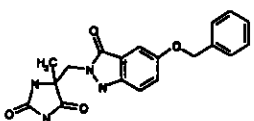
54. El compuesto de acuerdo con la reivindicación 50 en donde Z es $-O-$.

55. El compuesto de acuerdo con la reivindicación 50 en donde Z es un enlace covalente.

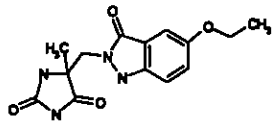
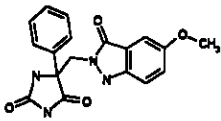
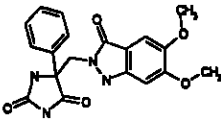
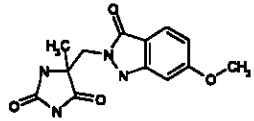
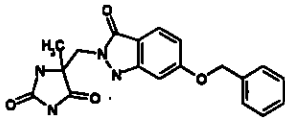
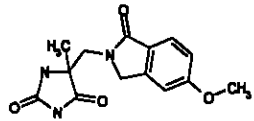
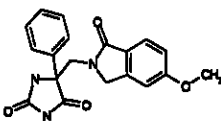
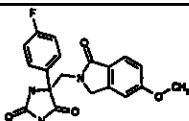
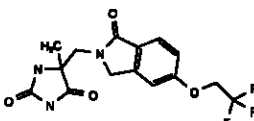
56. El compuesto de acuerdo con la reivindicación 50 en donde Z es $-N(R^4)-$.
57. El compuesto de acuerdo con la reivindicación 50 en donde Z es $-C(O)-$.
58. El compuesto de acuerdo con la reivindicación 56 en donde R^4 es alquilo.
59. El compuesto de acuerdo con la reivindicación 58 en donde dicho alquilo es $-CH_3$.
60. El compuesto de acuerdo con la reivindicación 50 en donde R^2 se selecciona del grupo formado por $-OR^4$, hidrógeno, alquilo, fluoralquilo, alquilarilo, halógeno y heteroarilo.
61. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es hidrógeno.
62. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es alquilo.
63. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es alquilarilo.
64. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es fluoralquilo.
65. El compuesto de acuerdo con la reivindicación 64 en donde dicho fluoralquilo es $-CH_2CF_3$.
66. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es halógeno.
67. El compuesto de acuerdo con la reivindicación 66 en donde dicho halógeno se selecciona del grupo formado por $-Br$, $-Cl$ y $-F$.
68. El compuesto de acuerdo con la reivindicación 60 en donde R^2 es heteroarilo.

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69. El compuesto de acuerdo con la reivindicación 60 en donde R⁴ es -CH₃.
70. El compuesto de acuerdo con la reivindicación 60 en donde R⁴ es -CH₂C≡CCH₃.
71. El compuesto de acuerdo con la reivindicación 60 en donde R⁴ es -CH₂C≡CCH₂OH.
72. El compuesto de acuerdo con la reivindicación 60 en donde R⁴ es -CH₂-.
73. El compuesto de acuerdo con la reivindicación 60 en donde dicho alquilo es -CH₃.
74. Un compuesto que exhibe actividad inhibitoria de una enzima conversora del factor-alfa de necrosis tumoral (TACE, correspondiente a "tumor necrosis factor-alpha-converting enzyme"), factor alfa de necrosis tumoral (TNF-α, correspondiente a "tumor necrosis factor-alpha"), metaloproteinasas de matriz (MMPs, correspondiente a "matrix metalloproteinases"), una desintegrina y metaloproteasas (ADAMs) o cualquier combinación de los mismos, incluyendo enantiómeros, estereoisómeros y tautómeros de dicho compuesto, y las sales o solvatos farmacéuticamente aceptables de dicho compuesto, seleccionándose dicho compuesto entre los compuestos de las estructuras mostradas a continuación:

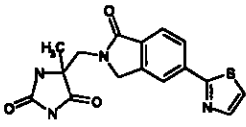
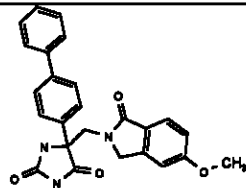
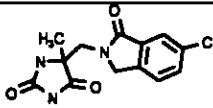
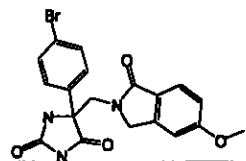
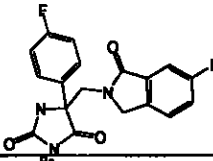
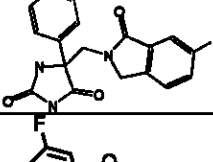
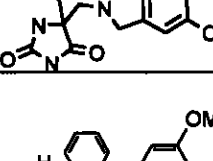
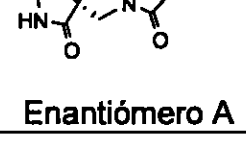
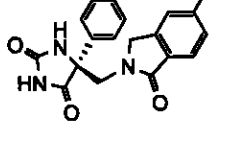
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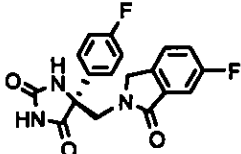
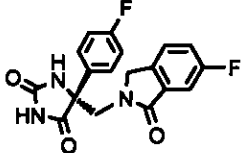
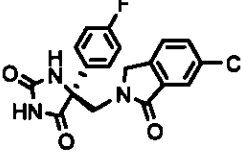
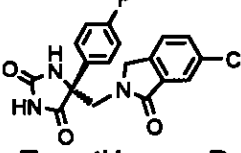
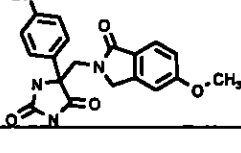
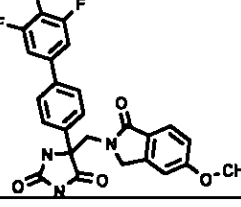
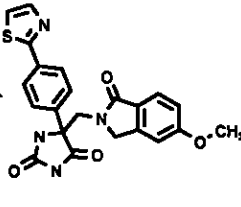
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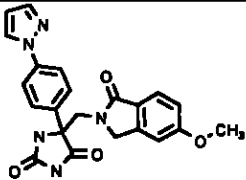
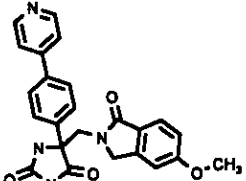
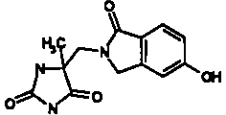
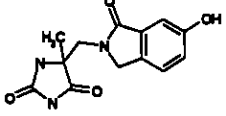
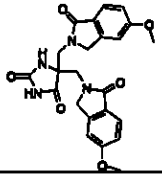
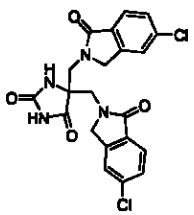
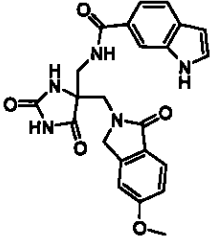
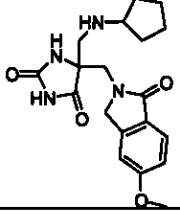
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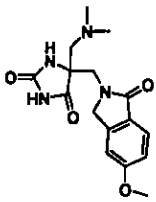
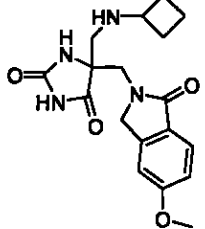
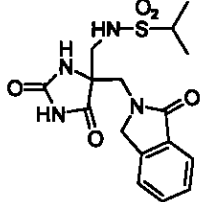
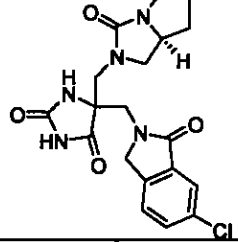
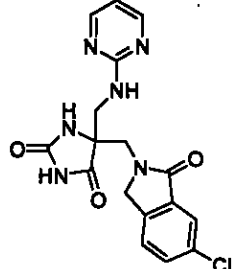
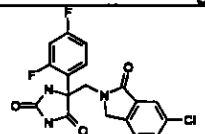
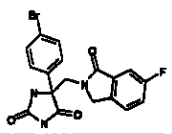
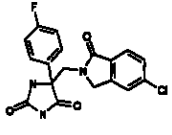
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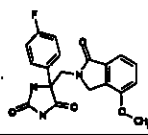
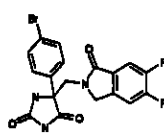
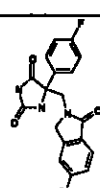
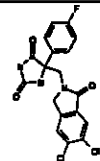
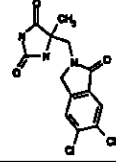
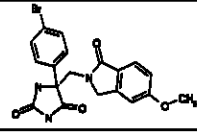
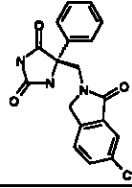
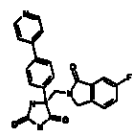
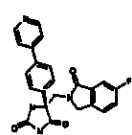
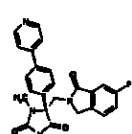
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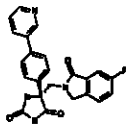
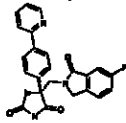
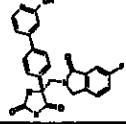
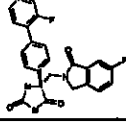
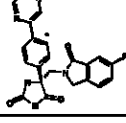
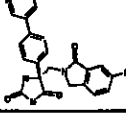
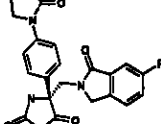
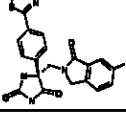
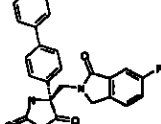
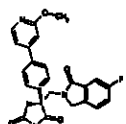
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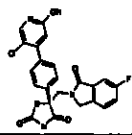
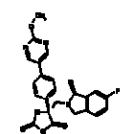
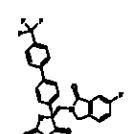
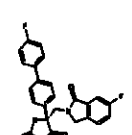
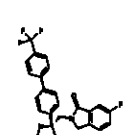
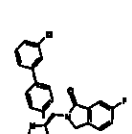
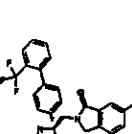
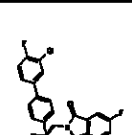
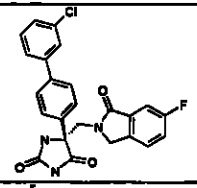
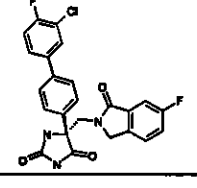
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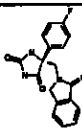
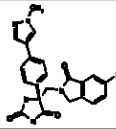
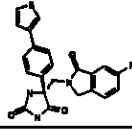
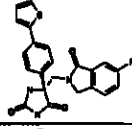
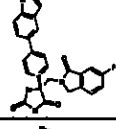
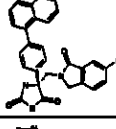
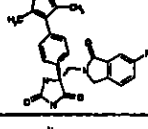
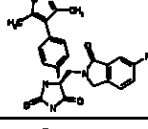
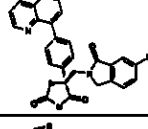
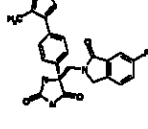
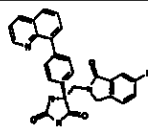
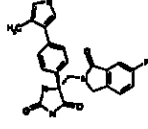
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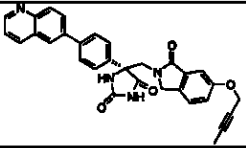
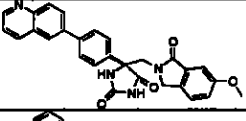
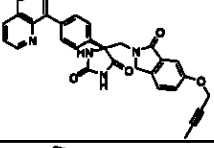
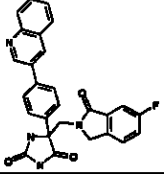
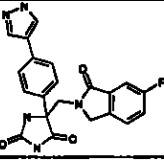
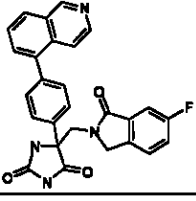
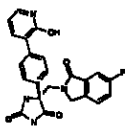
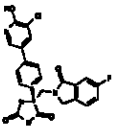
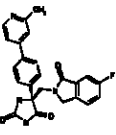
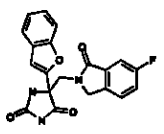
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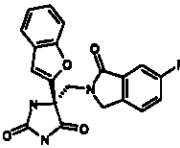
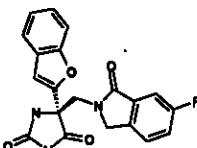
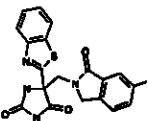
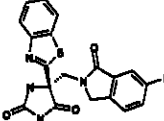
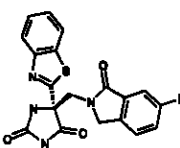
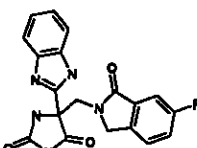
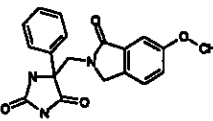
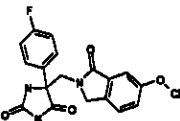
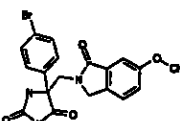
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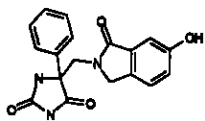
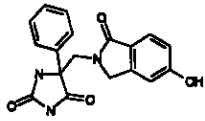
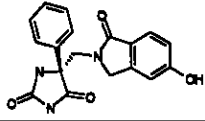
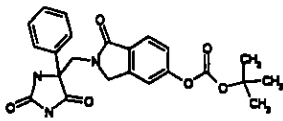
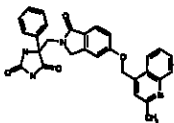
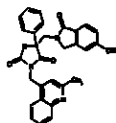
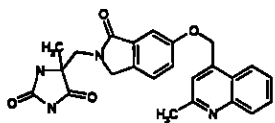
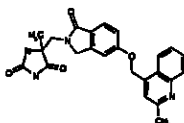
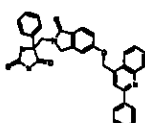
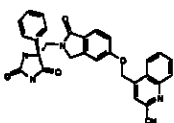
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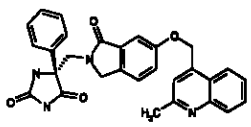
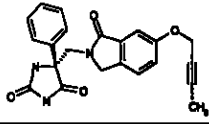
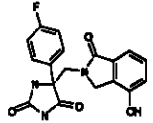
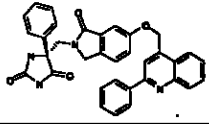
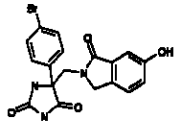
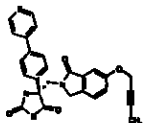
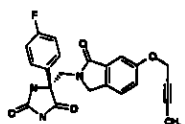
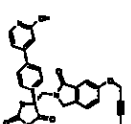
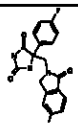
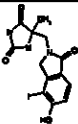
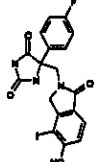
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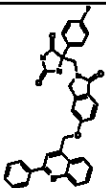
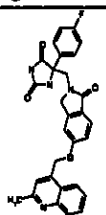
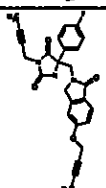
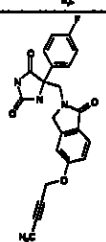
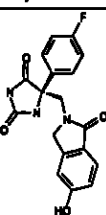
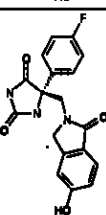
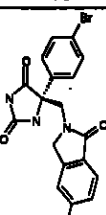
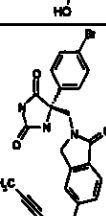
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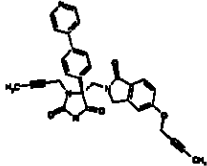
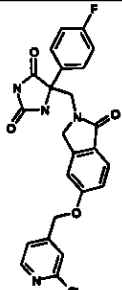
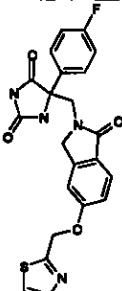
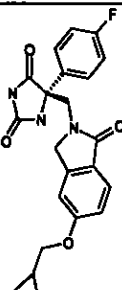
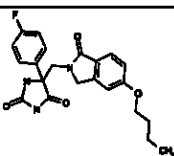
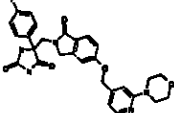
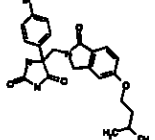
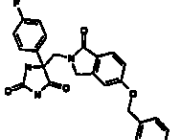
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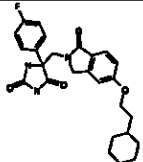
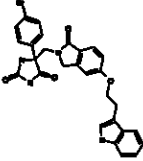
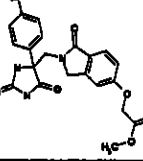
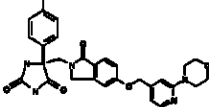
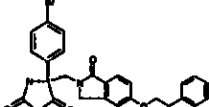
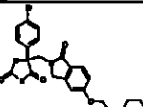
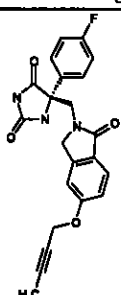
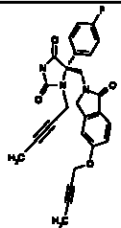
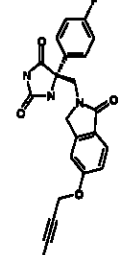
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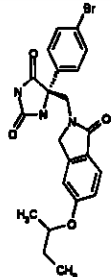
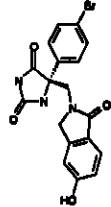
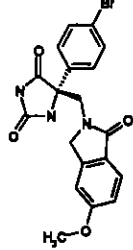
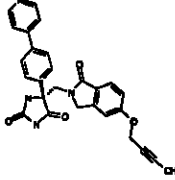
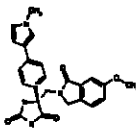
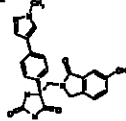
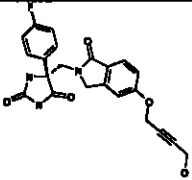
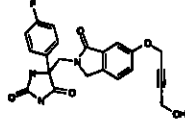
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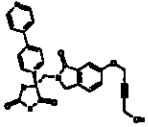
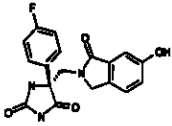
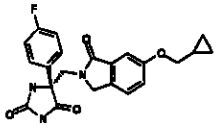
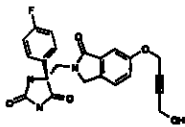
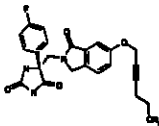
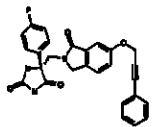
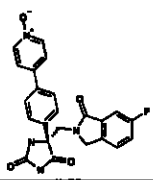
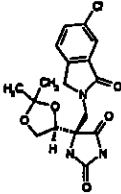
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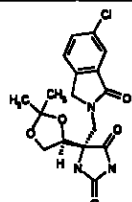
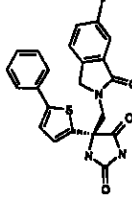
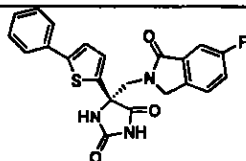
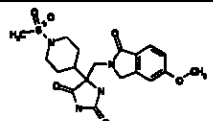
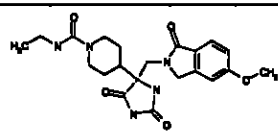
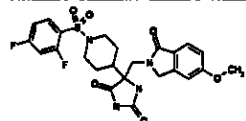
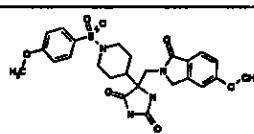
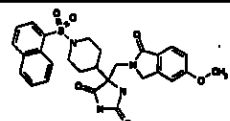
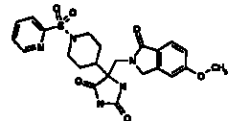
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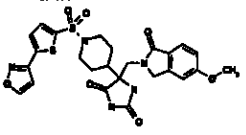
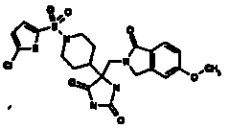
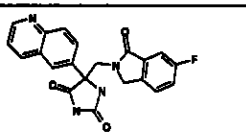
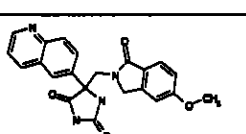
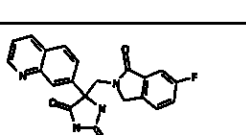
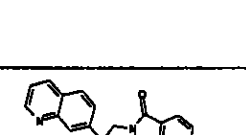
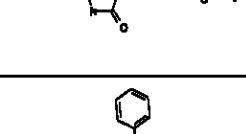
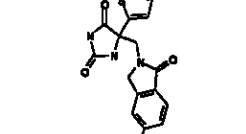
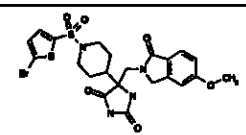
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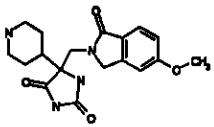
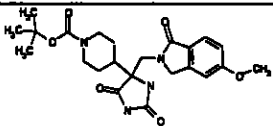
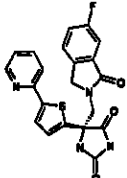
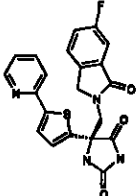
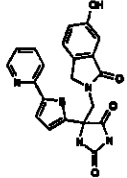
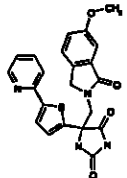
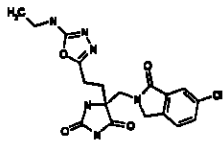
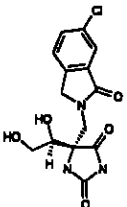
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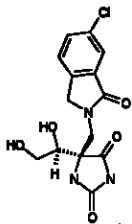
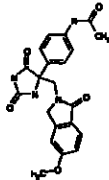
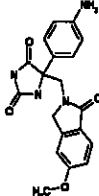
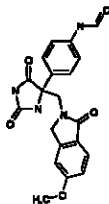
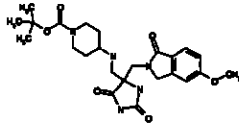
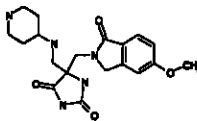
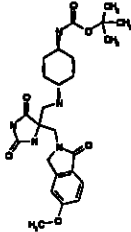
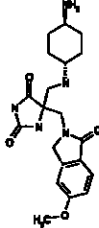
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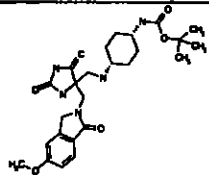
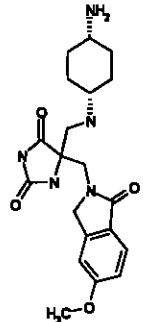
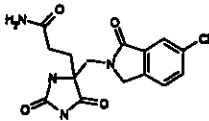
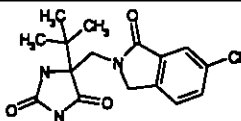
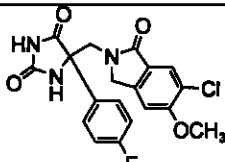
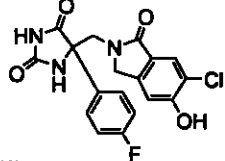
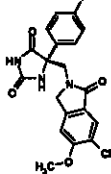
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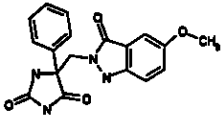
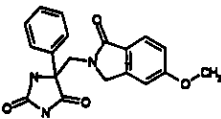
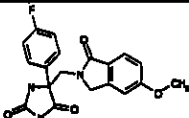
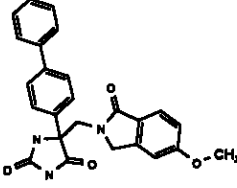
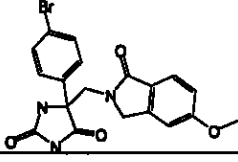
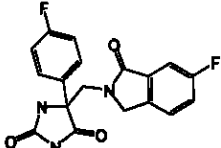
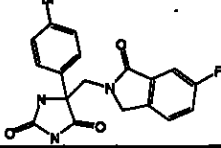
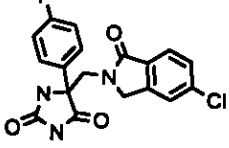
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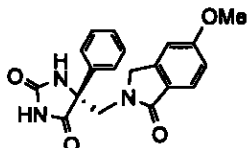
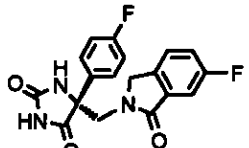
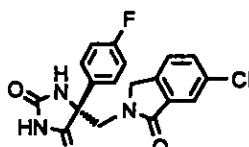
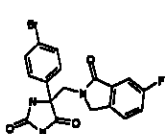
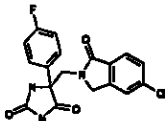
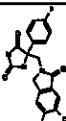
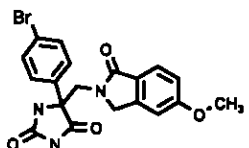
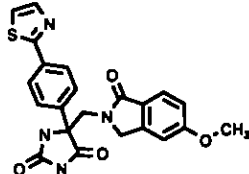
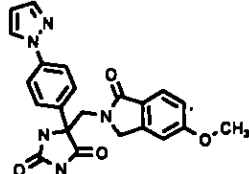
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A.B.

75. El compuesto de acuerdo con la reivindicación 74, en donde dicho compuesto se selecciona entre los compuestos de las estructuras mostradas a continuación:

Compuesto #	Estructura
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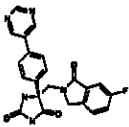
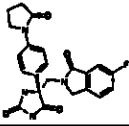
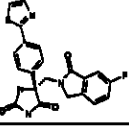
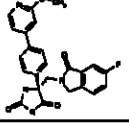
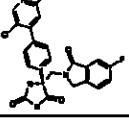
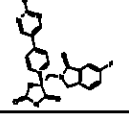
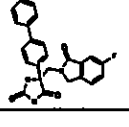
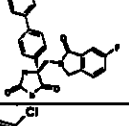
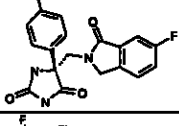
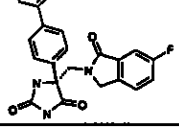
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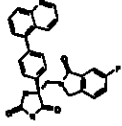
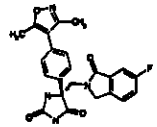
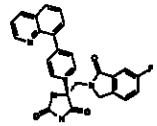
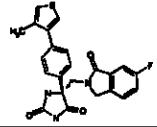
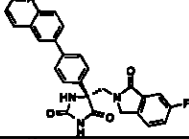
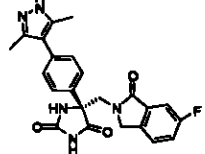
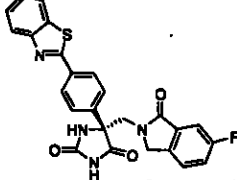
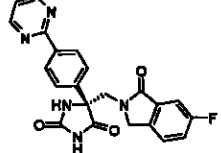
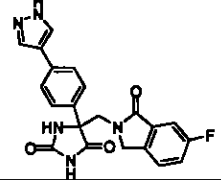
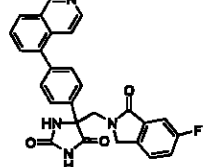
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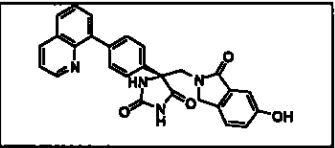
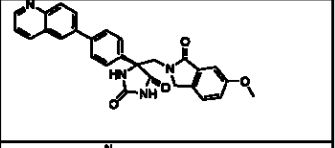
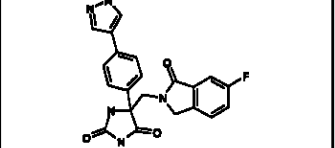
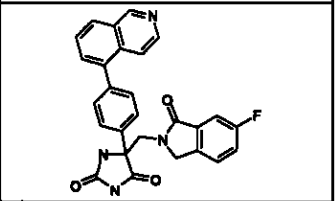
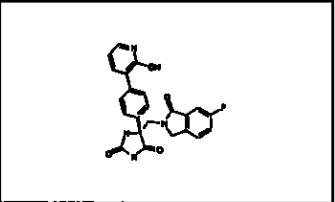
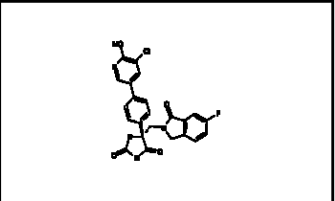
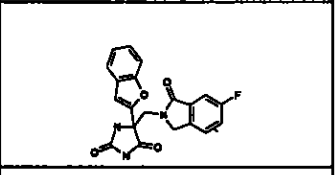
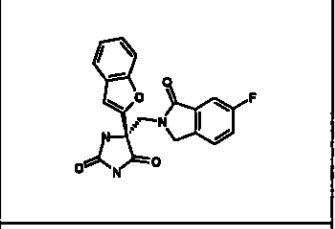
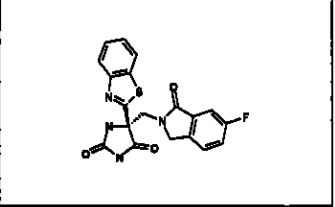
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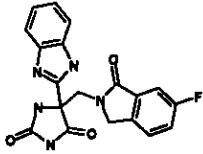
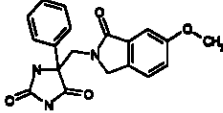
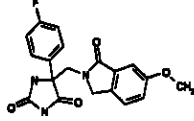
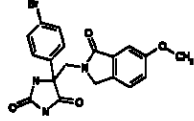
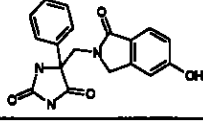
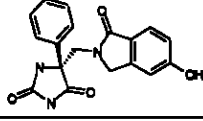
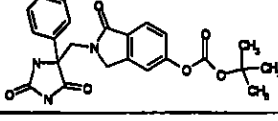
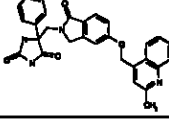
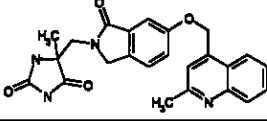
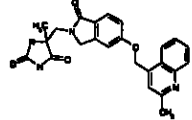
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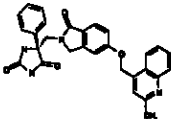
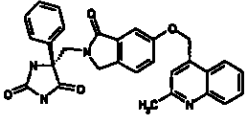
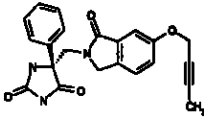
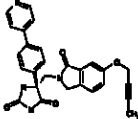
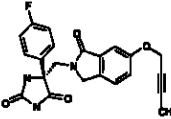
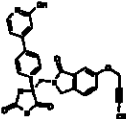
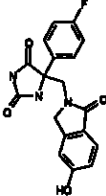
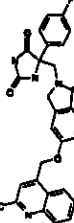
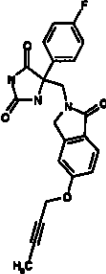
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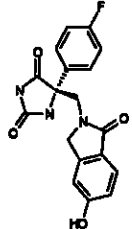
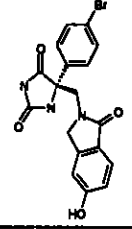
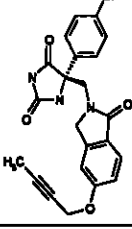
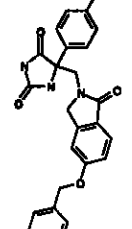
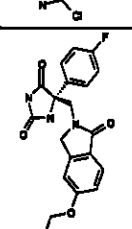
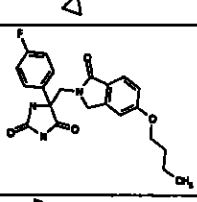
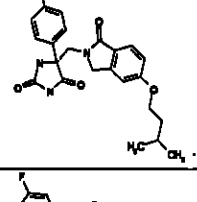
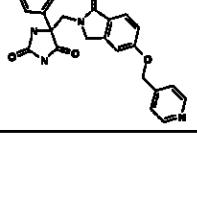
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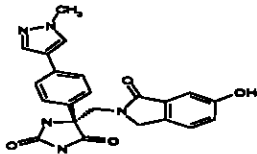
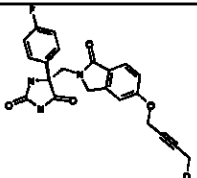
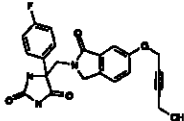
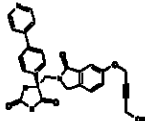
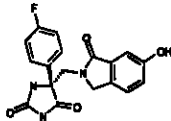
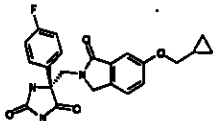
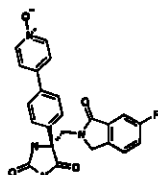
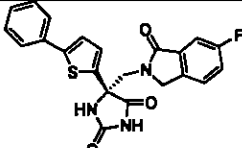
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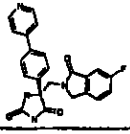
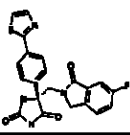
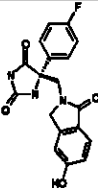
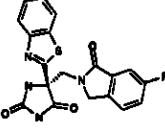
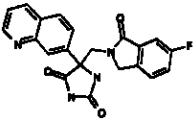
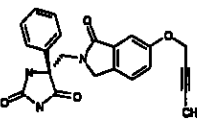
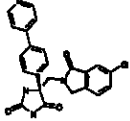
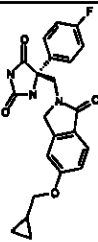
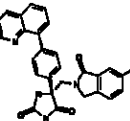
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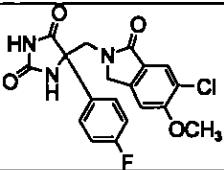
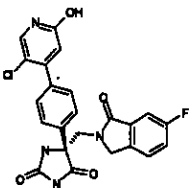
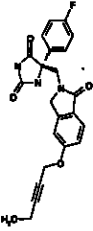
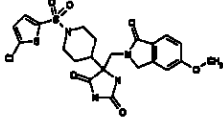
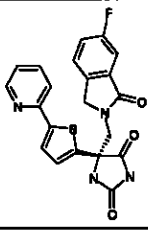
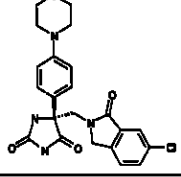
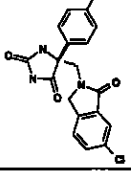
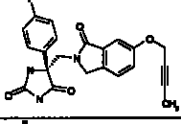
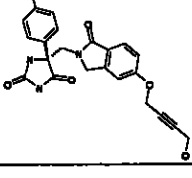
76. El compuesto de acuerdo con la reivindicación 75, en donde dicho compuesto se selecciona entre los compuestos de las estructuras mostradas a continuación:

453

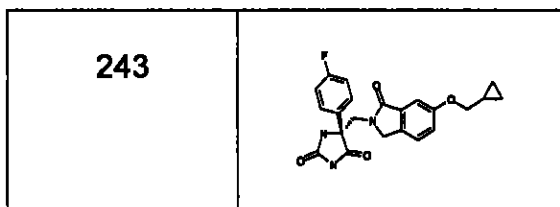
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Compuesto #	Estructura
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77. La composición farmacéutica de acuerdo con la reivindicación 1 que comprende adicionalmente por lo menos un portador farmacéuticamente aceptable.

78. Un método para tratar trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, comprendiendo dicho método administrar a un paciente que necesita de dicho tratamiento una composición farmacéutica la cual comprende cantidades terapéuticamente eficaces de por lo menos un compuesto de acuerdo con la reivindicación 1.

79. El uso de un compuesto de acuerdo con la reivindicación 1 para la manufactura de un medicamento para tratar trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos.

80. Un método para preparar una composición farmacéutica para el tratamiento de los trastornos asociados con TACE, TNF- α , MMPs, ADAMs o cualquier combinación de los mismos, comprendiendo dicho método poner en contacto íntimo por lo menos un compuesto de acuerdo con la reivindicación 1 y por lo menos un portador farmacéuticamente aceptable.

81. Una composición farmacéutica para tratar trastornos asociados con TACE, TNF- α , MMP, ADAM o cualquier combinación de los mismos en un sujeto que comprende, administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

82. Un compuesto de acuerdo con la reivindicación 1 en forma purificada.

83. Un método para tratar una afección o enfermedad mediada por TACE, MMPs, TNF- α , agrecanasa, o cualquier combinación de los mismos en un sujeto que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

84. Un método para tratar una afección o enfermedad seleccionada del grupo que consiste en artritis reumatoidea, osteoartritis, periodontitis, gingivitis, ulceración córnea, crecimiento de tumor sólido e invasión tumoral por metástasis secundaria, glaucoma neovascular, enfermedad inflamatoria del intestino, esclerosis múltiple y soriasis en un sujeto que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

85. Un método para tratar una afección o enfermedad seleccionada del grupo que consiste en fiebre, afecciones cardiovasculares, hemorragia, coagulación, caquexia, anorexia, alcoholismo, respuesta de fase aguda, infección aguda, choque, reacción injerto versus paciente, enfermedad autoinmune e infección de HIV en un sujeto que comprende, administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

86. Un método para tratar una afección o enfermedad seleccionada del grupo que consiste en choque séptico, choque hemodinámico, síndrome séptico, lesión por reperfusión pos-isquémica, malaria, infección micobacteriana, meningitis, soriasis, insuficiencia cardíaca congestiva, enfermedades fibróticas, caquexia, rechazo de injertos, cánceres tales como linfoma cutáneo de células T, enfermedades que involucran angiogénesis, enfermedades autoinmunes,

dermatitis, enfermedades inflamatorias del intestino tales como enfermedad de Crohn y colitis, osteoartritis y artritis reumatoidea, espondilitis anquilosante, artritis psoriásica, enfermedad de Still del adulto, ureitis, granulomatosis de Wegener, enfermedad de Behcehe, síndrome de Sjogren, sarcoidosis, polimiositis, dermatomiositis, esclerosis múltiple, ciática, síndrome de dolor regional complejo, lesión radiógena, lesión alveolar hiperóxica, enfermedad periodontal, HIV, diabetes mellitus insulina no dependiente, lupus eritematoso sistémico, glaucoma, sarcoidosis, fibrosis pulmonar idiopática, displasia broncopulmonar, enfermedad de la retina, esclerodermia, osteoporosis, isquemia renal, infarto de miocardio, accidente cerebrovascular, isquemia cerebral, nefritis, hepatitis, glomerulonefritis, alveolitis fibrosante criptogénica, soriasis, rechazo de órganos, dermatitis atópica, vasculitis, alergia, rinitis alérgica estacional, obstrucción reversible de las vías respiratorias, síndrome de distress respiratorio del adulto, asma, enfermedad pulmonar obstructiva crónica (COPD, correspondiente al término en inglés "chronic obstructive pulmonary disease") y bronquitis en un sujeto que comprende administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

87. Un método para tratar una afección o enfermedad asociada con COPD, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

88. Un método para tratar una afección o enfermedad asociada con artritis reumatoidea, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

89. Un método para tratar una afección o enfermedad asociada con la enfermedad de Crohn, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

90. Un método para tratar una afección o enfermedad asociada con soriasis, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

91. Un método para tratar una afección o enfermedad asociada con espondilitis anquilosante, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

92. Un método para tratar una afección o enfermedad asociada con ciática, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

93. Un método para tratar una afección o enfermedad asociada con el síndrome de dolor regional complejo, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

94. Un método para tratar una afección o enfermedad asociada con artritis soriásica, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto

de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable.

95. Un método para tratar una afección o enfermedad asociada con esclerosis múltiple, que comprende: administrar al sujeto que necesita de dicho tratamiento una cantidad terapéuticamente eficaz de por lo menos un compuesto de acuerdo con la reivindicación 1 o su sal, solvato o isómero farmacéuticamente aceptable, en combinación con un compuesto seleccionado del grupo que consiste en Avonex®, Betaseron, Copaxone u otros compuestos indicados para el tratamiento de la esclerosis múltiple.

96. El método de acuerdo con la reivindicación 84 que comprende además administrar a dicho sujeto una cantidad terapéuticamente eficaz de por lo menos un medicamento seleccionado del grupo formado por fármacos antirreumáticos modificadores de enfermedad (DMARDS, correspondiente a "disease modifying anti-rheumatic drugs"), fármacos antiinflamatorios no esteroides (NSAIDs, correspondiente a "non-steroidal anti-inflammatory drugs"), inhibidores selectivos de la ciclooxigenasa-2 (COX-2, correspondiente a "cycloxygenase-2"), inhibidores de COX-1, inmunosupresores, modificadores de la respuesta biológica (BRMs, correspondiente a "biological response modifiers"), agentes antiinflamatorios y antagonistas de H1.

97. Un método de acuerdo con la reivindicación 85, el cual comprende adicionalmente la administración a dicho sujeto de una cantidad terapéuticamente eficaz de por lo menos un medicamento seleccionado del grupo formado por DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1, inmunosupresores, BRMs, agentes antiinflamatorios y antagonistas de H1.

98. Un método de acuerdo con la reivindicación 86, el cual comprende adicionalmente la administración a dicho sujeto de una cantidad terapéuticamente eficaz de por lo menos un medicamento seleccionado del grupo formado por

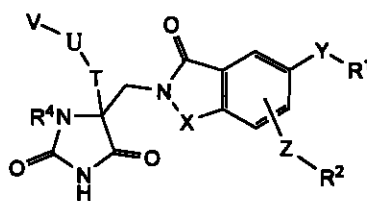
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DMARDS, NSAIDs, inhibidores de COX-2, inhibidores de COX-1,
inmunosupresores, BRMs, agentes antiinflamatorios y antagonistas de H1.

p.p.de: SCHERING CORPORATION

RESUMEN

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Esta invención se refiere a compuestos de la Fórmula (I):



(I)

o su sal, solvato o isómero farmacéuticamente aceptable, los cuales pueden ser útiles para el tratamiento de enfermedades o afecciones mediadas por MMPs, ADAMs, TACE, TNF- o sus combinaciones.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/06 C07D417/14 C07D401/14 C07D409/14 C07D413/14
A61P43/00 A61P29/00 A61K31/4178

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K 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, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KNABE J ET AL: "RAZEMATE UND ENANTIOMERE BASISCH SUBSTITUIERTER 5-PHENYLHYDANTOINE, SYNTHESE UND ANTIARRHYTHMISCHE WIRKUNG RACEMATES AND ENANTIOMERS OF BASIC SUBSTITUTED 5-PHENYLHYDANTOINS. SYNTHESSES AND ANTIARRHYTHMIC ACTIVITY" PHARMAZIE, DIE, PHARMAZEUTISCHER VERL., ESCHBORN, DE, vol. 52, no. 12, December 1997 (1997-12), pages 912-919, XP000995887 ISSN: 0031-7144 the whole document	1-98
A	WO 2004/024721 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; BURROWS, JEREMY, NICHOLAS; TUC) 25 March 2004 (2004-03-25) the whole document	1-98

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the International filing date but later than the priority date claimed

T later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the International search

9 November 2005

Date of mailing of the International search report

18/11/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

Authorized officer

Eberhard, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/024771

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AOP

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 78 and 83-98 are directed to methods of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004024721 A	25-03-2004	AU 2003263345 A1	30-04-2004
		AU 2003263347 A1	30-04-2004
		BR 0314275 A	09-08-2005
		CA 2497571 A1	25-03-2004
		CN 1681804 A	12-10-2005
		EP 1539740 A1	15-06-2005
		EP 1551826 A1	13-07-2005
		WO 2004024715 A1	25-03-2004



Industria y Comercio
SUPERINTENDENCIA

**REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT**

PATENTE DE INVENCION []

MODELO DE UTILIDAD []

- ♦ Indicación de que se solicita la concesión de 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 []

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ♦ Indicación de que se solicita el registro de Diseño Industrial []
- ♦ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ♦ Representación gráfica 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 []

- ♦ Indicación de que se solicita el registro de un Esquema de Trazado []
- ♦ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ♦ Representación gráfica del esquema trazado []
- ♦ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Fdo B

Firma Responsable

Fecha 16-Ene-6

Carrera 13.No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

466

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION

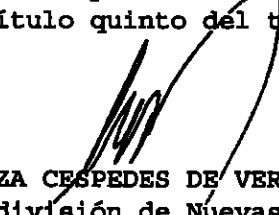
REFERENCIA	Radicación No.	07 3804
	Solicitud internacional	PCT/US2005/024771
	Fecha inicio fase nacional	16/02/2007
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	1543

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. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 02 FEB. 2007
adpa10