CSA296852

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Organización y Digitalización CSA Ltda

Industria y Comercio

SUPERINTENDENCIA

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-63496

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: DERIVADOS INDÓLICOS CON ANILLO UNIDO EN LAS POSICIONES 4,5 Y SUS MÉTODOS DE USO

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 18 de Junio de 2009

P2009/000123

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-063496- -00000-0000
Fecha: 2009-06-18 16:42:47 Dep: 2020 NUECREACIONE
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 658

PETITORIO - FORMULARIO
PATENTE
ENTRADA EN FASE NACIONAL **P2009/000123**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: SCHERING CORPORATION
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 E.U.A.
Nacionalidad o Domicilio: Estadounidense
Lugar de Constitución: Estados Unidos

Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

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E-mail: office@olarteraisbeck.com

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Número 79.782.747 Btá
TP 74.295

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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/025754 Fecha Diciembre 17, 2007

Publicación Internacional No. WO 2008/082484 Fecha Julio 10, 2008

(6) **Título (54)** **DERIVADOS INDÓLICOS CON ANILLO UNIDO EN LAS POSICIONES 4,5 Y SUS MÉTODOS DE USO**

Clasificación Internacional (51) C07D 209/60, C07D 401/06, C07D 401/14, C07D 403/06, C07D 471/04, C07D 491/04, A61K 31/407, A61P 31/12, C07D 401/04, C07D 487/04, C07D 495/04, C07D 513/04

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Diciembre 22, 2006	60/876.877

(9) **Comprobante de pago No.** 09-44,591 **Fecha** Junio 16 de 2009

ANEXOS

X	Comprobante de pago de la tasa de presentación de la solicitud.
X	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
X	Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-033682
	Documento de cesión del inventor al solicitante o a su causante.
	Declaraciones
X	Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
X	Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
	Traducción del examen preliminar internacional efectuado por la IPEA.
	De ser el caso, copia del contrato de acceso.
	De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
	De ser el caso, certificado de depósito del material biológico.
	Arte final 12 x 12.
	De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
	De ser el caso, modificaciones efectuadas a la solicitud internacional.
X	Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-063496- -00000-0000

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Act. 411 PRESENTACION Folios: 658

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 44,591
FECHA : JUNIO 16 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800155	16/06/2009	6,975,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
		TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

6

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 Marguertie 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 copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

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

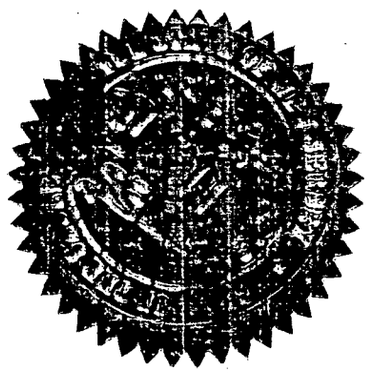
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK

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

Poder

El suscrito,

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

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

Signature/Firma: _____

Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

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

OLARTERAISBECK

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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.SA.
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.

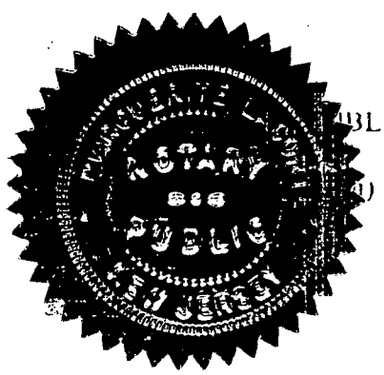
2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que
con sede principal ubicada en
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

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 July 2008 (10.07.2008)

PCT

(10) International Publication Number
WO 2008/082484 A1

(51) International Patent Classification:
C07D 209/60 (2006.01) *A61K 31/407* (2006.01)
C07D 401/06 (2006.01) *A61P 31/12* (2006.01)
C07D 401/14 (2006.01) *C07D 401/04* (2006.01)
C07D 403/06 (2006.01) *C07D 487/04* (2006.01)
C07D 471/04 (2006.01) *C07D 495/04* (2006.01)
C07D 491/04 (2006.01) *C07D 513/04* (2006.01)

(21) International Application Number:
PCT/US2007/025754

(22) International Filing Date:
17 December 2007 (17.12.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/876,877 22 December 2006 (22.12.2006) US

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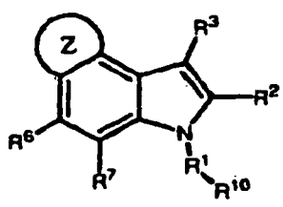
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN,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

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

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

(54) Title: 4,5-RING ANNULATED INDOLE DERIVATIVES FOR TREATING OR PREVENTING OF HCV AND RELATED VIRAL INFECTIONS



(I)

(57) Abstract: The present invention relates to 4,5-ring annulated indole derivatives, compositions comprising at least one 4,5-ring annulated indole derivatives, and methods of using the 4,5-ring annulated indole derivatives for treating or preventing a viral infection or a virus-related disorder in a patient. Wherein ring Z, of formula (I), is a cyclopentyl, cyclopentenyl, 5-membered heterocycloalkyl, 5-membered heterocycloalkenyl or 5-membered heteroaryl ring.

WO 2008/082484 A1

4,5-RING ANNULATED INDOLE DERIVATIVES FOR TREATING OR PREVENTING OF HCV AND RELATED VIRAL INFECTIONS

FIELD OF THE INVENTION

The present invention relates to 4,5-ring annulated indole derivatives, compositions comprising at least one 4,5-ring annulated indole derivatives, and methods of using the 4,5-ring annulated indole derivatives for treating or preventing a viral infection or a virus-related disorder in a patient.

BACKGROUND OF THE INVENTION

HCV is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH). NANBH is distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis delta virus (HDV), as well as from other forms of liver disease such as alcoholism and primary biliary cirrhosis.

Hepatitis C virus is a member of the hepacivirus genus in the family Flaviviridae. It is the major causative agent of non-A, non-B viral hepatitis and is the major cause of transfusion-associated hepatitis and accounts for a significant proportion of hepatitis cases worldwide. Although acute HCV infection is often asymptomatic, nearly 80% of cases resolve to chronic hepatitis. About 60% of patients develop liver disease with various clinical outcomes ranging from an asymptomatic carrier state to chronic active hepatitis and liver cirrhosis (occurring in about 20% of patients), which is strongly associated with the development of hepatocellular carcinoma (occurring in about 1-5% of patients). The World Health Organization estimates that 170 million people are chronically infected with HCV, with an estimated 4 million living in the United States.

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection remains poor as HCV infection is more difficult to treat than other forms of hepatitis. Current data indicates a four-year survival rate of below 50% for patients suffering from cirrhosis and a five-year survival rate of below 30% for patients diagnosed with localized resectable hepatocellular carcinoma. Patients diagnosed with localized unresectable hepatocellular carcinoma fare even worse, having a five-year survival rate of less than 1%.

HCV is an enveloped RNA virus containing a single-stranded positive-sense RNA genome approximately 9.5 kb in length. The RNA genome contains a 5'-nontranslated region (5' NTR) of 341 nucleotides, a large open reading frame (ORF) encoding a single polypeptide of 3,010 to 3,040 amino acids, and a 3'-nontranslated region (3'-NTR) of variable length of about 230 nucleotides. HCV is similar in amino acid sequence and genome organization to flaviviruses and pestiviruses, and therefore HCV has been classified as a third genus of the family Flaviviridae.

The 5' NTR, one of the most conserved regions of the viral genome, contains an internal ribosome entry site (IRES) which plays a pivotal role in the initiation of translation of the viral polyprotein. A single long open reading frame encodes a polyprotein, which is co- or post-translationally processed into structural (core, E1, E2 and p7) and nonstructural (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) viral proteins by either cellular or viral proteinases. The 3' NTR consists of three distinct regions: a variable region of about 38 nucleotides following the stop codon of the polyprotein, a polyuridine tract of variable length with interspersed substitutions of cytidines, and 98 nucleotides (nt) at the very 3' end which are highly conserved among various HCV isolates. By analogy to other plus-strand RNA viruses, the 3'-NTR is thought to play an important role in viral RNA synthesis. The order of the genes within the genome is: NH_2-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH.

Processing of the structural proteins core (C), envelope protein 1 and (E1, E2), and the p7 region is mediated by host signal peptidases. In contrast, maturation of the nonstructural (NS) region is accomplished by two viral enzymes. The HCV polyprotein is first cleaved by a host signal peptidase generating the structural proteins C/E1, E1/E2, E2/p7, and p7/NS2. The NS2-3 proteinase, which is a metalloprotease, then cleaves at the NS2/NS3 junction. The NS3/4A proteinase complex (NS3 being a serine protease and NS4A acting as a cofactor of the NS3 protease), is then responsible for processing all the remaining cleavage junctions. RNA helicase and NTPase activities have also been identified in the NS3 protein. One-third of the NS3 protein functions as a protease, and the remaining two-thirds of the molecule acts as the helicase/ATPase that is thought to be involved in HCV replication. NS5A may be phosphorylated and acts as a putative cofactor of NS5B. The fourth viral enzyme, NS5B, is a membrane-associated RNA-dependent RNA polymerase (RdRp) and a key component responsible for replication of the viral RNA genome. NS5B contains the "GDD" sequence motif, which is highly conserved among all RdRps characterized to date.

Replication of HCV is thought to occur in membrane-associated replication complexes. Within these, the genomic plus-strand RNA is transcribed into minus-strand RNA, which in turn can be used as a template for synthesis of progeny genomic plus-strands. At least two viral enzymes appear to be involved in this reaction: the NS3 helicase/NTPase, and the NS5B RNA-dependent RNA polymerase. While the role of NS3 in RNA replication is less clear, NS5B is the key enzyme responsible for synthesis of progeny RNA strands. Using recombinant baculoviruses to express NS5B in insect cells and a synthetic nonviral RNA as a substrate, two enzymatic activities have been identified as being associated with it: a primer-dependent RdRp and a terminal transferase (TNTase) activity. It was subsequently confirmed and further characterized through the use of the HCV RNA genome as a substrate. Other studies have shown that NS5B with a C-terminal 21 amino-acid truncation expressed in Escherichia coli is also active for *in vitro* RNA synthesis. On certain RNA templates, NS5B has been shown to catalyze RNA synthesis via a *de novo* initiation mechanism, which has been postulated to be the mode of viral replication *in vivo*. Templates with single-stranded 3' termini, especially those containing a 3'-terminal cytidylate moiety, have been found to direct *de novo* synthesis efficiently. There has also been evidence for NS5B to utilize di- or tri-nucleotides as short primers to initiate replication.

It is well-established that persistent infection of HCV is related to chronic hepatitis, and as such, inhibition of HCV replication is a viable strategy for the prevention of hepatocellular carcinoma. Present treatment approaches for HCV infection suffer from poor efficacy and unfavorable side-effects and there is currently a strong effort directed to the discovery of HCV replication inhibitors that are useful for the treatment and prevention of HCV related disorders. New approaches currently under investigation include the development of prophylactic and therapeutic vaccines, the identification of interferons with improved pharmacokinetic characteristics, and the discovery of agents designed to inhibit the function of three major viral proteins: protease, helicase and polymerase. In addition, the HCV RNA genome itself, particularly the IRES element, is being actively exploited as an antiviral target using antisense molecules and catalytic ribozymes.

Particular therapies for HCV infection include α-interferon monotherapy and combination therapy comprising α-interferon and ribavirin. These therapies have been shown to be effective in some patients with chronic HCV infection. The use of antisense oligonucleotides for treatment of HCV infection has also been proposed as has the use of free

bile acids, such as ursodeoxycholic acid and chenodeoxycholic acid, and conjugated bile acids, such as tauroursodeoxycholic acid. Phosphonoformic acid esters have also been proposed as potentially for the treatment of various viral infections including HCV. Vaccine development, however, has been hampered by the high degree of viral strain heterogeneity and immune evasion and the lack of protection against reinfection, even with the same inoculum.

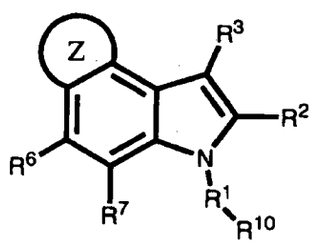
The development of small-molecule inhibitors directed against specific viral targets has become a major focus of anti-HCV research. The determination of crystal structures for NS3 protease, NS3 RNA helicase, and NS5B polymerase, with and without bound ligands, has provided important structural insights useful for the rational design of specific inhibitors.

NS5B, the RNA-dependent RNA polymerase, is an important and attractive target for small-molecule inhibitors. Studies with pestiviruses have shown that the small molecule compound VP32947 (3-[((2-dipropylamino)ethyl)thio]-5H-1,2,4-triazino[5,6-b]indole) is a potent inhibitor of pestivirus replication and most likely inhibits the NS5B enzyme since resistant strains are mutated in this gene. Inhibition of RdRp activity by (-)β-L-2',3'-dideoxy-3'-thiacytidine 5'-triphosphate (3TC; lamivudine triphosphate) and phosphonoacetic acid also has been observed.

Despite the intensive effort directed at the treatment and prevention of HCV and related viral infections, there exists a need in the art for non-peptide, small-molecule compounds having desirable or improved physicochemical properties that are useful for inhibiting viruses and treating viral infections and virus-related disorders.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides 4,5-ring annulated indole deriviatives (herein referred to as the "Compounds of Formula (I)"):



(I)

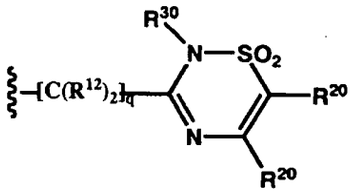
and pharmaceutically acceptable salts and solvates thereof,

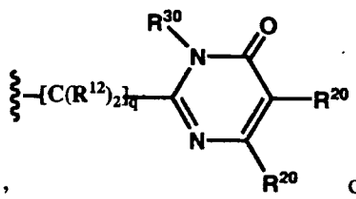
wherein

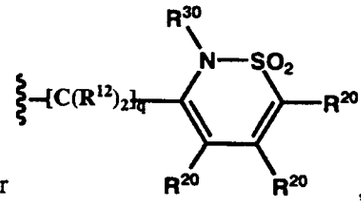
ring Z, of formula (I), is a cyclopentyl, cyclopentenyl, 5-membered heterocycloalkyl, 5-membered heterocycloalkenyl or 5-membered heteroaryl ring, wherein ring Z may be: (i) optionally substituted on one or more ring carbon atoms with substituents, which are the same or different, and which are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$; and/or (ii) optionally substituted on a ring nitrogen atom with substituents, which are the same or different, and which are selected from alkyl, aryl, haloalkyl, heteroaryl, hydroxyalkyl, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_r-OR^9$, $-[C(R^{12})_2]_r-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$;

R^1 is a bond, $-[C(R^{12})_2]_r-$, $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$, or $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$;

R^2 is $-C(O)R^9$, $-C(O)OR^9$, $-C(O)OCH_2OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)N(R^9)C=N(R^9)_2$, $-[C(R^{12})_2]_q$-aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heteroaryl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$, alkyl,



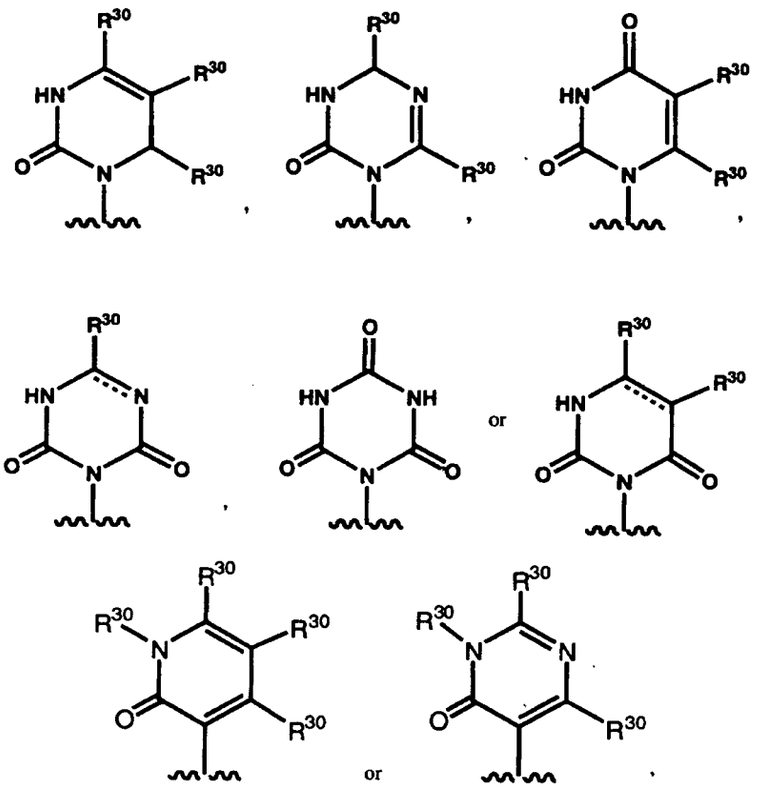
,


or


,

wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, group can be optionally substituted with up to 4 substituents, which are each independently selected from alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q$-heteroaryl, $-[C(R^{12})_2]_q$-haloalkyl, $-[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ and $-SO_2N(R^9)C(O)N(R^9)_2$;

R^3 is –H, $-[C(R^{12})_2]_q$-alkyl, $-[C(R^{12})_2]_q$-aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heteroaryl or $-[C(R^{12})_2]_q$-heterocycloalkenyl,



wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$;

R^6 and R^7 are each, independently, H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, $-[C(R^{12})_2]_q-$haloalkyl, $-[C(R^{12})_2]_q-$hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ or $-SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^8 is independently H, alkyl, alkenyl, alkynyl, $-[C(R^{12})_2]_q-$aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, haloalkyl or hydroxyalkyl;

each occurrence of R^9 is independently H, alkyl, alkenyl, alkynyl, -$[C(R^{12})_2]_q$-aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, haloalkyl or hydroxyalkyl, or two R^9 groups that are attached to a common nitrogen atom, together with the nitrogen atom to which they are attached, combine to form a heterocycloalkyl, heterocycloalkenyl or heteroaryl group;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from H, alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ and -$SO_2N(R^9)C(O)N(R^9)_2$, such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, haloalkyl, hydroxy or hydroxyalkyl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from –H, alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2$alkyl, -$[C(R^{12})_2]_q$-$NHSO_2$cycloalkyl, -$[C(R^{12})_2]_q$-$NHSO_2$aryl, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ and -$SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^{12} is independently H, halo, -$N(R^9)_2$, -OR^9, alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with up to 4 substituents, which are each independently selected from alkyl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)NHalkyl, -$C(O)N(alkyl)_2$, -O-alkyl, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -NHC(O)alkyl, -$NHSO_2$alkyl, -SO_2alkyl or -SO_2NH-alkyl, or two R^{12}

groups, together with the carbon atoms to which they are attached, join to form a cycloalkyl, heterocycloalkyl or C=O group;

each occurrence of R^{20} is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl, or both R^{20} groups and the carbon atoms to which they are attached, join to form a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group wherein a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group can be substituted with up to 4 groups, which are each independently selected from alkyl, alkenyl, alkynyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q$-haloalkyl, $-[C(R^{12})_2]_q$-hydroxyalkyl, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ and $-SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^{30} is independently H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q$-heteroaryl, $-[C(R^{12})_2]_q$-haloalkyl, $-[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ or $-SO_2N(R^9)C(O)N(R^9)_2$, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form a -3- to 7-membered ring selected from aryl, cycloalkyl, heteroaryl and heterocycloalkyl;

each occurrence of p is independently 0, 1 or 2;

each occurrence of q is independently an integer ranging from 0 to 4; and

each occurrence of r is independently an integer ranging from 1 to 4.

The Compounds of Formula (I) or pharmaceutically acceptable salts, solvates, prodrugs or esters thereof can be useful for treating or preventing a viral infection in a patient.

The Compounds of Formula (I) or pharmaceutically acceptable salts, solvates, prodrugs or esters thereof can be useful for treating or preventing a virus-related disorder in a patient.

Also provided by the invention are methods for treating or preventing a viral infection or a virus-related disorder in a patient, comprising administering to the patient an effective amount of at least one Compound of Formula (I).

The present invention further provides pharmaceutical compositions comprising an effective amount of at least one Compound of Formula (I) or a pharmaceutically acceptable salt, solvate thereof, and a pharmaceutically acceptable carrier. The compositions can be useful for treating or preventing a viral infection or a virus-related disorder in a patient.

The details of the invention are set forth in the accompanying detailed description below.

Although any methods and materials similar to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and the claims. All patents and publications cited in this specification are incorporated herein by reference.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides Compounds of Formula (I), pharmaceutical compositions comprising at least one Compound of Formula (I), and methods of using the Compounds of Formula (I) for treating or preventing a viral infection or a virus-related disorder in a patient.

Definitions and Abbreviations

The terms used herein have their ordinary meaning and the meaning of such terms is independent at each occurrence thereof. That notwithstanding and except where stated otherwise, the following definitions apply throughout the specification and claims. Chemical names, common names, and chemical structures may be used interchangeably to describe the same structure. If a chemical compound is referred to using both a chemical structure and a chemical name and an ambiguity exists between the structure and the name, the structure predominates. These definitions apply regardless of whether a term is used by itself or in combination with other terms, unless otherwise indicated. Hence, the definition of "alkyl" applies to "alkyl" as well as the "alkyl" portions of "hydroxyalkyl," "haloalkyl," "alkoxy," etc...

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

A "patient" is a human or non-human mammal. In one embodiment, a patient is a human. In another embodiment, a patient is a non-human mammal, including, but not limited

to, a monkey, dog, baboon, rhesus, mouse, rat, horse, cat or rabbit. In another embodiment, a patient is a companion animal, including but not limited to a dog, cat, rabbit, horse or ferret. In one embodiment, a patient is a dog. In another embodiment, a patient is a cat.

The term "alkyl" as used herein, refers to an aliphatic hydrocarbon group, wherein one of the aliphatic hydrocarbon group's hydrogen atoms is replaced with a single bond. An alkyl group can be straight or branched and can contain from about 1 to about 20 carbon atoms. In one embodiment, an alkyl group contains from about 1 to about 12 carbon atoms. In another embodiment, an alkyl group contains from about 1 to about 6 carbon atoms. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, isopentyl, n-hexyl, isohexyl and neohexyl. An alkyl group may be unsubstituted or optionally substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkenyl, alkynyl, -O-aryl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, cyano, -OH, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH-aryl, -NH-heteroaryl, -NHC(O)-alkyl, -NHC(O)NH-alkyl, $-NHSO_2$-alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NH(cycloalkyl), -OC(O)-alkyl, -OC(O)-aryl, -OC(O)-cycloalkyl, -C(O)alkyl, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkyl group is unsubstituted. In another embodiment, an alkyl group is a straight chain alkyl group. In another embodiment, an alkyl group is a branched alkyl group.

The term "alkenyl" as used herein, refers to an aliphatic hydrocarbon group having at least one carbon-carbon double bond, wherein one of the aliphatic hydrocarbon group's hydrogen atoms is replaced with a single bond. An alkenyl group can be straight or branched and can contain from about 2 to about 15 carbon atoms. In one embodiment, an alkenyl group contains from about 2 to about 10 carbon atoms. In another embodiment, an alkenyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of illustrative alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl. An alkenyl group may be unsubstituted or optionally 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, alkynyl, -O-aryl, aryl, cycloalkyl, cycloalkenyl, cyano, -OH, -O-alkyl, -O-haloalkyl, -alkylene-O-alkyl, alkylthio, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NH-aryl, -NH-heteroaryl, -NHC(O)-alkyl, -NHC(O)NH-alkyl, $-NHSO_2$-alkyl, $-NHSO_2$-aryl, $-NHSO_2$-heteroaryl, -NH(cycloalkyl), -OC(O)-alkyl, -OC(O)-aryl, -OC(O)-cycloalkyl, -

C(O)alkyl, -C(O)NH_2, -C(O)NH-alkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkenyl group is unsubstituted. In another embodiment, an alkenyl group is a straight chain alkenyl group. In another embodiment, an alkyl group is a branched alkenyl group.

The term "alkynyl" as used herein, refers to an aliphatic hydrocarbon group having at least one carbon-carbon triple bond, wherein one of the aliphatic hydrocarbon group's hydrogen atoms is replaced with a single bond. An alkynyl group can be straight or branched and can contain from about 2 to about 15 carbon atoms. In one embodiment, an alkynyl group contains from about 2 to about 10 carbon atoms. In another embodiment, an alkynyl group contains from about 2 to about 6 carbon atoms. Non-limiting examples of illustrative alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. An alkynyl group may be unsubstituted or optionally 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, alkenyl, -O-aryl, aryl, cycloalkyl, cycloalkenyl, cyano, -OH, -O-alkyl, -alkylene-O-alkyl, -O-haloalkyl, -alkylthio, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -NH-aryl, -NH-heteroaryl, -NHC(O)-alkyl, -NHC(O)NH-alkyl, -$NHSO_2$-alkyl, -$NHSO_2$-aryl, -$NHSO_2$-heteroaryl, -NH(cycloalkyl), -OC(O)-alkyl, -OC(O)-aryl, -OC(O)-cycloalkyl, -C(O)alkyl, -C(O)NH_2, -C(O)NH-alkyl, -C(O)OH and –C(O)O-alkyl. In one embodiment, an alkynyl group is unsubstituted. In another embodiment, an alkynyl group is a straight chain alkynyl group. In another embodiment, an alkynyl group is a branched alkynyl group.

The term "alkylene" as used herein, refers to an alkyl group, as defined above, wherein one of the alkyl group's hydrogen atoms is replaced with a bond. Illustrative examples of alkylene include, but are not limited to, -CH_2-, -CH_2CH_2-, -$CH_2CH_2CH_2$-, -$CH_2CH_2CH_2CH_2$-, -$CH(CH_3)CH_2CH_2$-, -$CH_2CH(CH_3)CH_2$- and -$CH_2CH_2CH(CH_3)$-. In one embodiment, an alkylene group is a straight chain alkylene group. In another embodiment, an alkylene group is a branched alkylene group.

"Aryl" means an aromatic monocyclic or multicyclic ring system having from about 6 to about 14 ring carbon atoms. In one embodiment, an aryl group has from about 6 to about 10 ring carbon atoms. An 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 below. Non-limiting examples of illustrative aryl groups include phenyl and naphthyl. In one embodiment, an aryl group is unsubstituted. In another embodiment, an aryl group is a phenyl group.

The term "cycloalkyl" as used herein, refers to a non-aromatic mono- or multicyclic ring system having from about 3 to about 10 ring carbon atoms. In one embodiment, a cycloalkyl has from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkyl has from about 5 to about 7 ring carbon atoms. Non-limiting examples of illustrative monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of illustrative multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like. A cycloalkyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkyl group is unsubstituted.

The term "cycloalkenyl" as used herein, refers to a non-aromatic mono- or multicyclic ring system comprising from about 3 to about 10 ring carbon atoms and containing at least one endocyclic double bond. In one embodiment, a cycloalkenyl contains from about 5 to about 10 ring carbon atoms. In another embodiment, a cycloalkenyl contains 5 or 6 ring carbon atoms. Non-limiting examples of illustrative monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. A cycloalkenyl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein below. In one embodiment, a cycloalkenyl group is unsubstituted.

The term "5-membered cycloalkenyl" as used herein, refers to a cycloalkenyl group, as defined above, which has 5 ring carbon atoms.

The term "halo" as used herein, means –F, -Cl, -Br or -I. In one embodiment, halo refers to –Cl or -F.

The term "haloalkyl" as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with a halogen. In one embodiment, a haloalkyl group has from 1 to 6 carbon atoms. In another embodiment, a halcalkyl group is substituted with from 1 to 3 F atoms. Non-limiting examples of illustrative haloalkyl groups include $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ and $-CCl_3$.

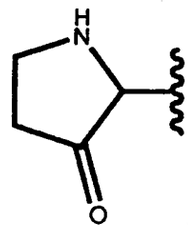
The term "hydroxyalkyl" as used herein, refers to an alkyl group as defined above, wherein one or more of the alkyl group's hydrogen atoms has been replaced with an –OH group. In one embodiment, a hydroxyalkyl group has from 1 to 6 carbon atoms. Non-limiting examples of illustrative hydroxyalkyl groups include hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 4-hydroxybutyl and $-CH(OH)CH_2CH_3$.

The term "heteroaryl" as used herein, refers to an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, wherein from 1 to 4 of the ring atoms is independently O, N or S and the remaining ring atoms are carbon atoms. In one embodiment, a heteroaryl group has 5 to 10 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms. In another embodiment, a heteroaryl group is monocyclic and has 5 or 6 ring atoms and at least one nitrogen ring atom. A heteroaryl group can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein below. A heteroaryl group is joined via a ring carbon atom and any nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. The term "heteroaryl" also encompasses a heteroaryl group, as defined above, which has been fused to a benzene ring. Non-limiting examples of illustrative heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl, indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, 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. In one embodiment, a heteroaryl group is a 6-membered heteroaryl group. In another embodiment, a heteroaryl group is a 5-membered heteroaryl group.

The term "5-membered heteroaryl" as used herein, refers to a heteroaryl group, as defined above, which has 5 ring atoms.

The term "heterocycloalkyl" as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 10 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S or N and the remainder of the ring atoms are carbon atoms. In one embodiment, a heterocycloalkyl group has from about 5 to about 10 ring atoms. In another embodiment, a heterocycloalkyl group has 5 or 6 ring atoms. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Any –NH group in a heterocycloalkyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protected heterocycloalkyl groups are considered part of this invention. A heterocycloalkyl group can be optionally substituted by one or more "ring system substituents"

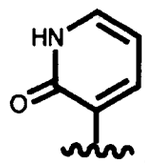
which may be the same or different, and are as defined herein below. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of illustrative monocyclic heterocycloalkyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. A ring carbon atom of a heterocycloalkyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocycloalkyl group is is pyrrolidonyl:



In one embodiment, a heterocycloalkyl group is a 6-membered heterocycloalkyl group. In another embodiment, a heterocycloalkyl group is a 5-membered heterocycloalkyl group.

The term "5-membered heterocycloalkyl" as used herein, refers to a heterocycloalkyl group, as defined above, which has 5 ring atoms.

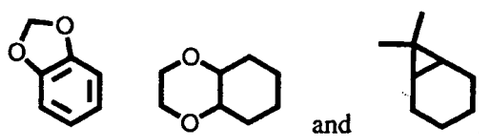
The term "heterocycloalkenyl" as used herein, refers to a heterocycloalkyl group, as defined above, wherein the heterocycloalkyl group contains from 3 to 10 ring atoms, and at least one endocyclic carbon-carbon or carbon-nitrogen double bond. In one embodiment, a heterocycloalkenyl group has from 5 to 10 ring atoms. In another embodiment, a heterocycloalkenyl group is monocyclic and has 5 or 6 ring atoms. A heterocycloalkenyl group can optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocycloalkenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of illustrative heterocycloalkenyl groups include 1,2,3,4- tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, pyridone, 2-pyridone, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, pyridone, 2-pyridone, dihydrothiophenyl, dihydrothiopyranyl, and the like. A ring carbon atom of a heterocyclenyl group may be functionalized as a carbonyl group. An illustrative example of such a heterocyclenyl group is:



In one embodiment, a heterocycloalkenyl group is a 6-membered heterocycloalkenyl group. In another embodiment, a heterocycloalkenyl group is a 5-membered heterocycloalkenyl group.

The term "5-membered heterocycloalkenyl" as used herein, refers to a heterocycloalkenyl group, as defined above, which has 5 ring atoms.

The term "ring system substituent" as used herein, refers to a substituent group 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, -OH, hydroxyalkyl, -O-alkyl, -alkylene-O-alkyl, -O-aryl, aralkoxy, acyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -OC(O)-alkyl, -OC(O)-aryl, -OC(O)-cycloalkyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkylene-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_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:



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

The terms "purified", "in purified form" or "in isolated and purified form" as used herein, for a compound refers to the physical state of said compound after being isolated from a synthetic process (e.g. from a reaction mixture), or natural source or combination thereof. Thus, the term "purified", "in purified form" or "in isolated and 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 (e.g., chromatography, recrystallization and the like) , 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, R^{11}, etc.) occurs more than one time in any constituent or in Formula (I) or (II), its definition on each occurrence is independent of its definition at every other occurrence, unless otherwise noted.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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. The term "prodrug" as used herein, refers to a compound (e.g, a drug precursor) that is transformed *in vivo* to provide a Compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through

hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a Compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C_1-C_2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a Compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, -P(O)(O(C_1-C_6)alkyl)$_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a Compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-

N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —C(Y^4)Y^5 wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "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 illustrative solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

One or more compounds of the invention may optionally be converted to a solvate. Preparation of solvates is generally known. Thus, for example, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

The term "effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention that is effective to treat or prevent a viral infection or a virus-related disorder.

Metabolic conjugates, such as glucuronides and sulfates which can undergo reversible conversion to the Compounds of Formula (I) are contemplated in the present invention.

The Compounds of Formula (I) may form salts, and all such salts are contemplated 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.

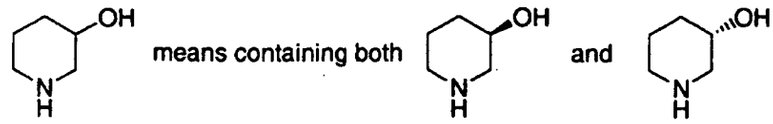
All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

The Compounds of Formula (I) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the Compounds of Formula (I) as well as mixtures thereof, including racemic mixtures, form part of the present invention. In addition, the present invention embraces all geometric and positional isomers. For example, if a Compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

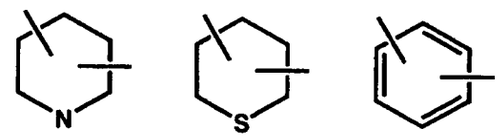
Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. Also, some of the Compounds of Formula (I) may be atropisomers (e.g., substituted biaryls) and are considered as part of this invention. Enantiomers can also be separated by use of chiral HPLC column.

The straight line ——— as a bond generally indicates a mixture of, or either of, the possible isomers, non-limiting example(s) include, containing (R)- and (S)- stereochemistry. For example,



A dashed line (-----) represents an optional bond.

Lines drawn into the ring systems, such as, for example:



indicate that the indicated line (bond) may be attached to any of the substitutable ring atoms, non limiting examples include carbon, nitrogen and sulfur ring atoms.

As well known in the art, a bond drawn from a particular atom wherein no moiety is depicted at the terminal end of the bond indicates a methyl group bound through that bond to the atom, unless stated otherwise. For example:



All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates, hydrates, esters and prodrugs of the compounds as well as the salts, solvates and esters 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). For example, if a Compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention.

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", "ester", "prodrug" and the like, is intended to equally apply to the salt, solvate, ester and prodrug of enantiomers, stereoisomers, rotamers, positional isomers, racemates or prodrugs of the inventive compounds.

The present invention also embraces isotopically-labelled compounds of the present invention which are identical to those recited herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Such compounds are useful as therapeutic, diagnostic or research reagents. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

Certain isotopically-labelled Compounds of Formula (I) (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled Compounds of Formula (I) can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein below, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

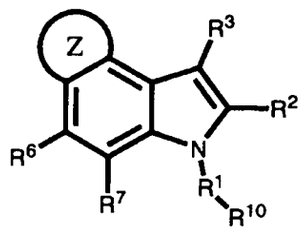
Polymorphic forms of the Compounds of Formula (I), and of the salts, solvates, hydrates, esters and prodrugs of the Compounds of Formula (I), are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings: BINAP is racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; CSA is camphorsulfonic acid; DBPD is 2-(Di-t-butylphosphino)biphenyl, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, DBN is 1,5-diazabicyclo[4.3.0]non-5-ene; DCC is dicyclohexylcarbodiimide; DCM is dichloromethane; Dibal-H is diisobutylaluminum hydride; DMF is dimethylformamide; EDCI is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; HATU is N-(diethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-1-ylmethylene]-N-methylmethanaminium Hexafluorophosphate N-oxide; HOBT is 1-hydroxybenzotriazole; LAH is lithium aluminum hydride; LDA is lithium diisopropylamide; m-CPBA is m-chloroperbenzoic acid;

$NaBH(OAc)_3$ is sodium triacetoxyborohydride; $NaBH_4$ is sodium borohydride; $NaBH_3CN$ is sodium cyanoborohydride; NaHMDS is sodium hexamethyl disilylazide; p-TsOH is p-toluenesulfonic acid; p-TsCl is p-toluenesulfonyl chloride; PPTS is pyridinium p-toluenesulfonate; TMAD is N,N,N',N'-tetramethylazodicarboxamide; HRMS is high resolution mass spectrometry; HPLC is high performance liquid chromatography; LRMS is low resolution mass spectrometry; Tr is triphenylmethyl; Tris is tris (hydroxymethyl)aminomethane; THF is tetrahydrofuran; TFA is trifluoroacetic acid; Ci/mmol is Curie/mmol (a measure of specific activity); and Ki represents the dissociation constant for a substrate/receptor complex.

The Compounds of Formula (I)

The present invention provides Compounds of Formula (I):



(I)

and pharmaceutically acceptable salts and solvates thereof, wherein R^1, R^2, R^3, R^6, R^7, R^{10} and Z are defined above for the Compounds of Formula (I).

In one embodiment, when R^1 is a bond, R^{10} is not H.

In another embodiment, R^1 is a bond or $-[C(R^{12})_2]_r-$.

In another embodiment, R^1 is a bond.

In another embodiment, R^1 is $-CH_2-$.

In still another embodiment, R^1 is $-[C(R^{12})_2]_r-$.

In another embodiment, R^1 is $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$.

In still another embodiment, R^1 is $-[C(R^{12})_2]_r-NR^9-[C(R^{12})_2]_q-$.

In yet another embodiment, R^1 is $-[C(R^{12})_2]_q-C=C-[C(R^{12})_2]_q-$.

In a further embodiment, R^1 is $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$.

In another embodiment, R^1 is $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$.

In one embodiment, R^{10} is –H.

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

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

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

In a further embodiment, R^{10} is heterocycloalkyl.

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

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

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

In one embodiment, R^{10} is aryl or heteroaryl.

In another embodiment, R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

In another embodiment, R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from methyl, cyclopropyl, halo, -OH, $-NH_2$, $-NHCH_3$ and $-N(CH_3)_2$.

In another embodiment, R^{10} is quinoline, quinolinone, pteridine or pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

In still another embodiment, R^{10} is pteridine or pteridinone, either of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

In one embodiment, R^{10} is quinoline or quinolinone, either of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

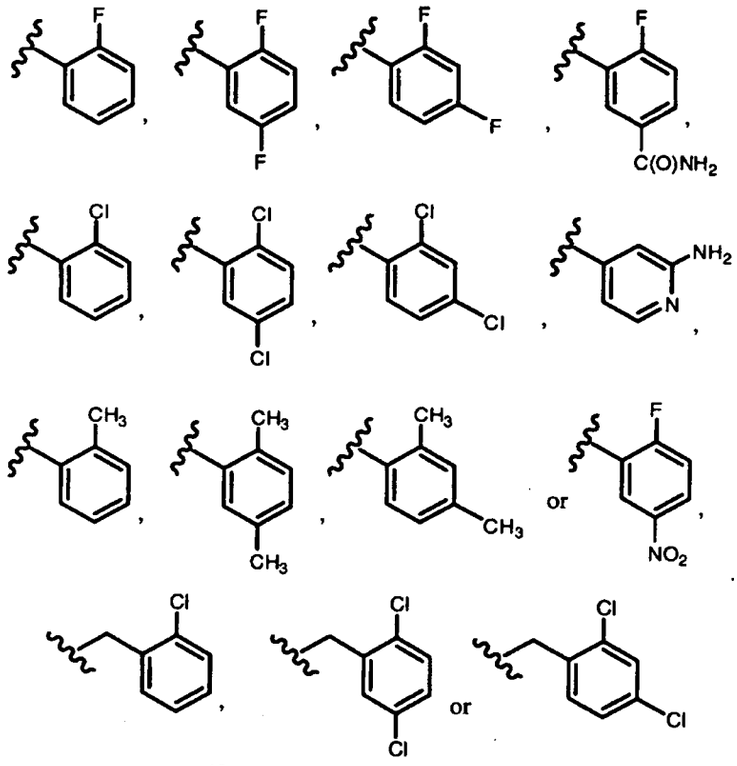
In another embodiment, R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or

different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO_2R^{11}, -S(O)$_p R^{11}$ or -SO_2N(R^9)$_2$.

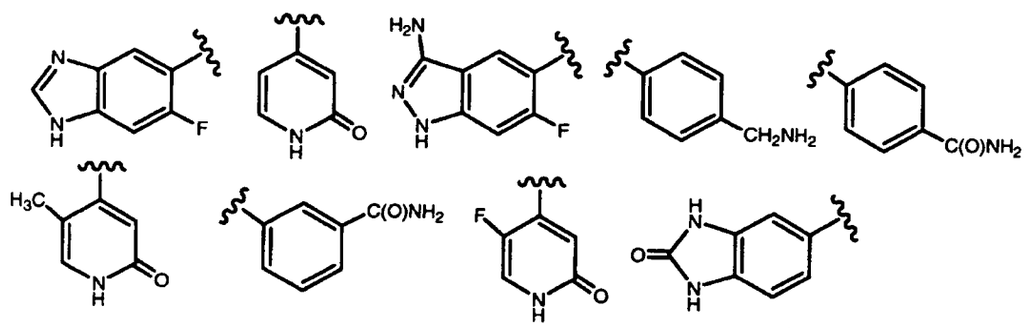
In one embodiment, R^{10} is phenyl.

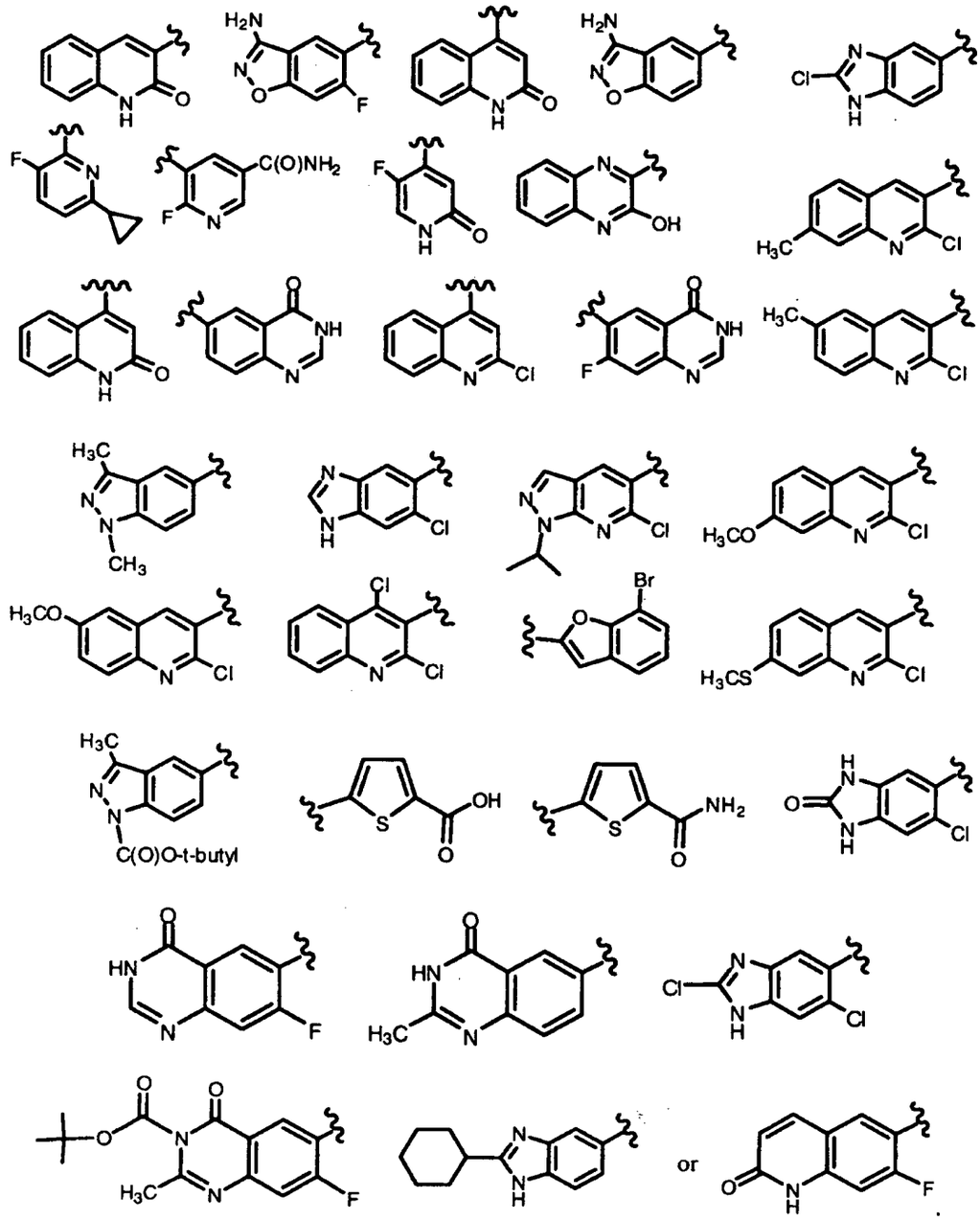
In another embodiment, R^{10} is pyridyl.

In one embodiment, R^{10} is:

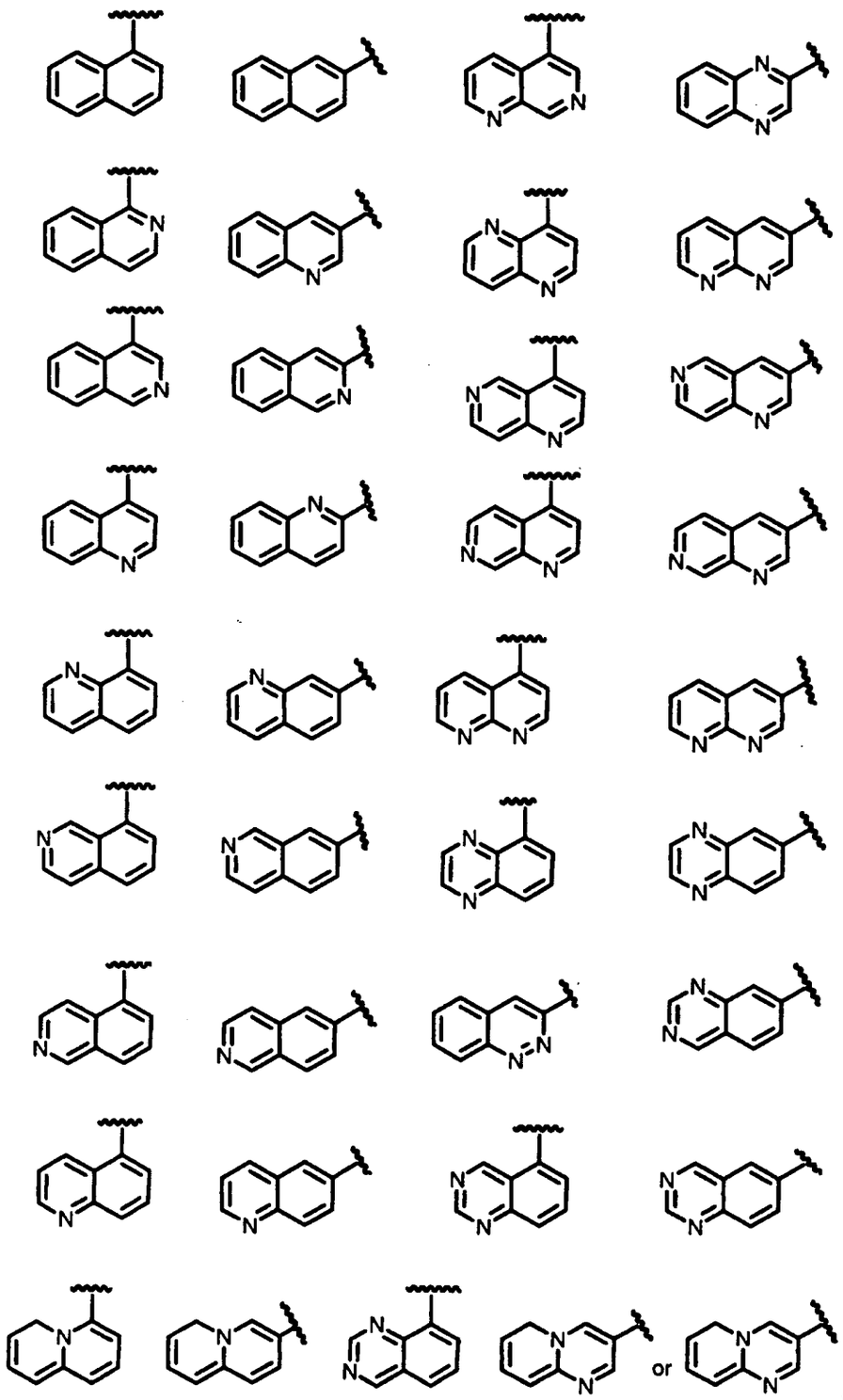


In another embodiment, R^{10} is:



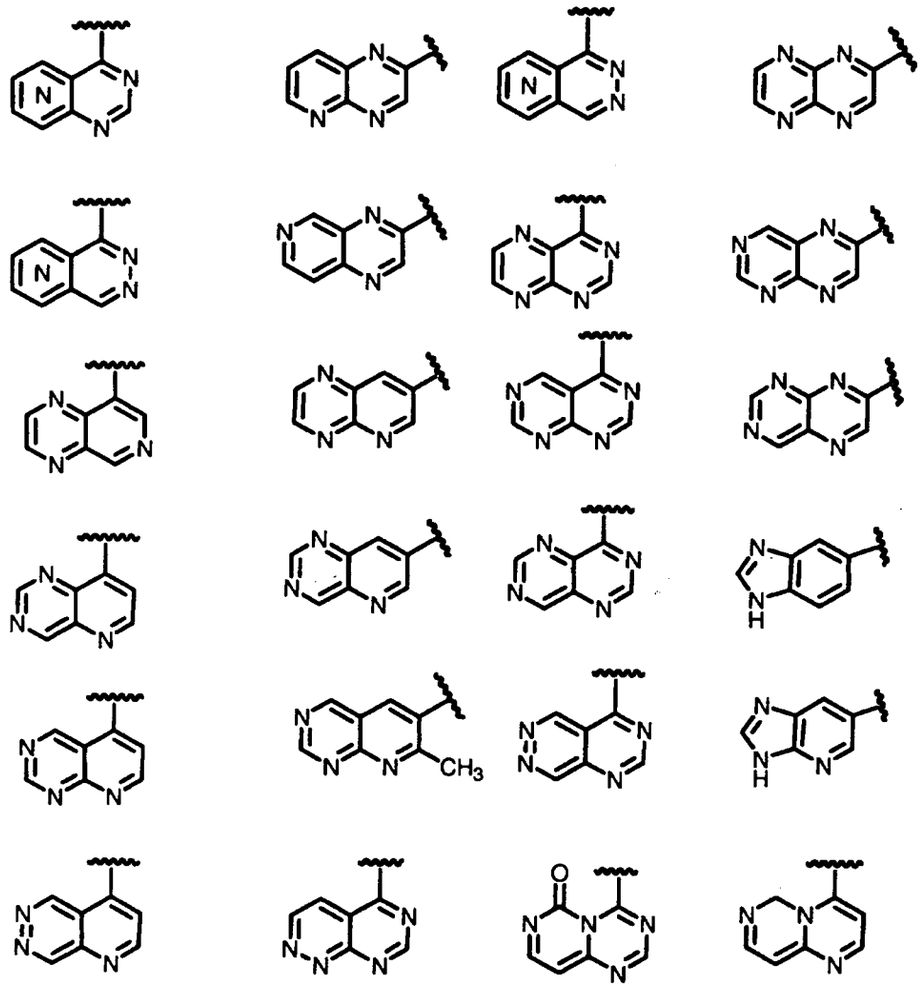


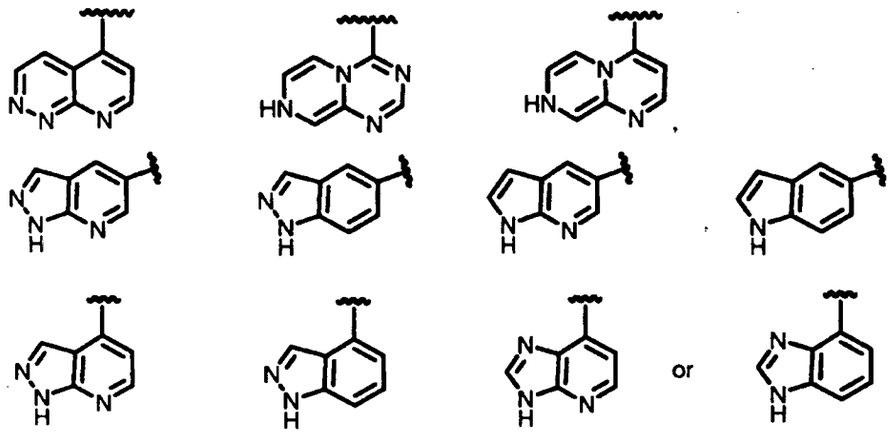
In another embodiment, R^{10} is:


or

each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

In another embodiment, R^{10} is:





, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –$NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

In one embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is –H.

In another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is alkyl.

In another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H,and R^{10} is aryl.

In still another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is cycloalkyl.

In yet another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is cycloalkylene.

In a further embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is heterocycloalkyl.

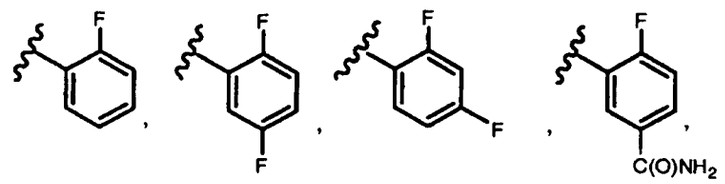
In another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is heterocycloalkylene.

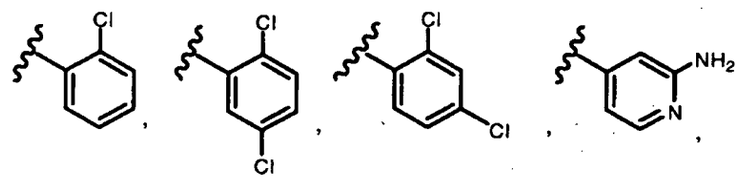
In another embodiment, R^1 is -[$C(R^{12})_2$]$_r$-, each occurrence of R^{12} is H, and R^{10} is heteroaryl.

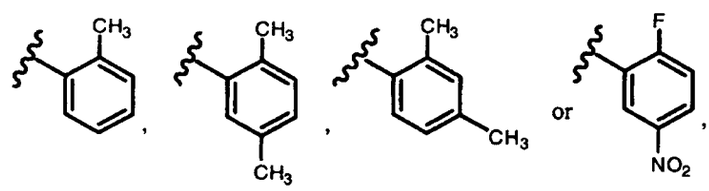
In still another embodiment, R^1 is a bond or -[$C(R^{12})_2$]$_r$-, and R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –$NHSO_2$-alkyl.

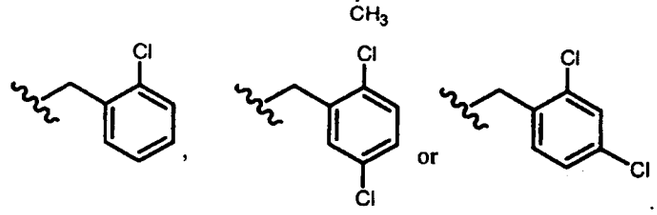
In a further embodiment, R^1 is a bond or -$[C(R^{12})_2]_r$-, and R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from methyl, cyclopropyl, halo, -OH, -NH_2, -$NHCH_3$ and –$N(CH_3)_2$.

In one embodiment, R^1 is –CH_2- and R^{10} is:

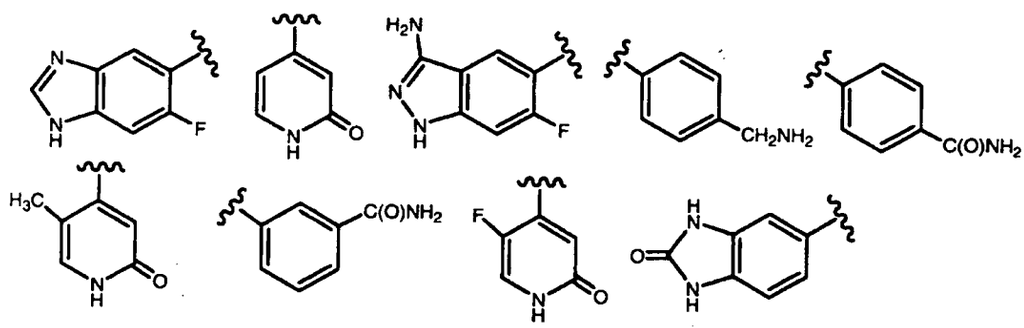


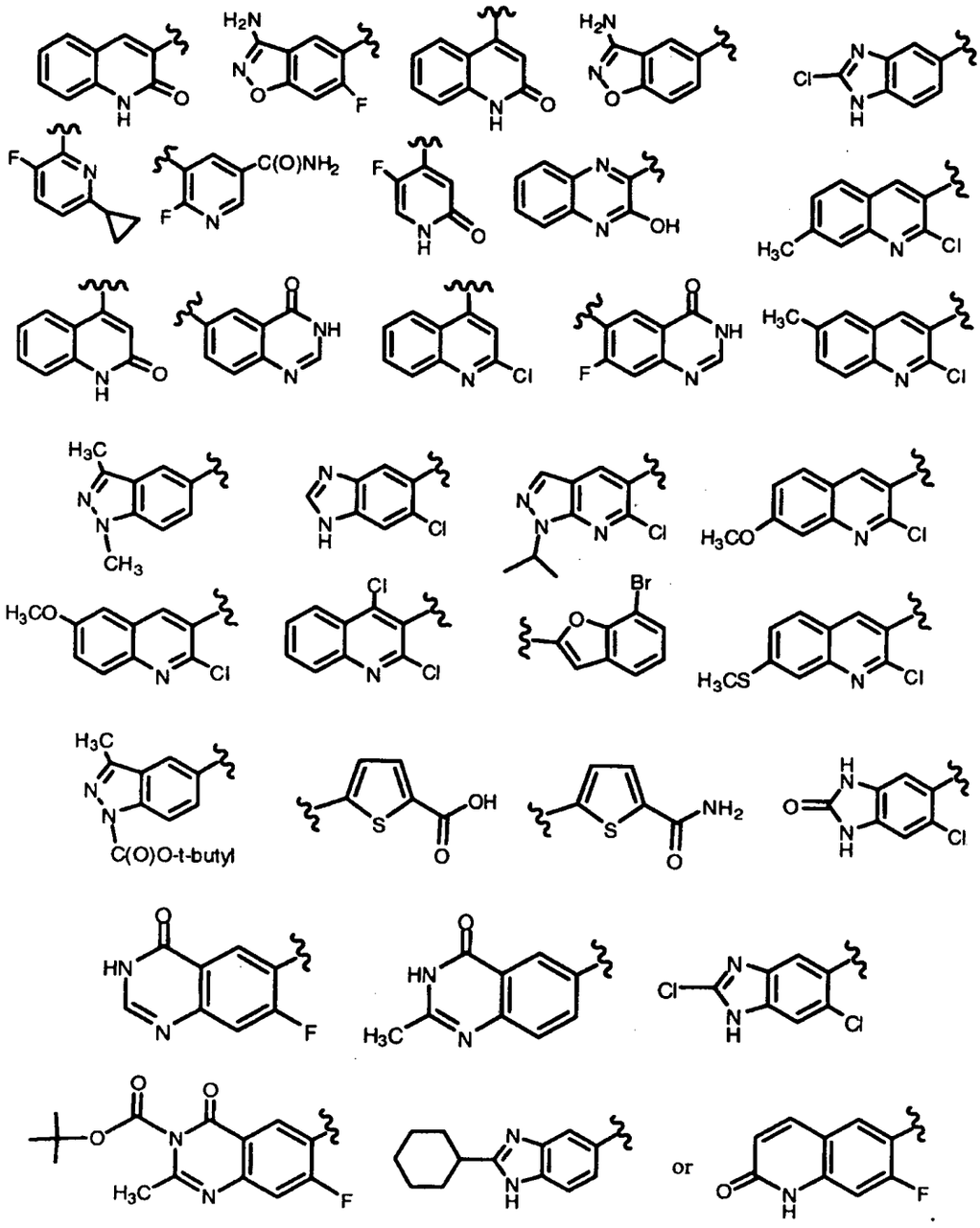




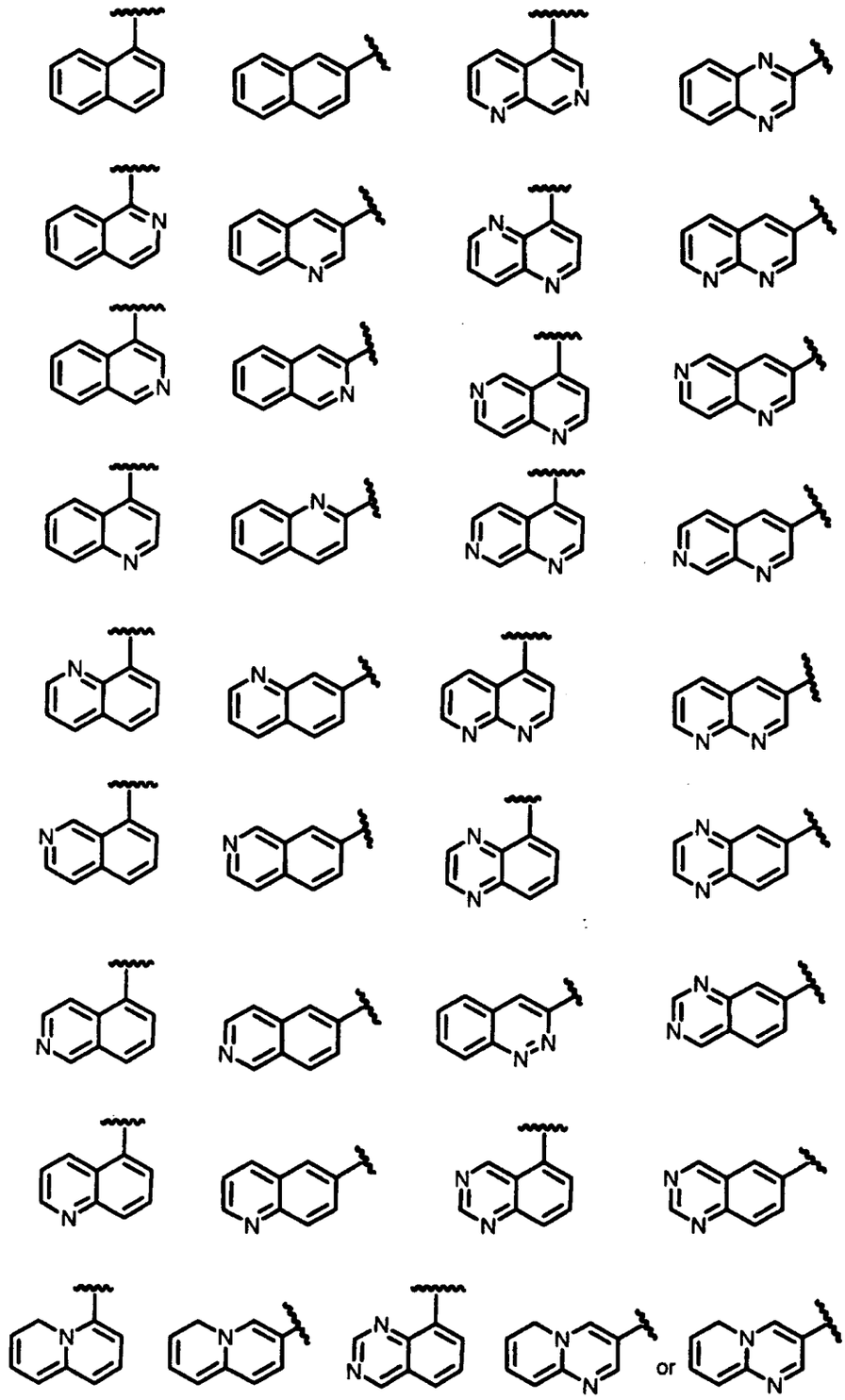


In another embodiment, R^1 is –CH_2- and R^{10} is:



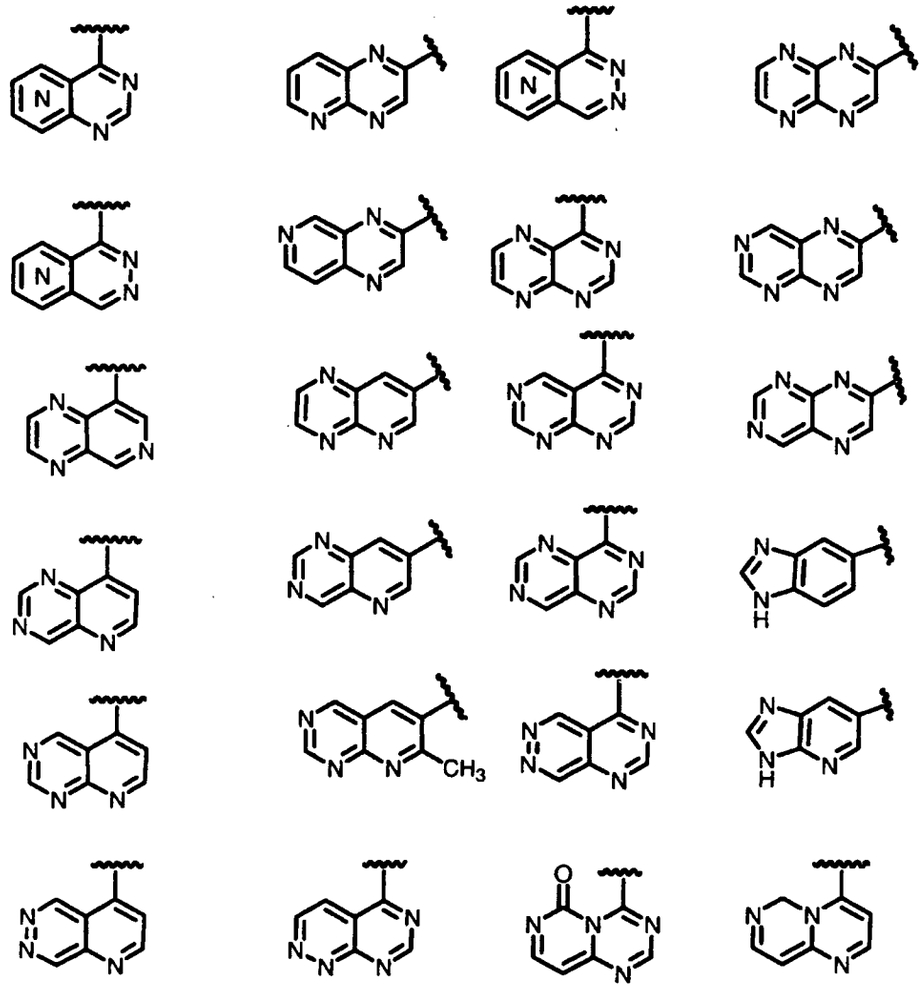


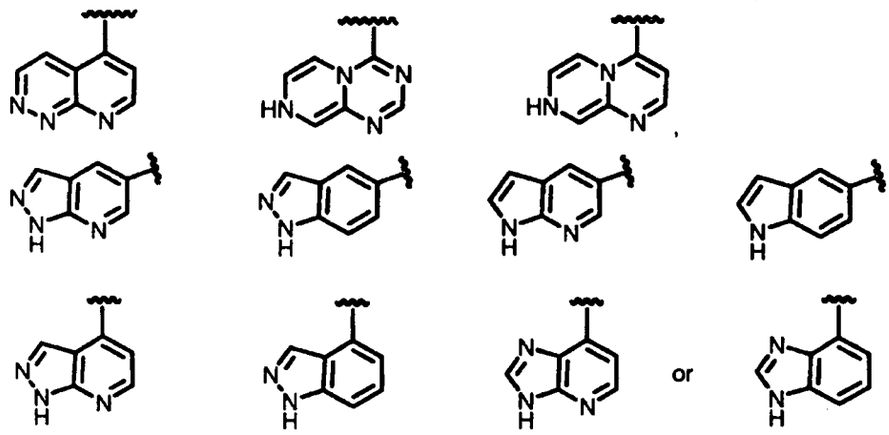
In another embodiment, R^1 is $-CH_2-$ and R^{10} is:


or

each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

In still another embodiment, R^1 is $-CH_2-$ and R^{10} is:



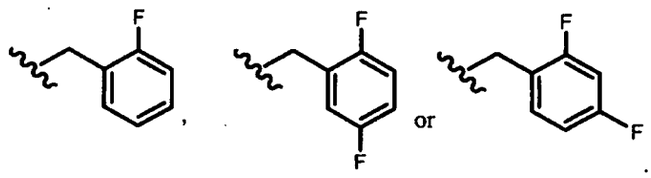


, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –$NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

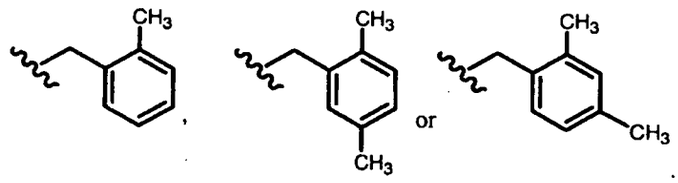
In one embodiment, -R^1-R^{10} is methyl.

In another embodiment, -R^1-R^{10} is benzyl.

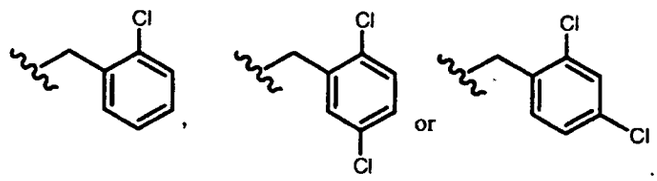
In another embodiment, -R^1-R^{10} is:



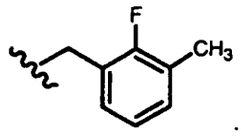
In still another embodiment, -R^1-R^{10} is:



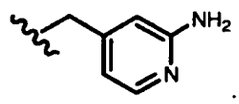
In yet another embodiment, -R^1-R^{10} is:



In a further embodiment, -R^1-R^{10} is:



In another embodiment, -R^1-R^{10} is:



In one embodiment, R^2 is –C(O)OR^9.

In another embodiment, R^2 is -C(O)N(R^9)$_2$.

In another embodiment, R^2 is -C(O)N(R^9)SO_2R^{11}.

In still another embodiment, R^2 is -C(O)NHSO_2R^{11}.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_r$–C(O)OR^9.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_r$-C(O)N(R^9)$_2$.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_r$-C(O)N(R^9)SO_2R^{11}.

In yet another embodiment, R^2 is alkyl.

In a further embodiment, R^2 is -[C(R^{12})$_2$]$_q$-aryl.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_q$-cycloalkyl.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_q$-cycloalkenyl.

In another embodiment, R^2 is -[C(R^{12})$_2$]$_q$-heterocycloalkyl.

In still another embodiment,-[C(R^{12})$_2$]$_q$ –heteroaryl-.

In yet another embodiment, R^2 is -[C(R^{12})$_2$]$_q$-heterocycloalkenyl.

In a further embodiment, R^2 is -arylthiazin-yl.

In another embodiment, R^2 is arylthiadiazol-yl-.

In one embodiment, R^2 is –C(O)OH.

In another embodiment, R^2 is –C(O)OCH_3

In another embodiment, R^2 is –C(O)OCH_2CH_3 .

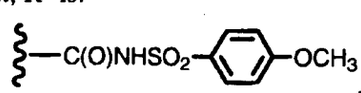
In still another embodiment, R^2 is –C(O)NHSO_2CH_3.

In yet another embodiment, R^2 is –C(O)NH$SO_2CH_2CH_3$.

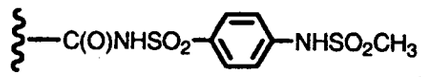
In another embodiment, R^2 is –C(O)NHSO_2-isopropyl.

In another embodiment, R^2 is –C(O)NHSO_2-cyclopropyl.

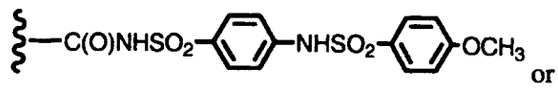
In a further embodiment, R^2 is:



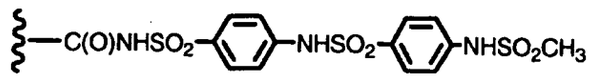
In yet another embodiment, R^2 is:



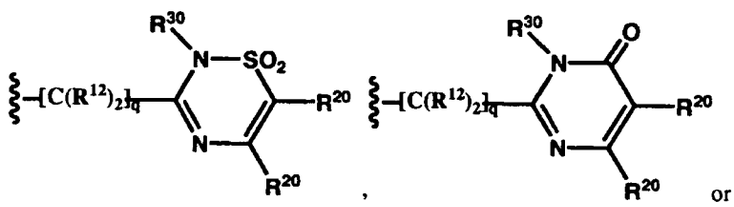
In a further embodiment, R^2 is:



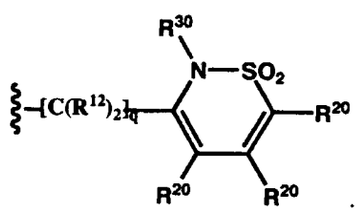
or



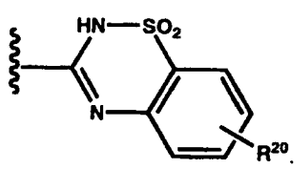
In one embodiment, R^2 is:



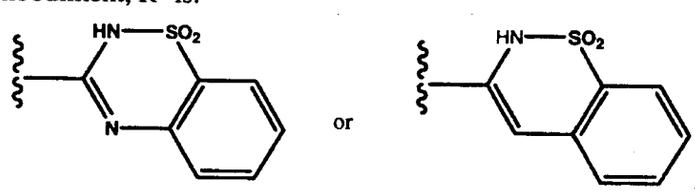
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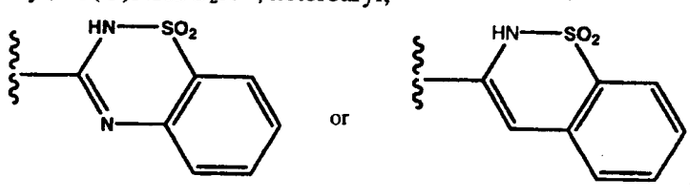
In another embodiment, R^2 is:



In another embodiment, R^2 is:



In still another embodiment, R^2 is -C(O)OH, -C(O)Oalkyl, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)NH-cycloalkyl, $-C(O)NHSO_2R^{11}$, heteroaryl,

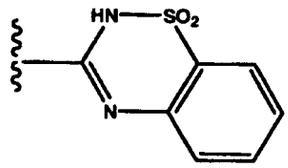


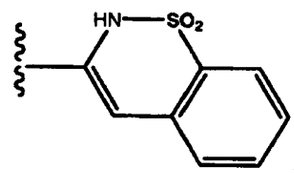
wherein a heteroaryl, arylthiazin-yl- or arylthiadiazol-yl- group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In one embodiment, R^2 is $-C(O)OH$, $-C(O)NHSO_2$-alkyl, $-C(O)NHSO_2$-aryl, $-C(O)NHSO_2$-cycloalkyl or $-C(O)NHSO_2$-alkylene-cycloalkyl.

In another embodiment, R^2 is $-C(O)OH$, $-C(O)NHSO_2CH_3$ or $-C(O)NHSO_2$-cyclopropyl.

In another embodiment, R^2 is $-C(O)OH$, $-C(O)Oalkyl$, $-C(O)NH_2$, $-C(O)NH$-alkyl, $-C(O)NH$-cycloalkyl, $-C(O)NHSO_2R^{11}$, heteroaryl,



or


wherein the heteroaryl, arylthiazin-yl- or arylthiadiazol-yl- group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$; such that if Z is thiophene-yl, R^2 is other than $-C(O)O$-alkyl.

In still another embodiment, R^2 is $-C(O)NHSO_2$-alkyl, $-C(O)NHSO_2$-aryl, $-C(O)NHSO_2$-cycloalkyl or $-C(O)NHSO_2$-alkylene-cycloalkyl.

In one embodiment, R^3 is $-H$.

In another embodiment, R^3 is $-[C(R^{12})_2]_q$-alkyl.

In another embodiment, R^3 is $-[C(R^{12})_2]_q$-aryl.

In still another embodiment, R^3 is $-[C(R^{12})_2]_q$-cycloalkyl.

In yet another embodiment, R^3 is $-[C(R^{12})_2]_q$-cycloalkylene.

In a further embodiment, R^3 is $-[C(R^{12})_2]_q$-heterocycloalkyl.

In another embodiment, R^3 is $-[C(R^{12})_2]_q$-heterocycloalkylene.

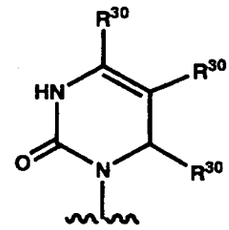
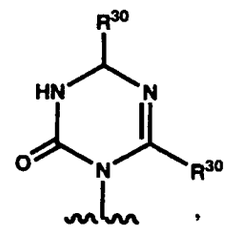
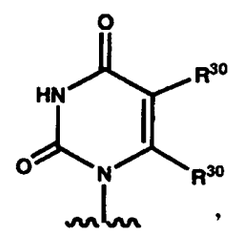
In one embodiment, R^3 is $-[C(R^{12})_2]_q$-heteroaryl.

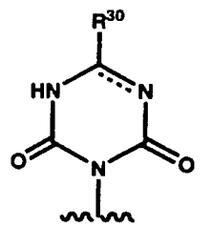
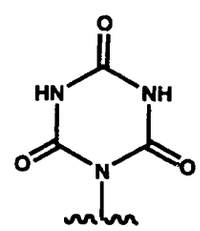
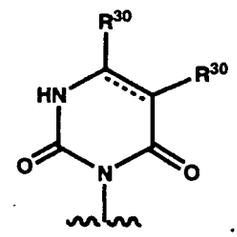
In one embodiment, R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo,

haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$.

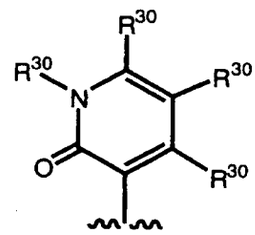
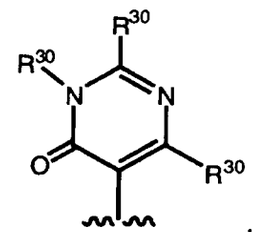
In another embodiment, R^3 is pyridyl or phenyl which is unsubstituted or optionally substituted with 1to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, or $-NHC(O)R^8$.

In another embodiment, R^3 is:

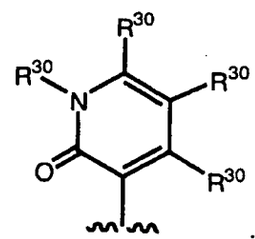

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or

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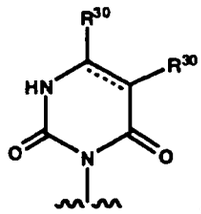
In another embodiment, R^3 is:


or

.

In still another embodiment, R^3 is:


.

In one embodiment, R^3 is:



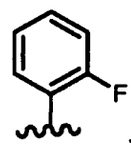
, wherein both R^{30} groups, together with the carbon atoms to which they are attached, join to form a -3- to 7-membered ring selected from aryl, cycloalkyl, heteroaryl and heterocycloalkyl.

In another embodiment, R^3 is aryl.

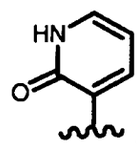
In another embodiment, R^3 is phenyl.

In still another embodiment, R^3 is benzyl.

In yet another embodiment, R^3 is:



In another embodiment, R^3 is:



In one embodiment, R^6 is –H.

In another embodiment, R^6 is alkyl.

In another embodiment, R^6 is haloalkyl.

In another embodiment, R^6 is hydroxyalkyl.

In still another embodiment, R^6 is aryl.

In yet another embodiment, R^6 is halo.

In a further embodiment, R^6 is -OH.

In another embodiment, R^6 is –O-haloalkyl.

In one embodiment, R^6 is -alkoxy.

In another embodiment, R^6 is -CN.

In another embodiment, R^6 is $-[C(R^{12})_2]_q-OR^9$.

In another embodiment, R^6 is $-[C(R^{12})_2]_q-N(R^9)_2$.

In still another embodiment, R^6 is $-C(O)R^8$.

In another embodiment, R^6 is $-C(O)OR^9$.

In yet another embodiment, R^6 is $-C(O)N(R^9)_2$.

In a further embodiment, R^6 is $-NHC(O)R^8$.

In another embodiment, R^6 is $-NHSO_2R^{11}$.

In another embodiment, R^6 is $-S(O)_pR^{11}$

In another embodiment, R^6 is $-SO_2N(R^9)_2$.

In one embodiment, R^7 is –H.

In another embodiment, R^7 is alkyl.

In another embodiment, R^7 is haloalkyl.

In another embodiment, $R^7$is hydroxyalkyl.

In still another embodiment, R^7 is aryl.

In yet another embodiment, R^7 is halo.

In a further embodiment, R^7 is -OH.

In another embodiment, R^7 is –O-haloalkyl.

In one embodiment, R^7 is -alkoxy.

In another embodiment, R^7 is -CN.

In another embodiment, $R^7$is $-[C(R^{12})_2]_q-OR^9$.

In another embodiment, R^7 is $-[C(R^{12})_2]_q-N(R^9)_2$.

In still another embodiment, R^7 is $-C(O)R^8$.

In another embodiment, R^7 is $-C(O)OR^9$.

In yet another embodiment, R^7 is $-C(O)N(R^9)_2$.

In a further embodiment, R^7 is $-NHC(O)R^8$.

In another embodiment, R^7 is $-NHSO_2R^{11}$.

In another embodiment, R^7 is $-S(O)_pR^{11}$

In another embodiment, R^7 is $-SO_2N(R^9)_2$.

In one embodiment, R^6 and R^7 are each –H.

In another embodiment, one, but not both, of R^6 and R^7 is –H.

In another embodiment, each of R^6 and R^7 are other than –H.

In a further embodiment, R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl.

In one embodiment, ring Z is cyclopentenyl.

In another embodiment, the invention provides compounds of formula (I), wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl.

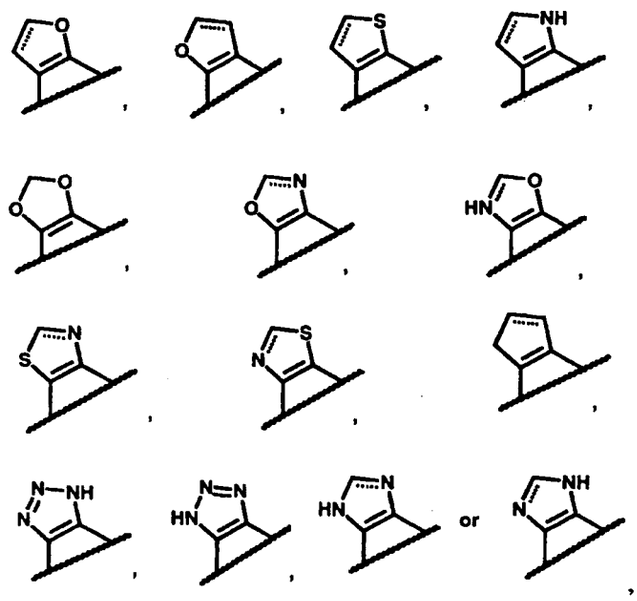
In another embodiment, ring Z is a 5-membered heterocycloalkyl.

In still another embodiment, ring Z is a 5-membered heterocycloalkenyl.

In yet another embodiment, ring Z is a 5-membered heteroaryl.

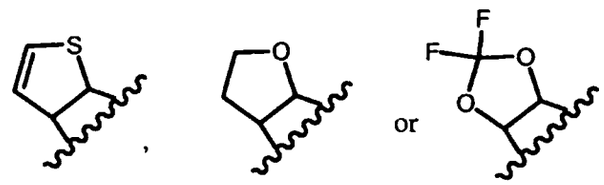
In another embodiment, ring Z is a cyclopentyl.

In one embodiment, ring Z is:

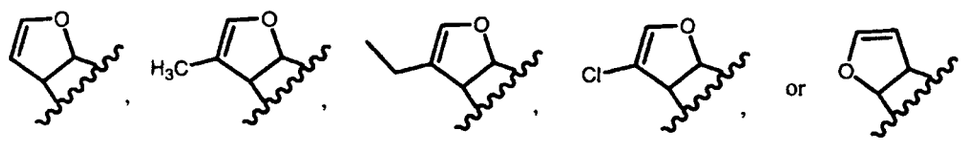


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I).

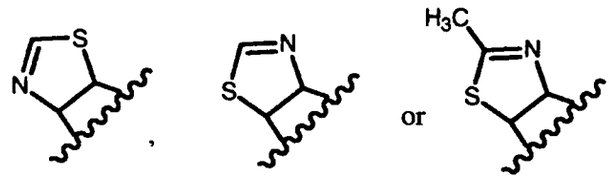
In another embodiment, ring Z is:



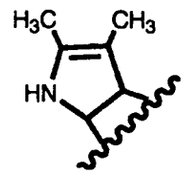
In another embodiment, ring Z is:



In another embodiment, ring Z is:



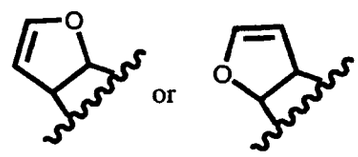
In another embodiment, ring Z is:



In one embodiment, ring Z is a 5-membered heterocycloalkyl, $-R^1-R^{10}$ is alkyl, -alkylene-aryl or –alkylene-heteroaryl, R^2 is $–C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

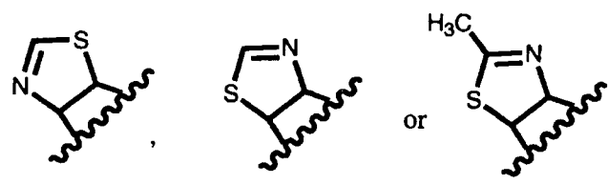
In another embodiment, ring Z is a 5-membered heterocycloalkenyl or a 5-membered heteroaryl, $-R^1-R^{10}$ is alkyl, $-(alkylene)_q$-aryl or $-(alkylene)_q$-heteroaryl, R^2 is $–C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

In another embodiment, ring Z is



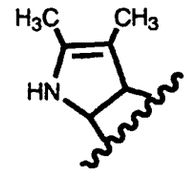
$-R^1-R^{10}$ is alkyl, $-(alkylene)_q$-aryl or $-(alkylene)_q$-heteroaryl, R^2 is $–C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

In another embodiment, ring Z is



$-R^1-R^{10}$ is alkyl, $-(alkylene)_q$-aryl or $-(alkylene)_q$-heteroaryl, R^2 is $–C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

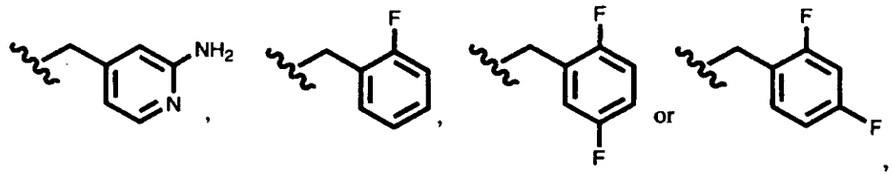
In still another embodiment, ring Z is



,

$-R^1-R^{10}$ is alkyl, $-(alkylene)_q$-aryl or $-(alkylene)_q$-heteroaryl, R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

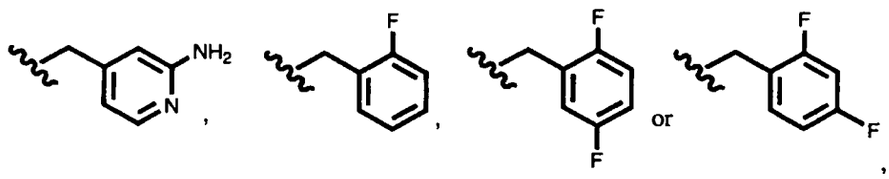
In one embodiment, ring Z is a cyclopentyl or cyclopentenyl group, $-R^1-R^{10}$ is:



,

R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

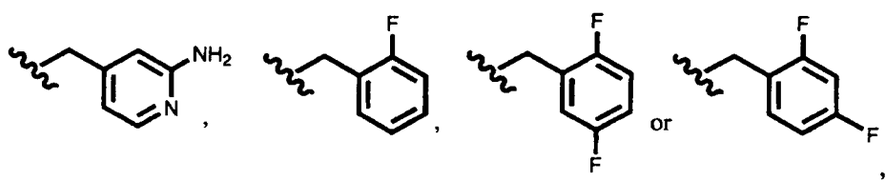
In another embodiment, ring Z is a 5-membered heterocycloalkyl group, $-R^1-R^{10}$ is:



,

R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

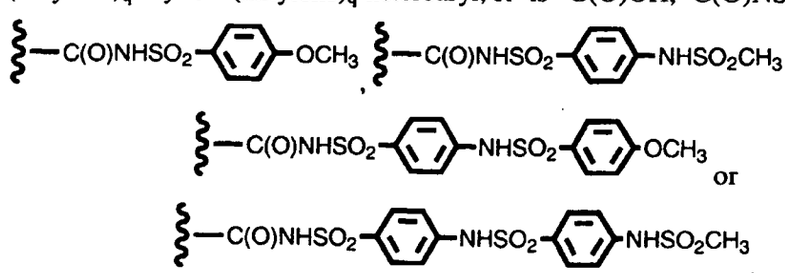
In another embodiment, ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl group, $-R^1-R^{10}$ is:



,

R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is aryl or heterocycloalkenyl.

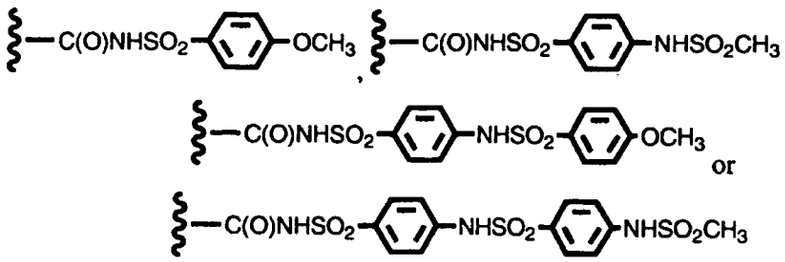
In another embodiment, ring Z is a cyclopentyl or cyclopentenyl group, $-R^1-R^{10}$ is alkyl, $-(alkylene)_q$-aryl or $-(alkylene)_q$-heteroaryl, R^2 is $-C(O)OH$, $-C(O)NSO_2CH_3$,



,

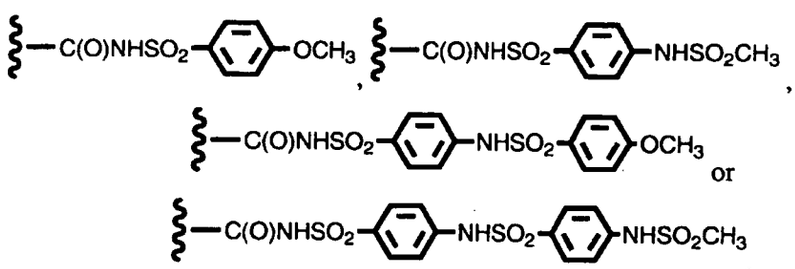
and R^3 is aryl or heterocycloalkenyl.

In another embodiment, ring Z is a 5-membered heterocycloalkyl group, $-R^1-R^{10}$ is alkyl, -(alkylene)$_q$-aryl or -(alkylene)$_q$-heteroaryl, R^2 is –C(O)OH, $-C(O)NSO_2CH_3$,



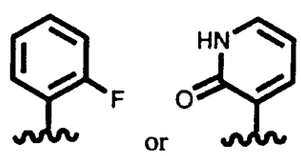
and R^3 is aryl or heterocycloalkenyl.

In another embodiment, ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl group, $-R^1-R^{10}$ is alkyl, -(alkylene)$_q$-aryl or -(alkylene)$_q$-heteroaryl, R^2 is –C(O)OH, $-C(O)NSO_2CH_3$,

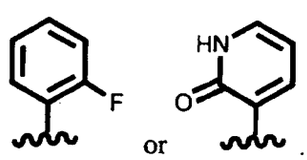


and R^3 is aryl or heterocycloalkenyl.

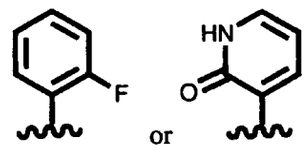
In still another embodiment, ring Z is a cyclopentyl or cyclopentenyl group, $-R^1-R^{10}$ is alkyl, -(alkylene)$_q$-aryl or -(alkylene)$_q$-heteroaryl, R^2 is R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is



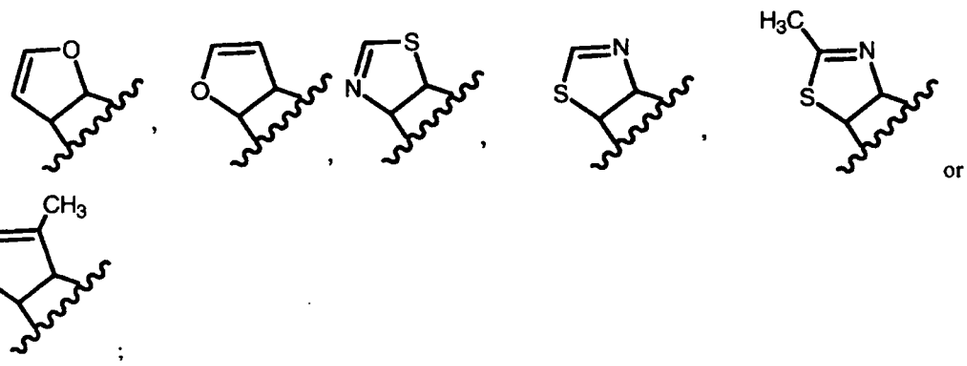
In yet another embodiment, ring Z is a 5-membered heterocycloalkyl group, $-R^1-R^{10}$ is alkyl, -(alkylene)$_q$-aryl or -(alkylene)$_q$-heteroaryl, R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is



In yet another embodiment, ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl group, $-R^1-R^{10}$ is alkyl, -(alkylene)$_q$-aryl or -(alkylene)$_q$-heteroaryl, R^2 is $-C(O)OR^8$ or $-C(O)NHSO_2R^{11}$, and R^3 is

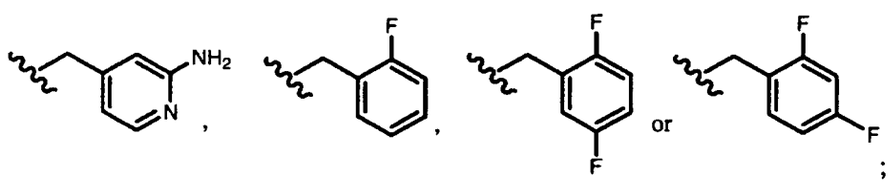


In another embodiment, ring Z is



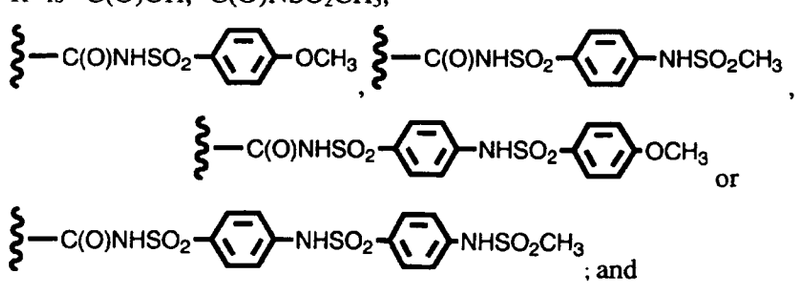
;

$-R^1-R^{10}$ is:



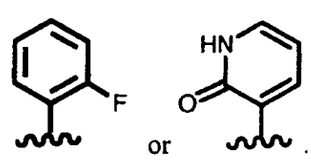
;

R^2 is $-C(O)OH$, $-C(O)NSO_2CH_3$,

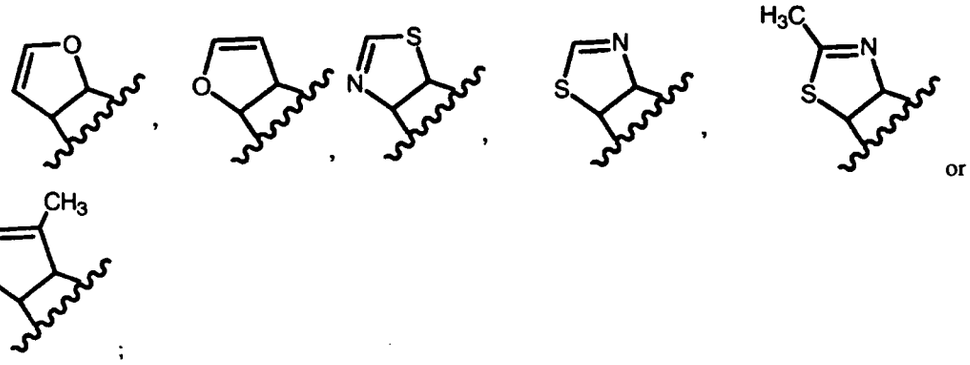


; and

R^3 is:



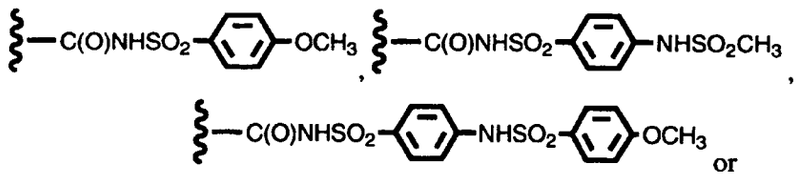
In another embodiment, ring Z is



;

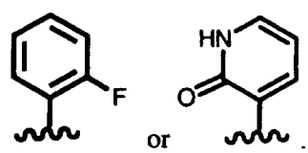
R^{10} is bicyclic heteroaryl;

R^2 is –C(O)OH, -C(O)NSO_2CH_3,

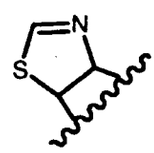


; and

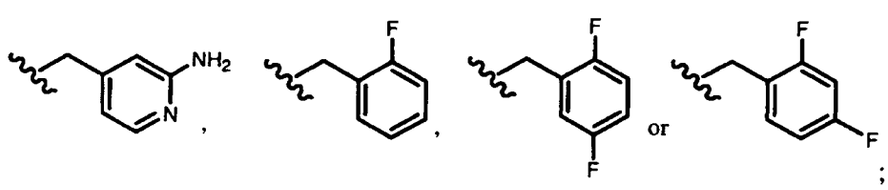
R^3 is:



In a further embodiment, ring Z is

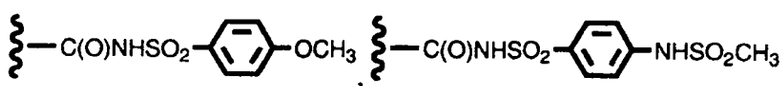


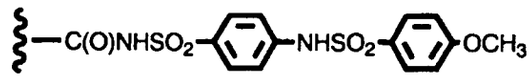
$-R^1-R^{10}$ is:



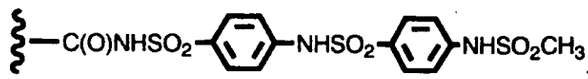
;

R^2 is –C(O)OH, -C(O)NSO_2CH_3,



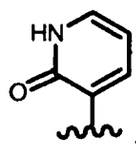


or



; and

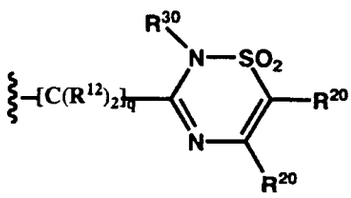
R^3 is:



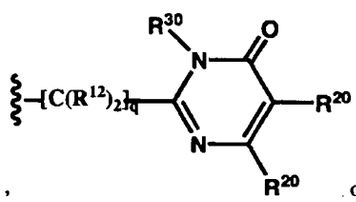
.

In one embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

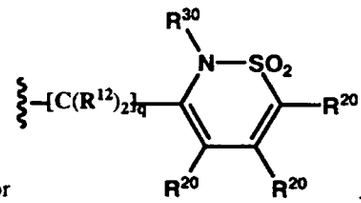
In another embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and R^2 is -C(O)OH, -C(O)Oalkyl, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)NH-cycloalkyl, $-C(O)NHSO_2R^{11}$,



,



or



.

In another embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and R^2 is $-C(O)NHSO_2$-alkyl, $-C(O)NHSO_2$-aryl, $-C(O)NHSO_2$-cycloalkyl or $-C(O)NHSO_2$-$(alkylene)_q$-cycloalkyl.

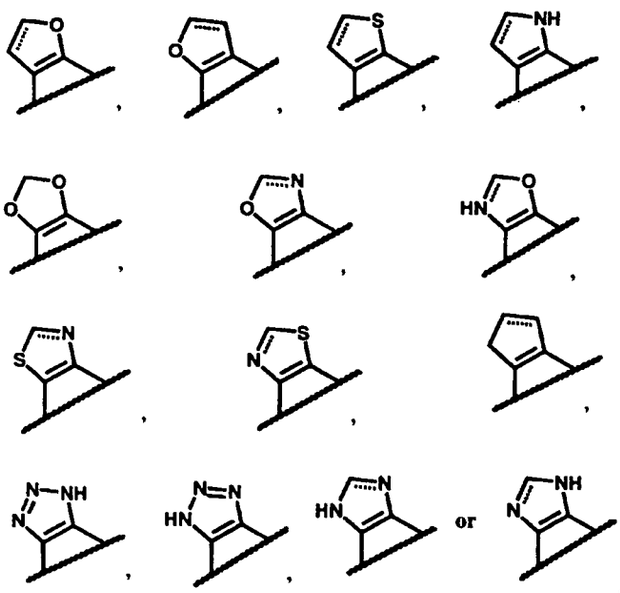
In another embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$.

In still another embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and R^3 is pyridyl, wherein the pyridyl group can be unsubstituted or optionally substituted with up to 3 substituents, which

are the same or different, and are selected from alkyl, haloalkyl, hydroxyalkyl, halo, -OH, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -O-hydroxyalkyl, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$alkyl or $-SO_2$NHalkyl.

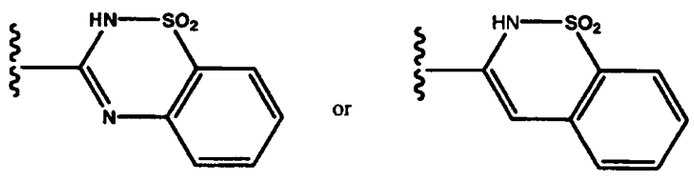
In yet another embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl group.

In a further embodiment, R^1 is a bond or $-[C(R^{12})_2)]_r-$, and ring Z is one of the following:



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I).

In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms; R^2 is -C(O)OH, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,



;

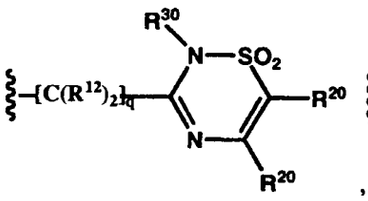
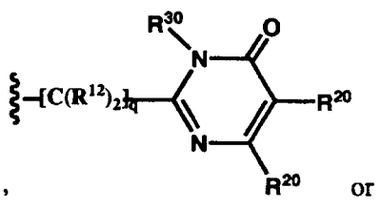
R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, -

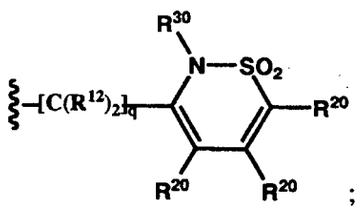
$NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$; ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, -C(O)O-alkyl, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,



or


;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

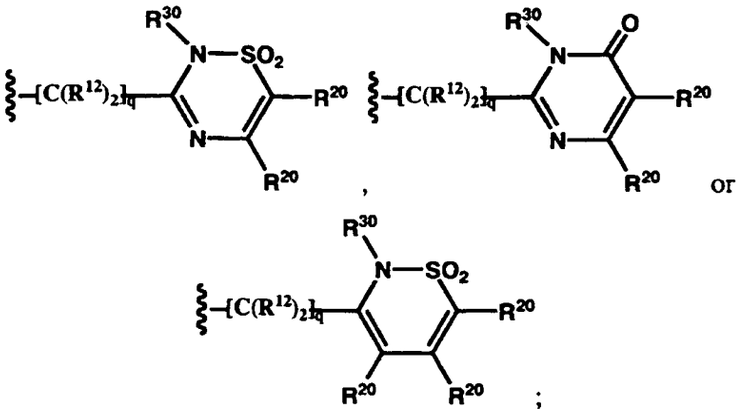
ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In still another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, -C(O)O-alkyl, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,



or

;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

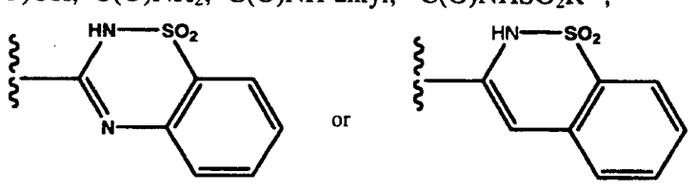
ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

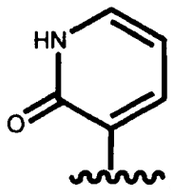
In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, -C(O)NH$_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,



;

R^3 is:



, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

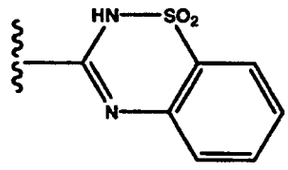
ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

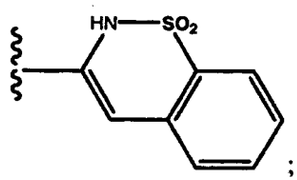
R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,

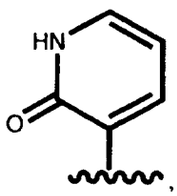


or



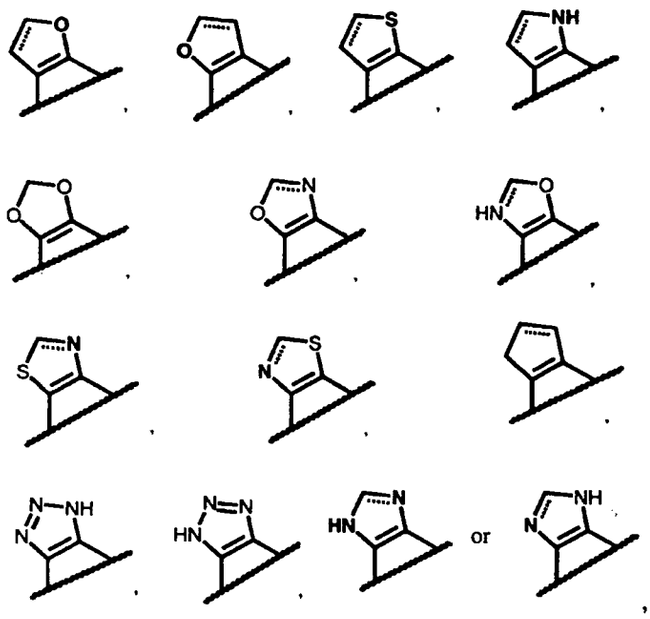
;

R^3 is:



, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

ring Z is:



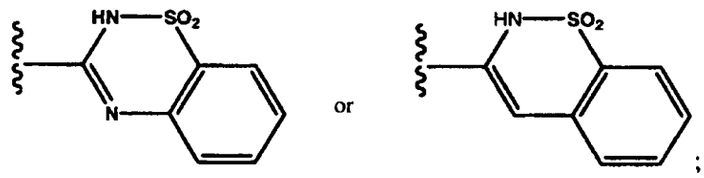
wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, -OCF_3, -NH_2 or -$NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -$C(O)N(R^9)_2$, -alkylene-OR^9, -OR^9, -$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ or -$SO_2N(R^9)_2$.

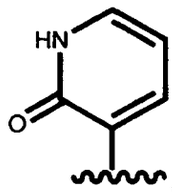
In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, -$C(O)NH_2$, -C(O)NH-alkyl, -$C(O)NHSO_2R^{11}$,



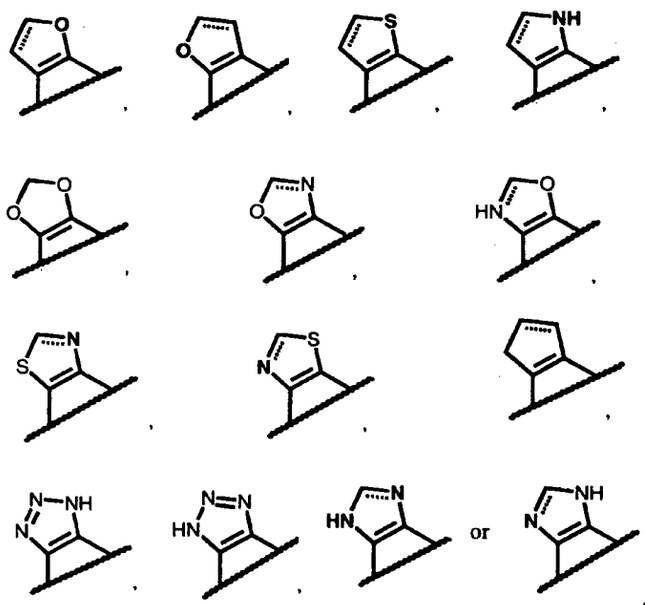
;

R^3 is:



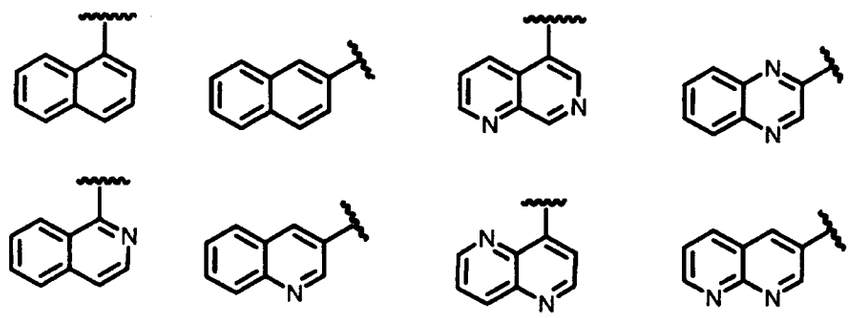
, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

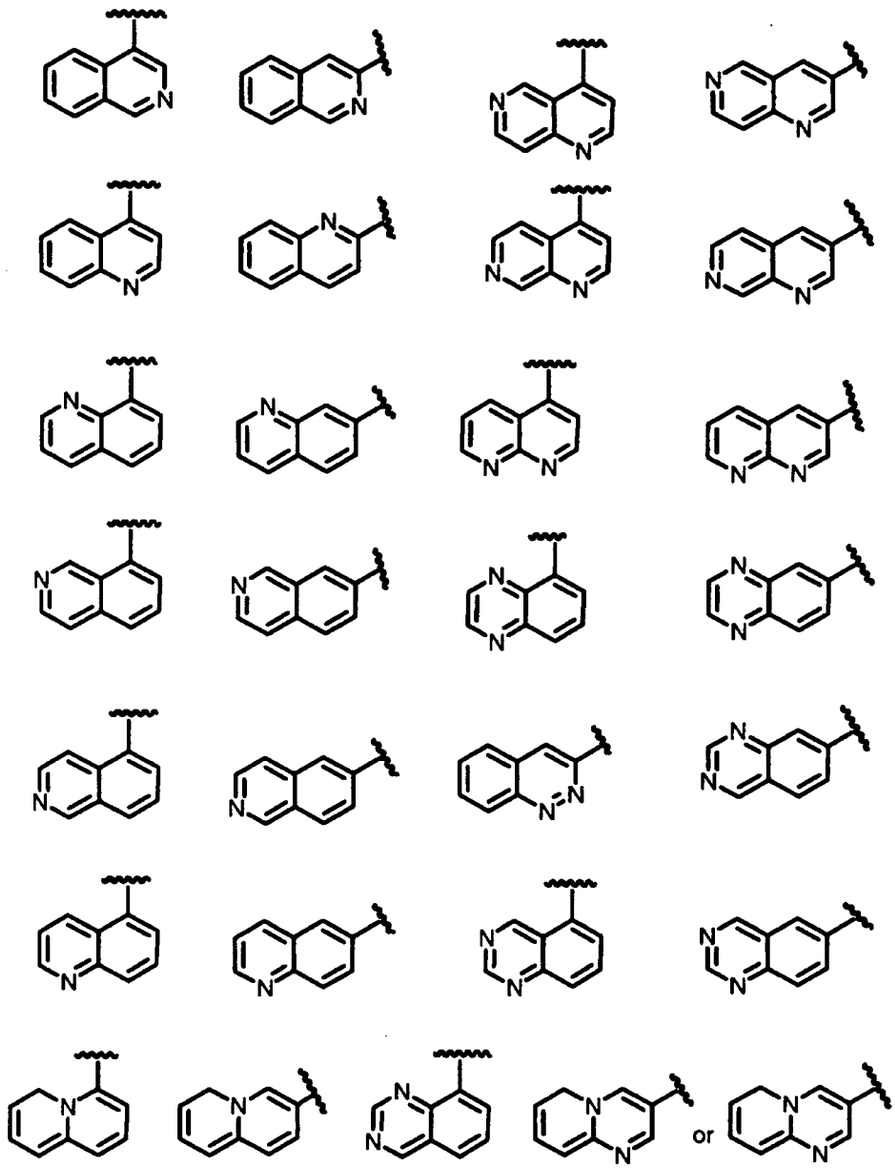
ring Z is:



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and R^{10} is:

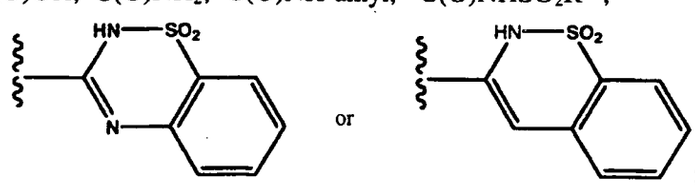




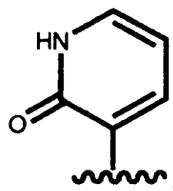
each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -$N(alkyl)_2$ or $-NHSO_2$-alkyl;

In one embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

R^2 is -C(O)OH, -$C(O)NH_2$, -C(O)NH-alkyl, -$C(O)NHSO_2R^{11}$,

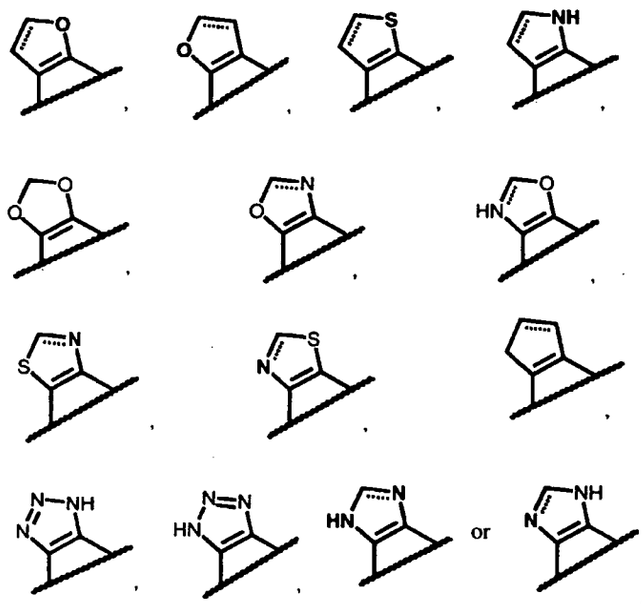


R^3 is:



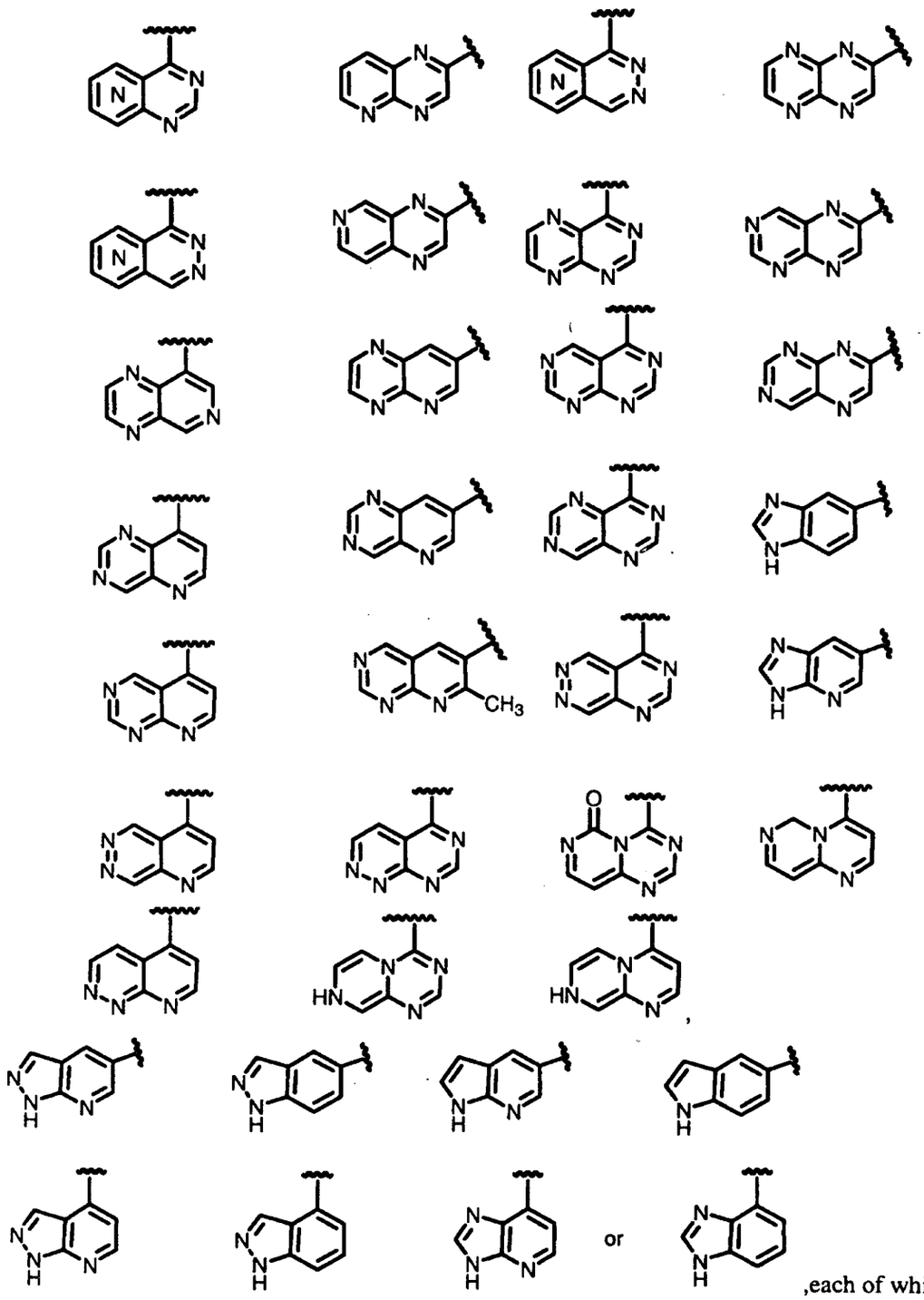
, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

ring Z is:



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and R^{10} is:

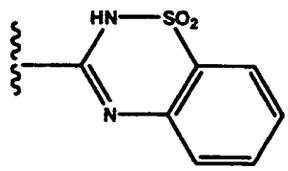


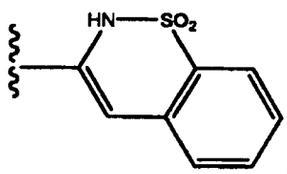
,each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-

haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –$NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

In one embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms;

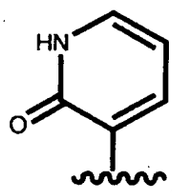
R^2 is -C(O)OH, -$C(O)NH_2$, -C(O)NH-alkyl, -$C(O)NHSO_2R^{11}$,



or


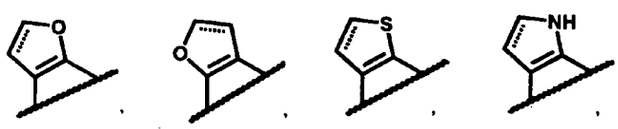
;

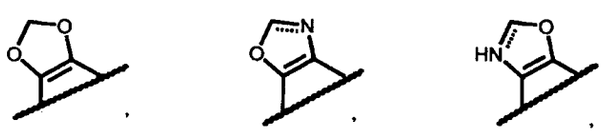
R^3 is:

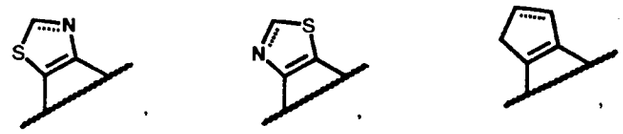


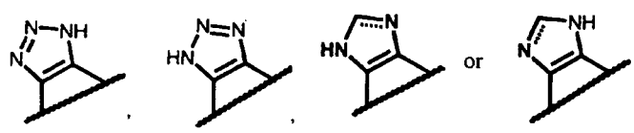
, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, -CF_3, -$C(O)CH_3$, -$C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, -OCF_3, -NH_2, -NHalkyl, -$NHC(O)NH_2$, -NHC(O)NH-alkyl, -$NHSO_2$alkyl, -$S(O)_2$-alkyl or -SO_2NHalkyl;

ring Z is:



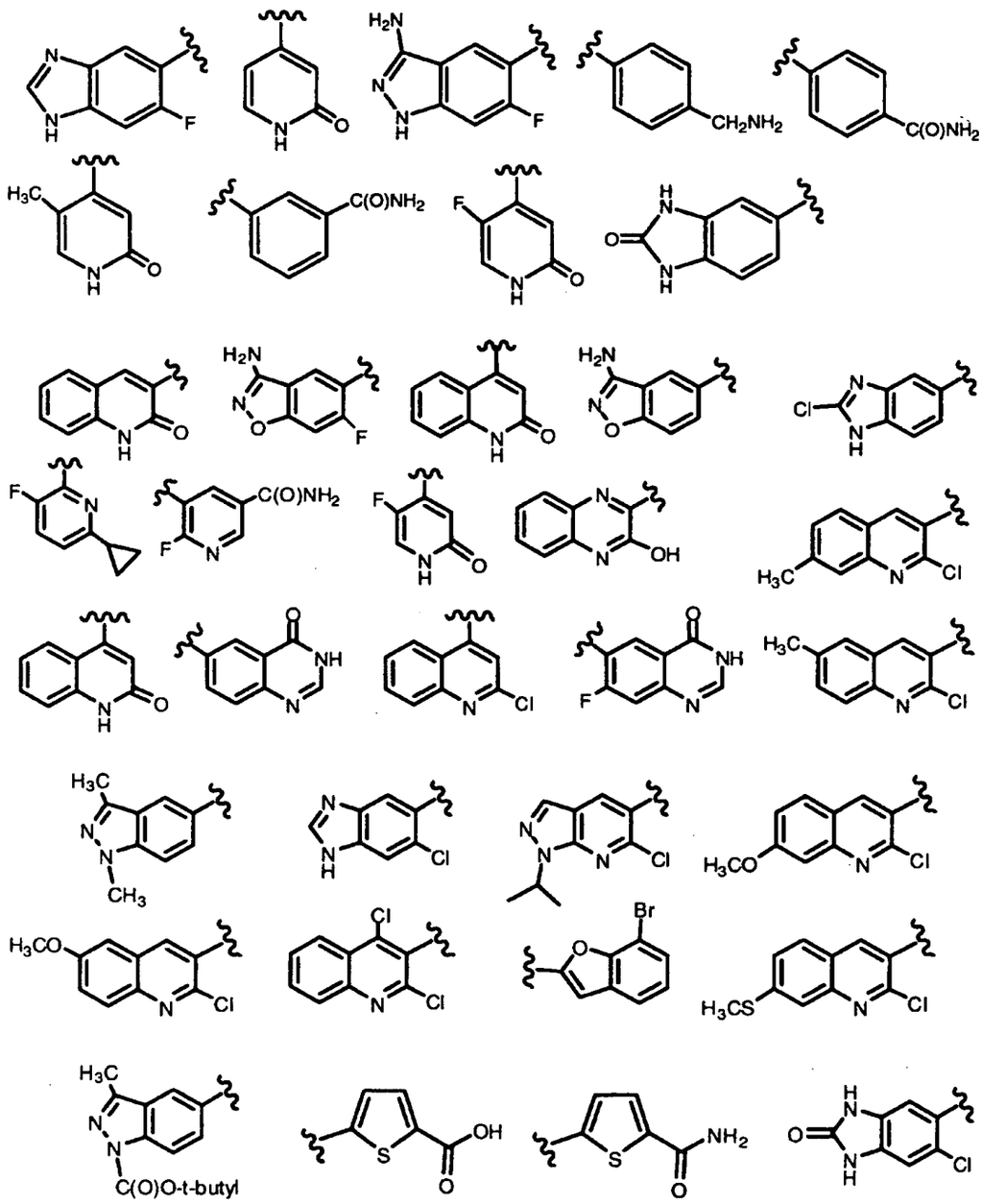


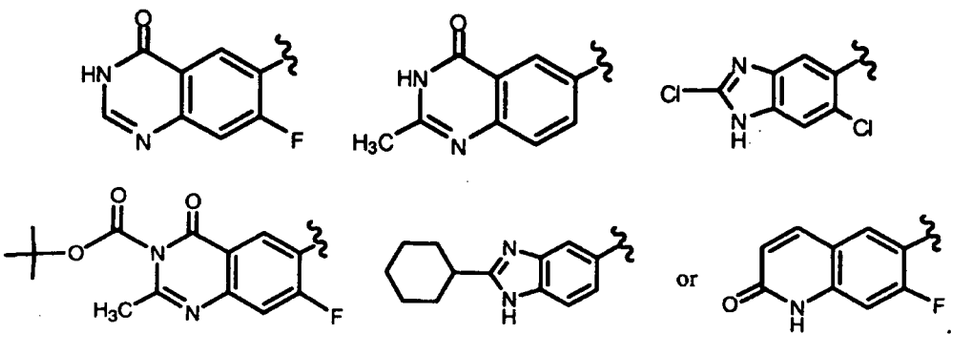




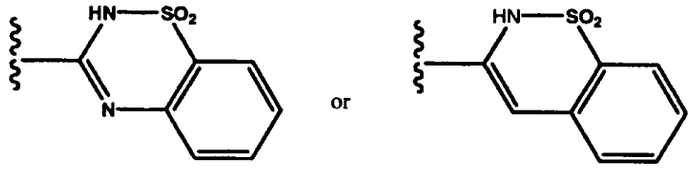
wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, -OCF_3, -NH_2 or -$NHSO_2$-alkyl; and R^{10} is:



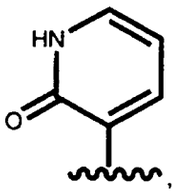


In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms; R^2 is -C(O)OH, -C(O)NH_2, -C(O)NH-alkyl, -C(O)$NHSO_2R^{11}$,



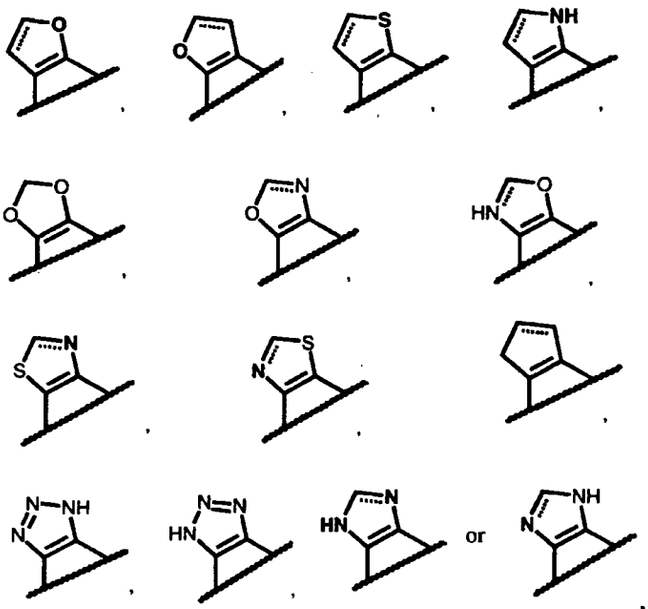
;

R^3 is:



, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, -CF_3, -C(O)CH_3, -C(O)NH_2, -C(O)NHalkyl, -F, -Cl, -OH, -OCF_3, -NH_2, -NHalkyl, -$NHC(O)NH_2$, -NHC(O)NH-alkyl, -$NHSO_2$alkyl, -$S(O)_2$-alkyl or -SO_2NHalkyl;

ring Z is:

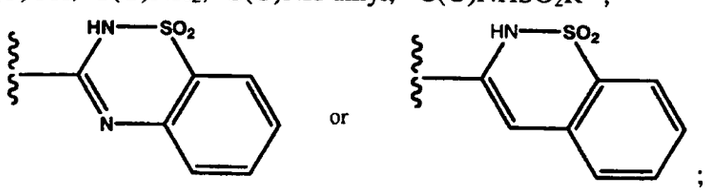


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, -OCF_3, -NH_2 or -$NHSO_2$-alkyl; and

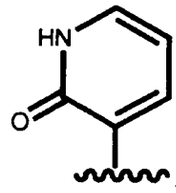
R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO_2R^{11}, -S(O)$_p R^{11}$ or -SO_2N(R^9)$_2$.

In another embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms, R^2 is -C(O)OH, -C(O)NH_2, -C(O)NH-alkyl, -C(O)NHSO_2R^{11},

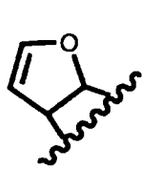
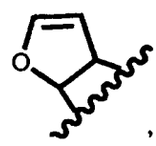
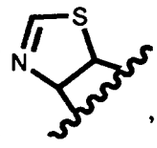


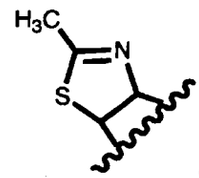
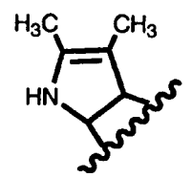
;

R^3 is:


, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

ring Z is:


,

,

,

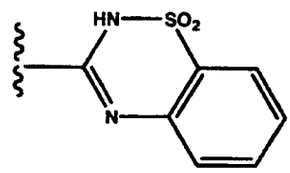
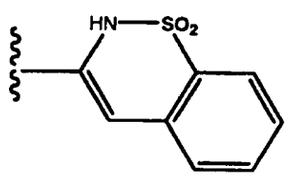
,

or

,

wherein ring Z can be optionally substituted on one or more ring carbon atoms with alkyl, -OH, -F, -Cl, -O-alkyl, $-CF_3$, cycloalkylalkyl, aryl or cycloalkyl.

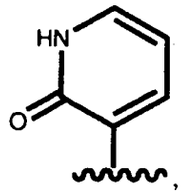
R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In a further embodiment, R^1 is a bond, or an alkyl group having from 1-6 carbon atoms, R^2 is -C(O)OH, $-C(O)NH_2$, -C(O)NH-alkyl, $-C(O)NHSO_2R^{11}$,

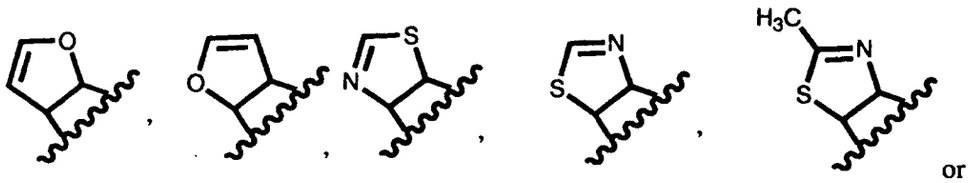

or

;

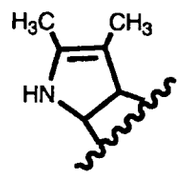
R^3 is:



, which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

ring Z is:





wherein ring Z can be optionally substituted on one or more ring carbon atoms with alkyl, -OH, -F, -Cl, -O-alkyl, $-CF_3$, cycloalkylalkyl, aryl or cycloalkyl.

R^6 and R^7 are each independently selected from –H, alkyl, -F, -Cl, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, the invention provides compounds of formula (I), wherein R^1 is a bond or $-[C(R^{12})_2]_r-$; and R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, the invention provides compounds of formula (I), wherein

ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^1 is a bond or -$[C(R^{12})_2]_r$-;

R^2 is -C(O)OH, heteroaryl, or -$C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -$C(O)N(R^9)_2$, -$N(R^9)_2$, -O-haloalkyl, -$NHC(O)NH_2$, -NHC(O)NH-alkyl, -$NHSO_2R^{11}$, -$S(O)_2R^{11}$ or -SO_2NHR^{11};

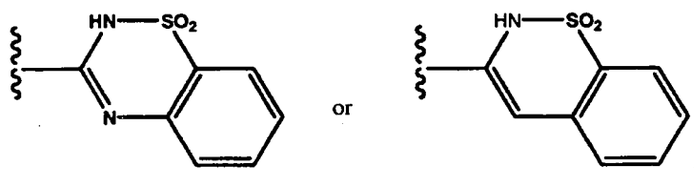
R^6 and R^7 are each independently selected from H, alkyl, F, Cl, -CF_3, -OH, -O-alkyl, -OCF_3, -NH_2 or -$NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -$C(O)N(R^9)_2$, -(alkylene)-OR^9, -OR^9, -$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ or -$SO_2N(R^9)_2$.

In still another embodiment, the invention provides compounds of formula (I), wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^1 is a bond or -$[C(R^{12})_2]_r$-;

R^2 is -C(O)OH, -$C(O)NH_2$, -C(O)NH-alkyl, -$C(O)NHSO_2R^{11}$;



wherein the heteroaryl, arylthiazin-yl- or arylthiadiazol-yl- group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ or -$SO_2N(R^9)_2$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -$C(O)N(R^9)_2$, -$N(R^9)_2$, -O-haloalkyl, -$NHC(O)NH_2$, -NHC(O)NH-alkyl, -$NHSO_2R^{11}$, -$S(O)_2R^{11}$ or -SO_2NHR^{11};

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

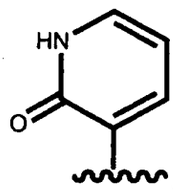
R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In yet another embodiment, the invention provides compounds of formula (I), wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^1 is a bond or $-[C(R^{12})_2]_r-$;

R^2 is -C(O)OH, heteroaryl, or $-C(O)NHSO_2R^{11}$;

R^3 is phenyl, pyridyl or

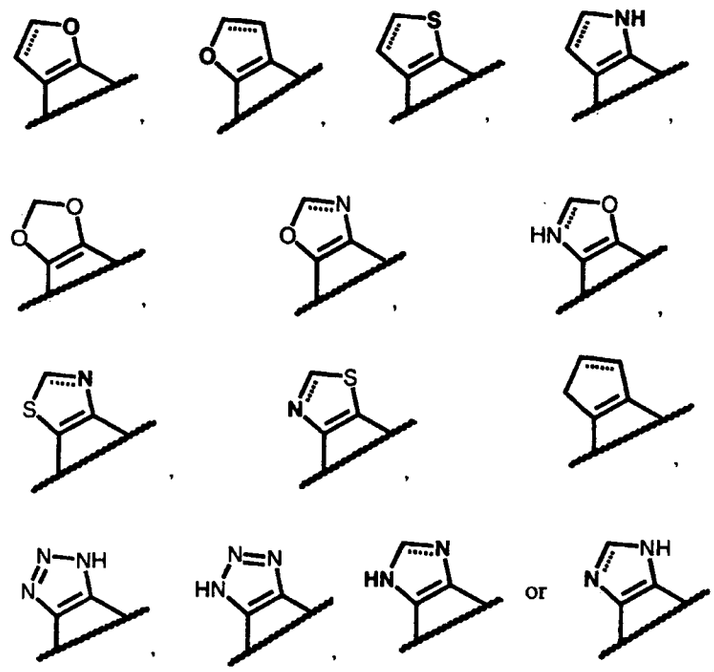


, each of which can be optionally substituted with one to 3 substituents, which are the same or different, and are selected from alkyl, $-CF_3$, -CN, -C(O)alkyl, $-C(O)NH_2$, -C(O)NHalkyl, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In a further embodiment, the invention provides compounds of formula (I), wherein ring Z is:



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above for the compounds of formula (I);

R^1 is a bond or $-[C(R^{12})_2]_r-$;

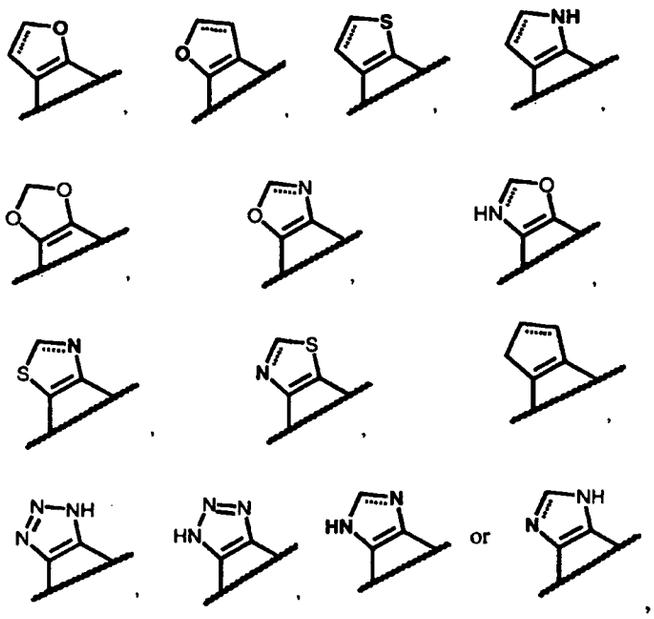
R^2 is -C(O)OH, heteroaryl, or $-C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

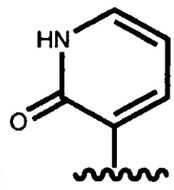
In one embodiment, the invention provides compounds of formula (I), wherein ring Z is:



wherein ring Z can be substituted with up to 3 optional ring carbon substituents, which are the same or different, and which are selected from H, alkyl, -OH, F, Cl, -O-alkyl, $-CF_3$, $-OCF_3$ and cycloalkyl;

R^1 is a bond or $-[C(R^{12})_2]_r-$;

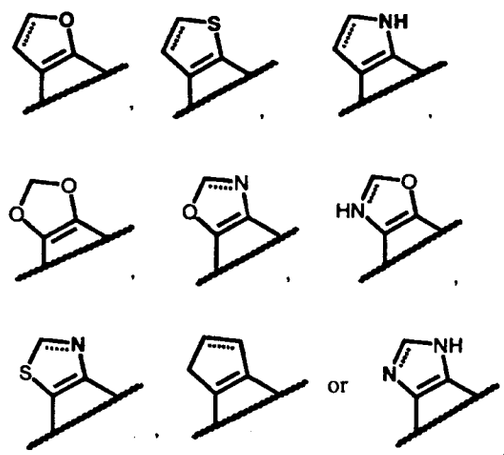
R^2 is -C(O)OH, heteroaryl, or $-C(O)NHSO_2R^{11}$;

R^3 is:  ;

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, the invention provides compounds of formula (I), wherein ring Z is:



wherein ring Z can be substituted with up to 3 optional ring carbon substituents, which are the same or different, and which are selected from H, alkyl, -OH, F, Cl, -O-alkyl, $-CF_3$, $-OCF_3$ and cycloalkyl;

R^1 is a bond or $-[C(R^{12})_2]_r-$;

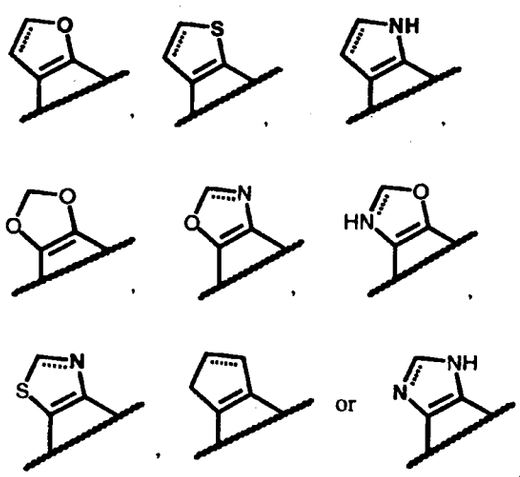
R^2 is -C(O)OH, heteroaryl, or $-C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, the invention provides compounds of formula (I), wherein ring Z is

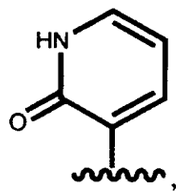


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-[C(R^{12})_2]_r-$;

R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is phenyl, pyridyl or



, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

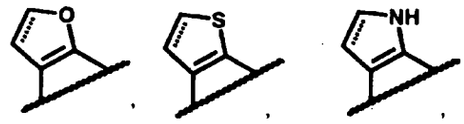
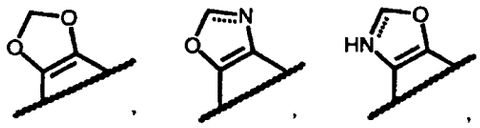
R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, F, Cl, $-CF_3$, -

CN, -C(O)alkyl, -C(O)NH_2, -OR^9, -NH_2, -$NHCH_3$, -$NHC(O)R^8$, -$NHSO_2CH_3$, -SO_2CH_3 or -SO_2NH_2.

In one embodiment, the invention provides compounds of formula (I), wherein ring Z is


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or –CH_2-;

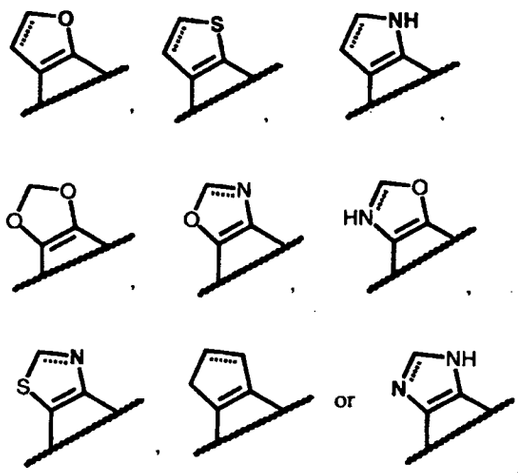
R^2 is -C(O)OH or -$C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -$C(O)N(R^9)_2$, -$N(R^9)_2$, -O-haloalkyl, -$NHC(O)NH_2$, -NHC(O)NH-alkyl, -$NHSO_2R^{11}$, -$S(O)_2R^{11}$ or -SO_2NHR^{11};

R^6 and R^7 are each independently selected from H, methyl, F, Cl, -CF_3, -OH, methoxy, -OCF_3, -NH_2 or -$NHSO_2CH_3$; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, F, Cl, -CF_3, -CN, -C(O)alkyl, -C(O)NH_2, -OR^9, -NH_2, -$NHCH_3$, -$NHC(O)R^8$, -$NHSO_2CH_3$, -SO_2CH_3 or -SO_2NH_2.

In another embodiment, the invention provides compounds of formula (I), wherein ring Z is

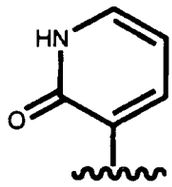


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-CH_2-$;

R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is phenyl, pyridyl or

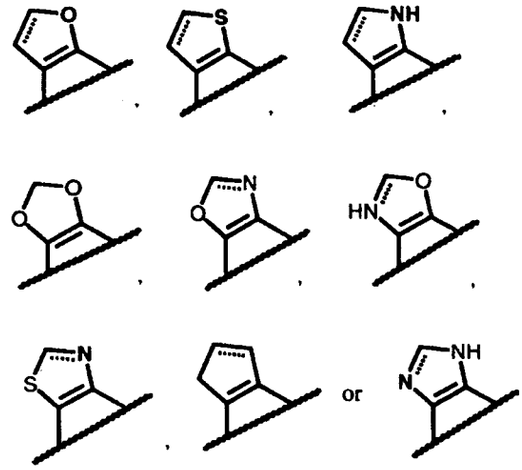


, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, F, Cl, $-CF_3$, -CN, -C(O)alkyl, $-C(O)NH_2$, $-OR^9$, $-NH_2$, $-NHCH_3$, $-NHC(O)R^8$, $-NHSO_2CH_3$, $-SO_2CH_3$ or $-SO_2NH_2$.

In still another embodiment, the invention provides compounds of formula (I), wherein ring Z is

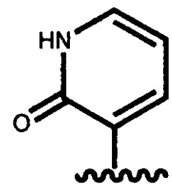


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-CH_2-$;

R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

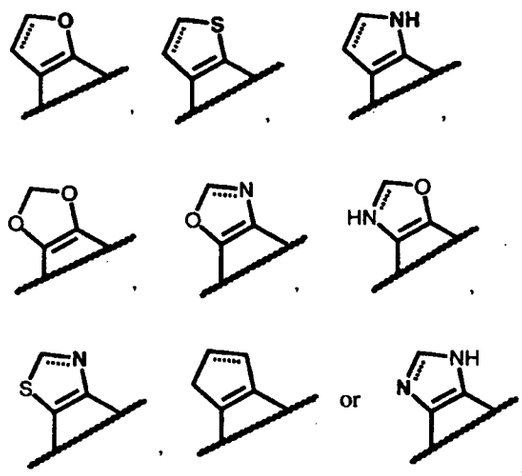
R^3 is



R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, F, Cl, $-CF_3$, -CN, -C(O)alkyl, $-C(O)NH_2$, $-OR^9$, $-NH_2$, $-NHCH_3$, $-NHC(O)R^8$, $-NHSO_2CH_3$, $-SO_2CH_3$ or $-SO_2NH_2$.

In one embodiment, the invention provides compounds of formula (I), wherein ring Z is



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-CH_2-$;

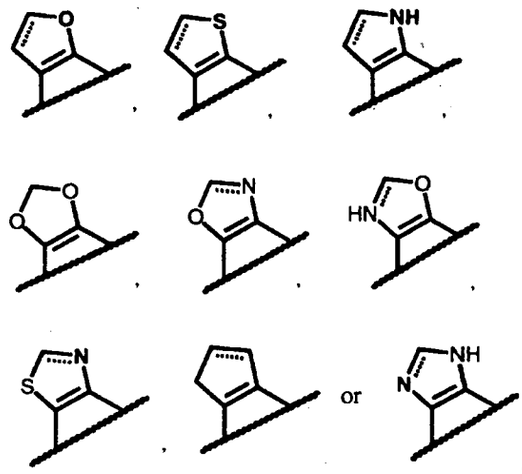
R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and

R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, the invention provides compounds of formula (I), wherein ring Z is

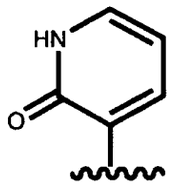


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-CH_2-$;

R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is phenyl, pyridyl or

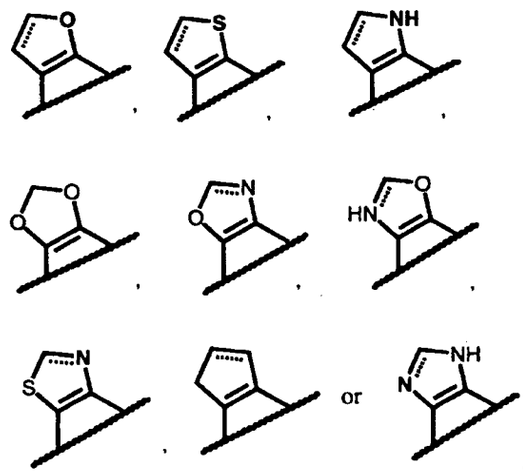


, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalkyl, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl;

R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and

R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In still another embodiment, the invention provides compounds of formula (I), wherein ring Z is

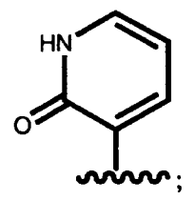


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

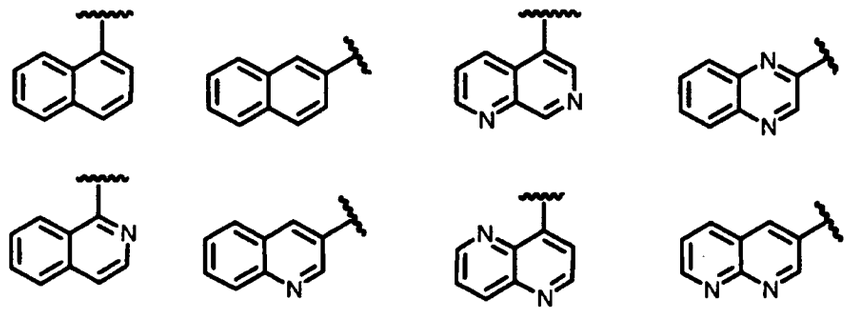
R^1 is a bond or $-CH_2-$;

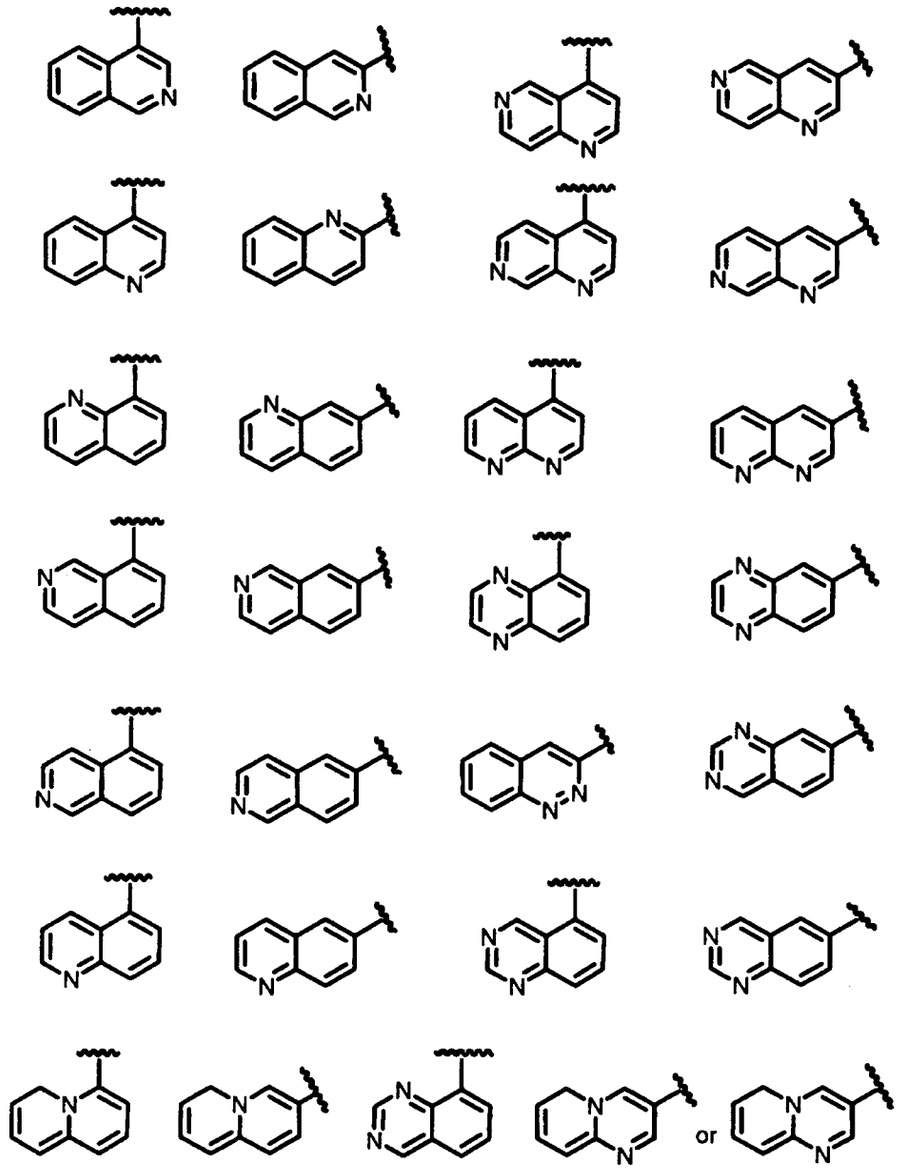
R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is



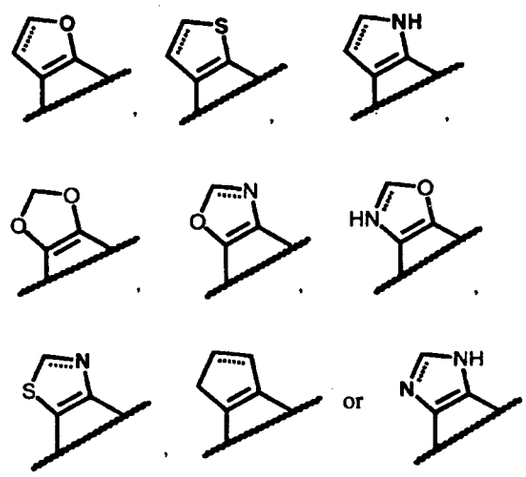
R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and R^{10} is :





each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl;

In a further embodiment, the invention provides compounds of formula (I), wherein ring Z is

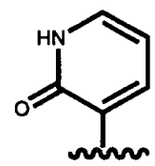


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

R^1 is a bond or $-CH_2-$;

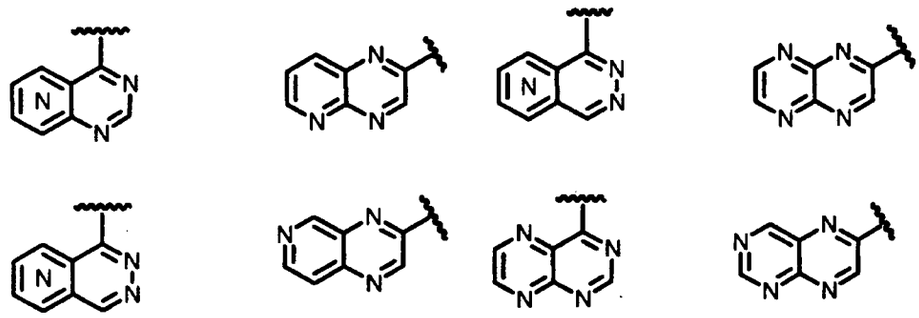
R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

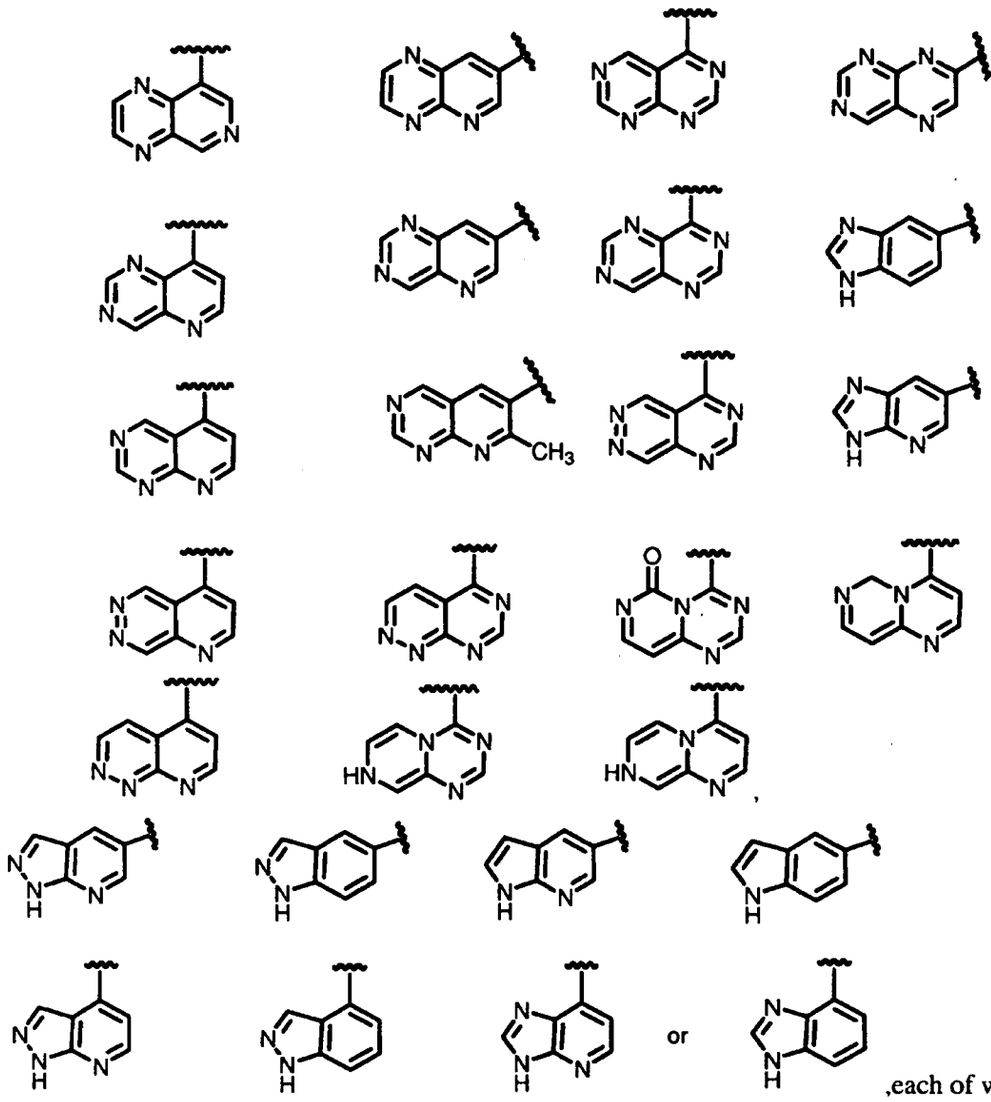
R^3 is



;

R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and R^{10} is:

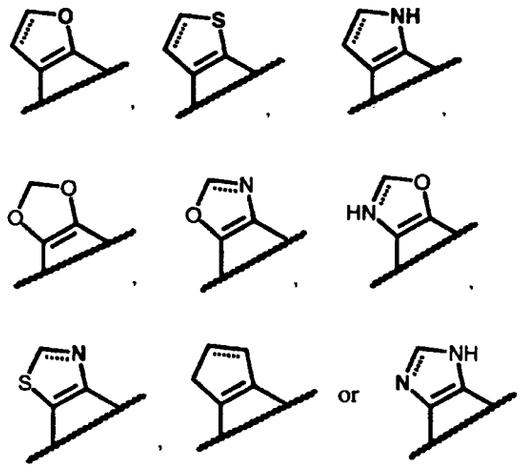




or

,each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

In still another embodiment, the invention provides compounds of formula (I), wherein ring Z is

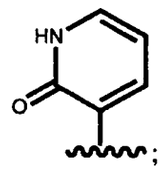


wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1;

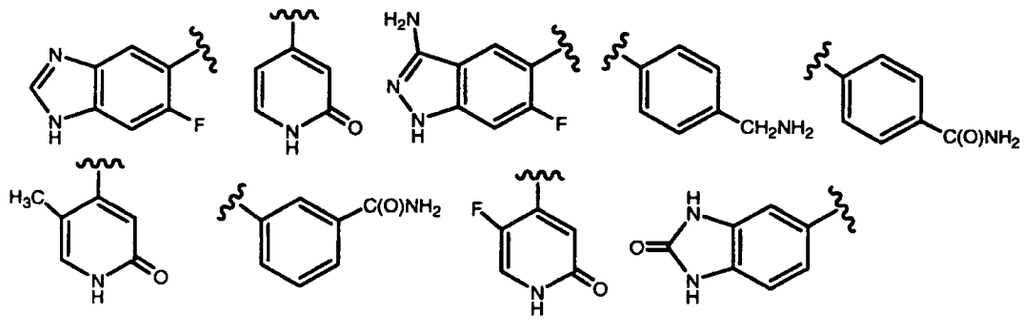
R^1 is a bond or $-CH_2-$;

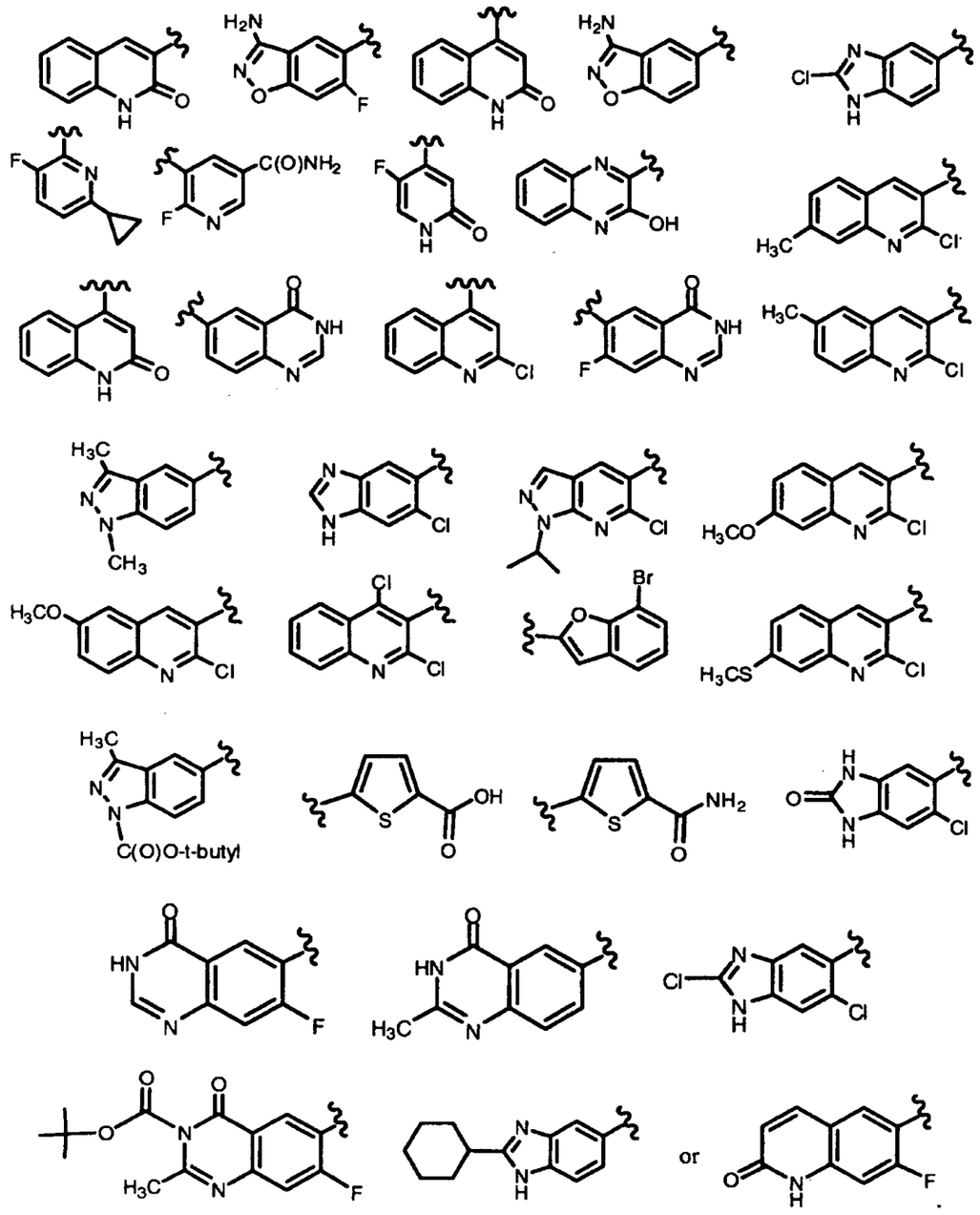
R^2 is -C(O)OH or $-C(O)NHSO_2R^{11}$;

R^3 is

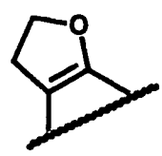


R^6 and R^7 are each independently selected from H, methyl, F, Cl, $-CF_3$, -OH, methoxy, $-OCF_3$, $-NH_2$ or $-NHSO_2CH_3$; and R^{10} is :





In one embodiment, the invention provides compounds of formula (I), wherein ring Z is:



which can be substituted with up to 3 optional ring carbon substituents, which are the same or different, and which are selected from H, alkyl, -OH, F, Cl, -O-alkyl, $-CF_3$, $-OCF_3$ and cycloalkyl;

R^1 is a bond or $-[C(R^{12})_2]_r-$;

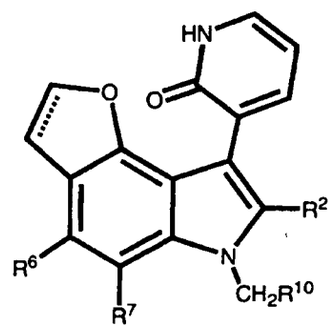
R^2 is $-C(O)OH$ or $-C(O)NHSO_2R^{11}$;

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ or $-SO_2NHR^{11}$;

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In one embodiment, the compounds of formula (I) have the formula (Ia):



(Ia)

wherein the dotted line indicates an optional and additional bond;

R^2 is $-C(O)OR^9$ or $-C(O)NHSO_2R^{11}$;

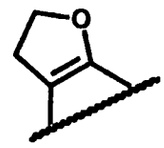
R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ and $-NHSO_2$-alkyl;

R^9 is H or alkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q$-heteroaryl, $-[C(R^{12})_2]_q$-haloalkyl, $-[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ and $-SO_2N(R^9)C(O)N(R^9)_2$; and

R^{11} is alkyl, aryl or cycloalkyl.

In one embodiment, ring Z is:



In another embodiment, R^2 is -C(O)OH.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$.

In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$, wherein R^{11} is alkyl, aryl or cycloalkyl.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$, wherein R^{11} is methyl, ethyl, isopropyl, t-butyl, phenyl or cyclopropyl.

In another embodiment, R^6 and R^7 are each H.

In a further embodiment, R^6 is other than H and R^7 is H.

In one embodiment, R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

In another embodiment, R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or

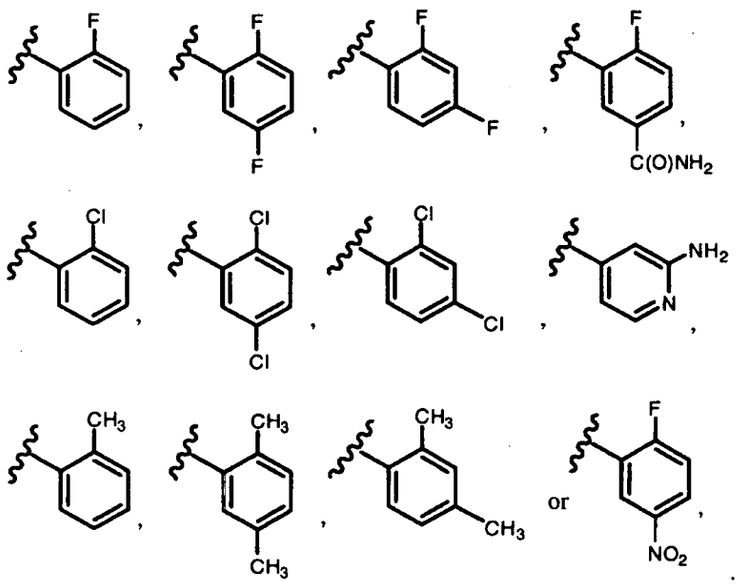
different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO$_2$R^{11}, -S(O)$_p$R^{11} or -SO$_2$N(R^9)$_2$.

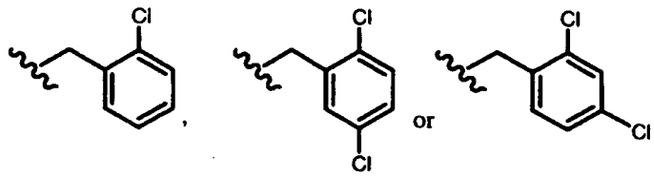
In still another embodiment, R^{10} is bicyclic heteroaryl, which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -(alkylene)-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO$_2$R^{11}, -S(O)$_p$R^{11} or -SO$_2$N(R^9)$_2$.

In another embodiment, R^{10} is quinoline, quinolinone, pteridine or pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH$_2$, -NH-alkyl, -N(alkyl)$_2$ or –NHSO$_2$-alkyl.

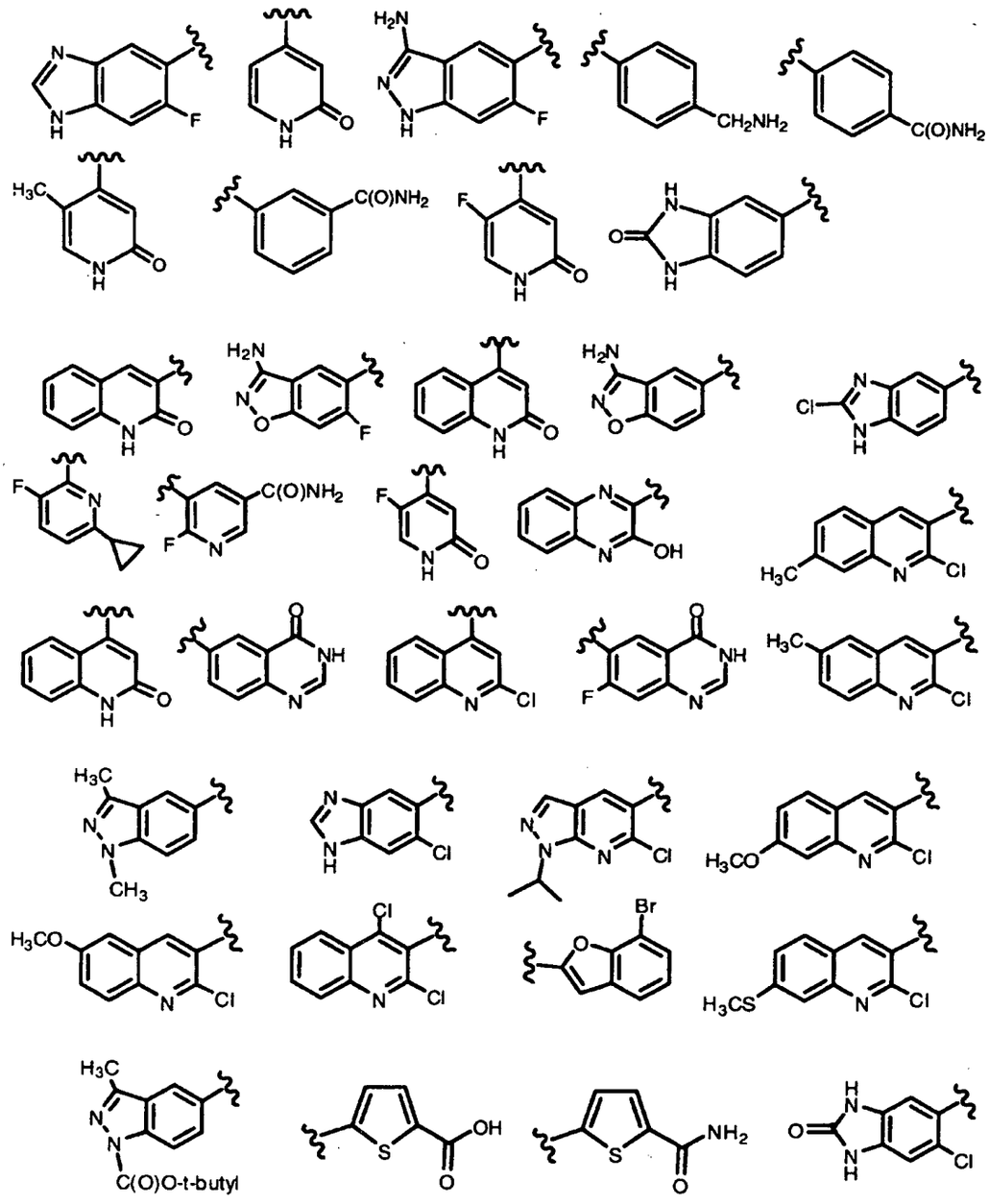
In one embodiment, R^{10} is quinoline or quinolinone, either of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH$_2$, -NH-alkyl, -N(alkyl)$_2$ or –NHSO$_2$-alkyl.

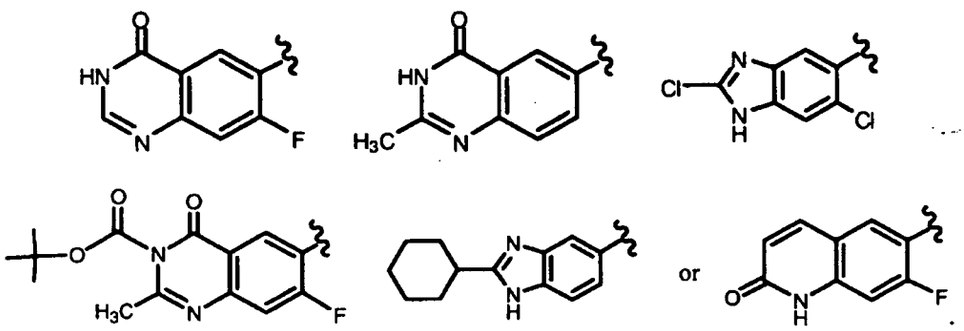
In one embodiment, R^{10} is:



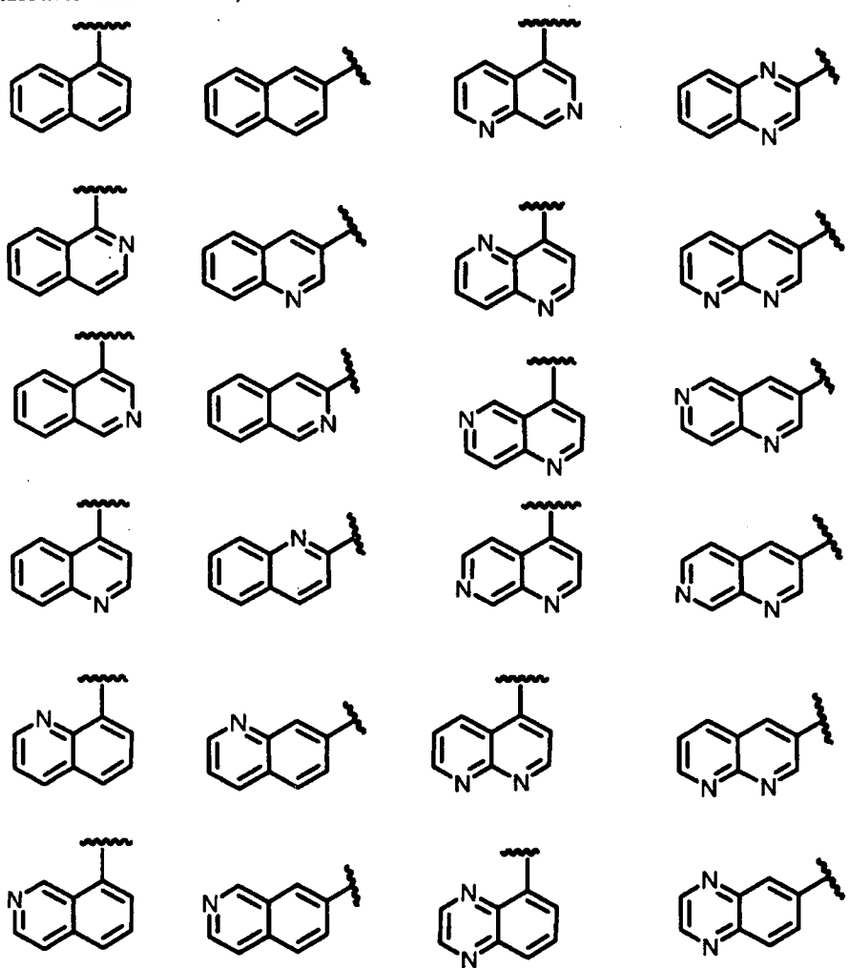


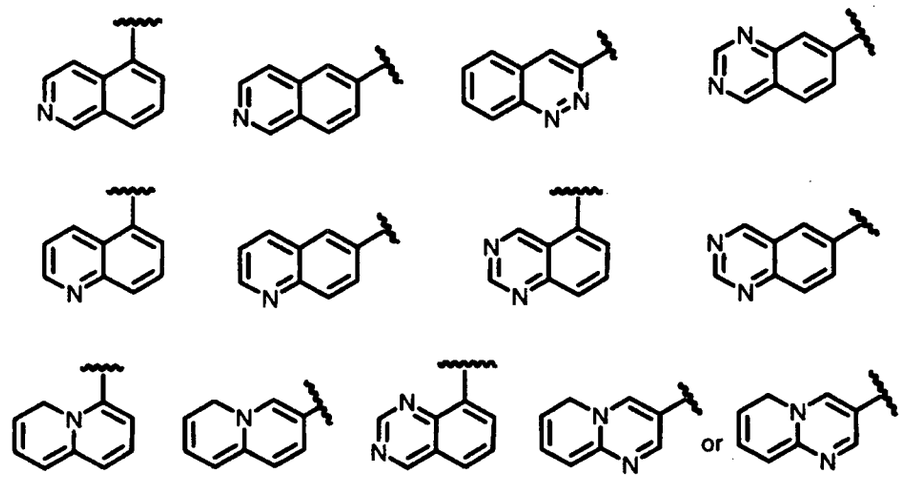
In another embodiment, R^{10} is:





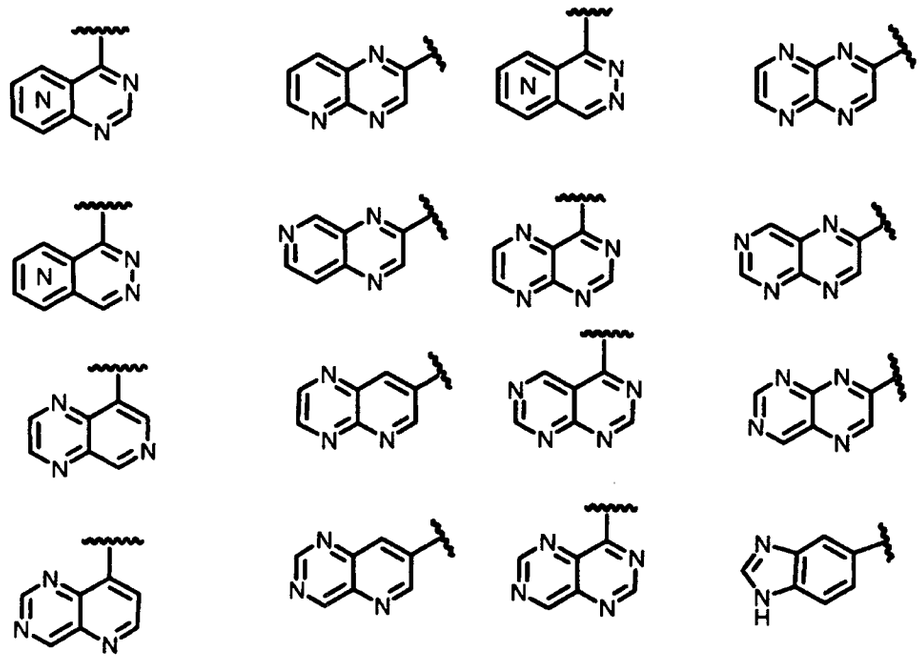
In another embodiment, R^{10} is:

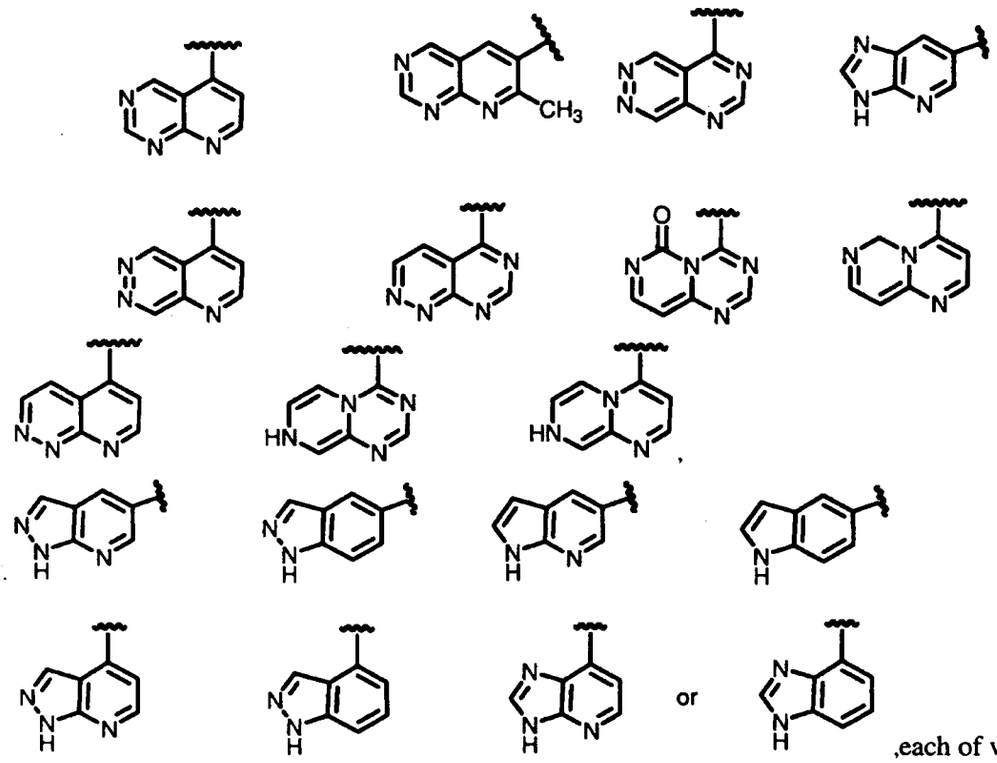




each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

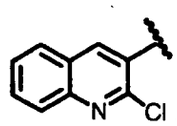
In still another embodiment, R^{10} is:





or ,each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -$N(alkyl)_2$ or –$NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

In one embodiment, R^{10} is:



.

In one embodiment, R^2 is –C(O)OH; the optional bond is absent; and R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -$C(O)N(R^9)_2$, -alkylene-OR^9, -OR^9, -$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ or -$SO_2N(R^9)_2$.

In another embodiment, R^2 is –C(O)OH; the optional bond is absent; and R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up

to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO_2R^{11}, -S(O)$_p R^{11}$ or -SO_2N(R^9)$_2$.

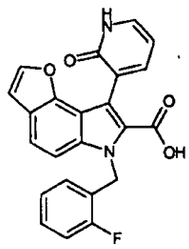
In another embodiment, R^2 is –C(O)OH; the optional bond is absent; and R^{10} is quinoline, quinolinone, pteridine or pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –NHSO_2-alkyl.

In one embodiment, for the Compounds of Formula (I), R^1, R^2, R^3, R^6, R^7, R^{10} and Z are selected independently from each other.

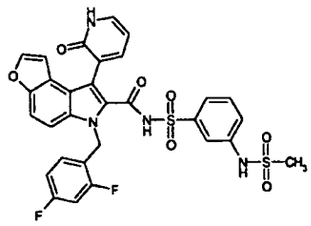
In another embodiment, a Compound of Formula (I) is in purified form.

Non-limiting examples of the Compounds of Formula (I) include, but are not limited to, the following compounds:

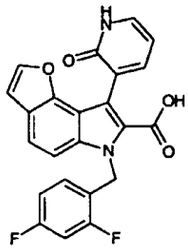
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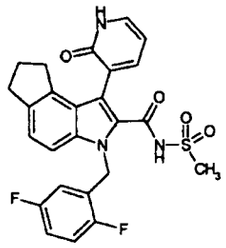
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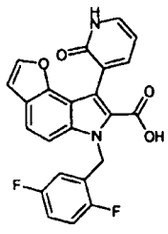
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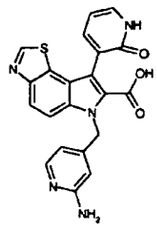
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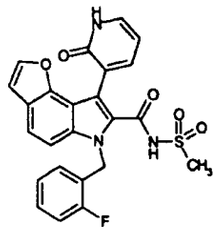


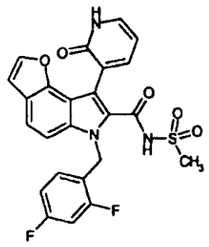
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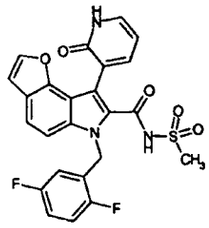


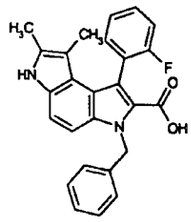
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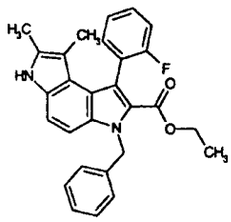


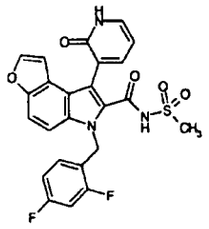
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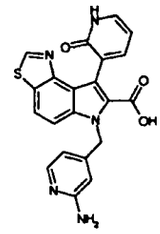
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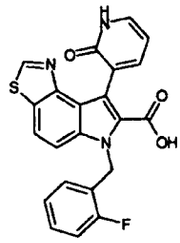
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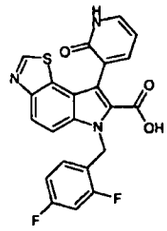
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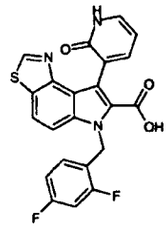
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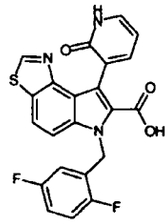
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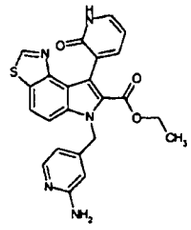
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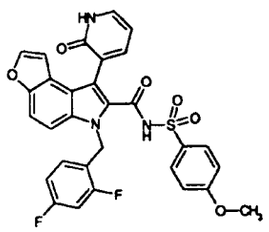
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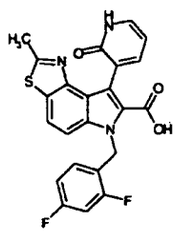
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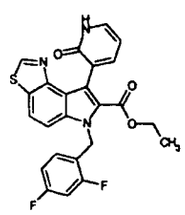
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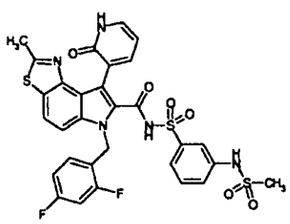
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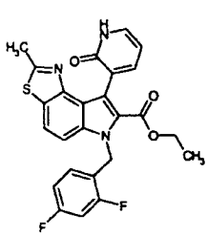
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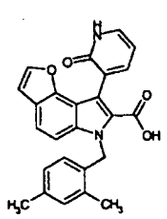
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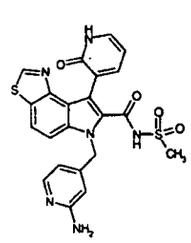
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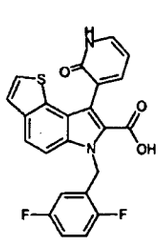
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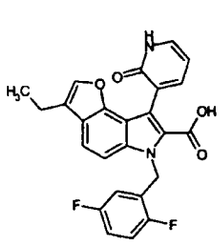
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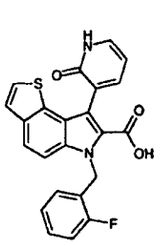
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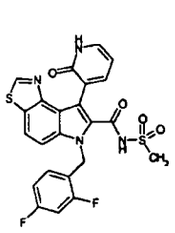
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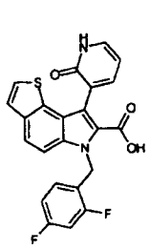
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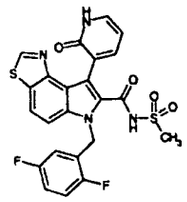
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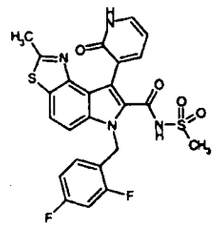
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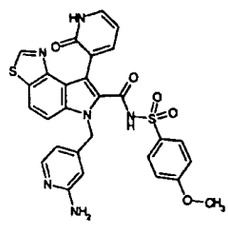
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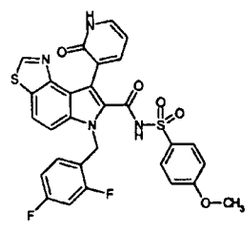
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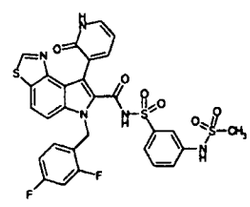
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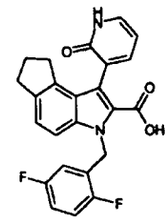
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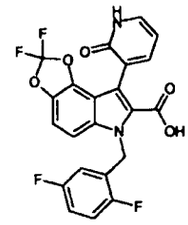
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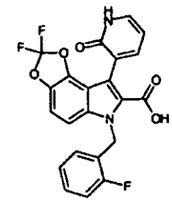
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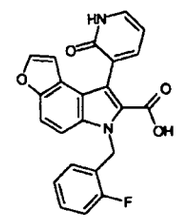
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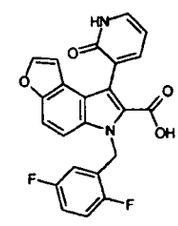
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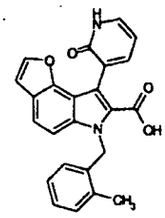
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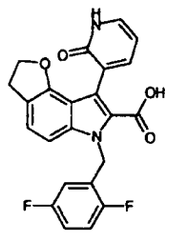
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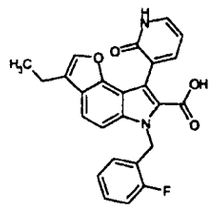
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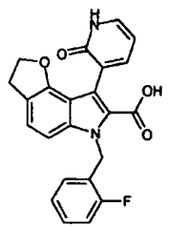
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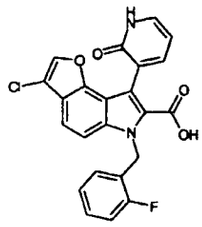
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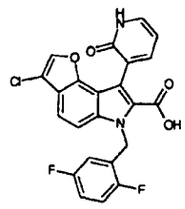
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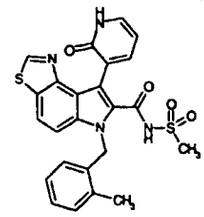
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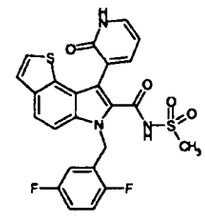
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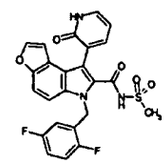
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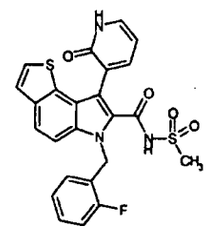
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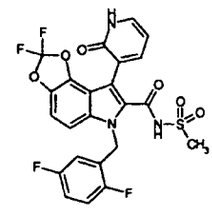
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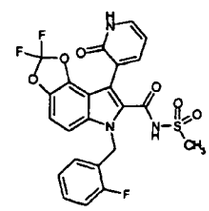
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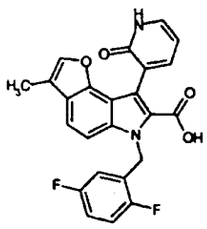
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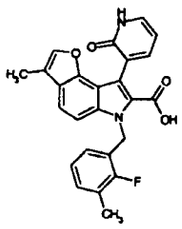
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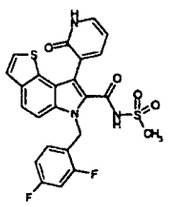
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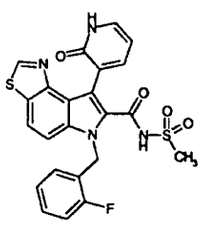
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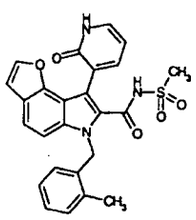
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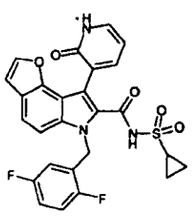
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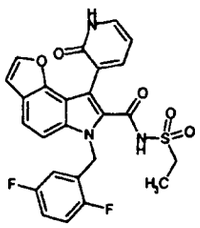
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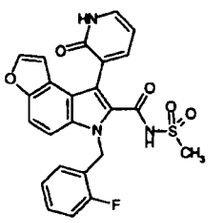
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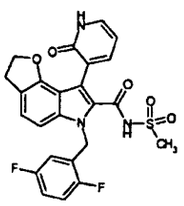
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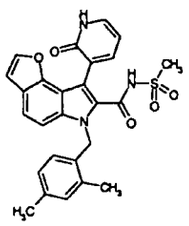
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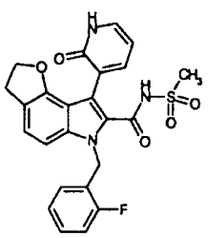
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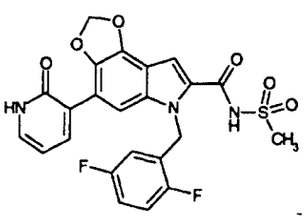
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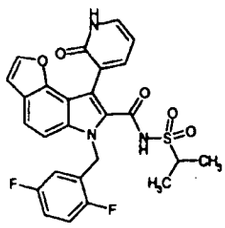
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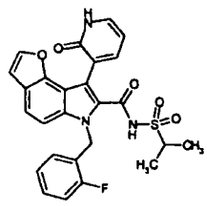
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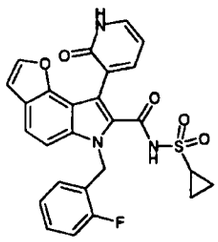
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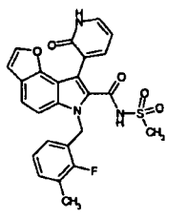
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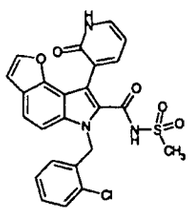
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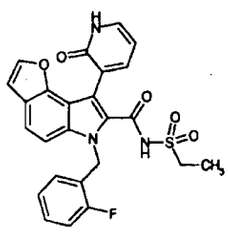
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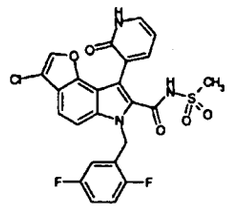
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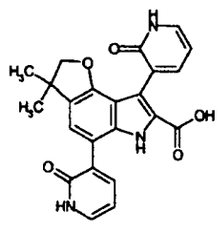
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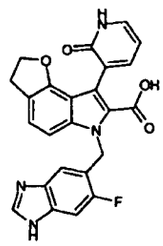
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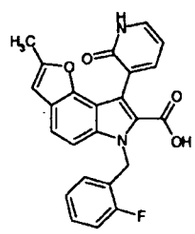
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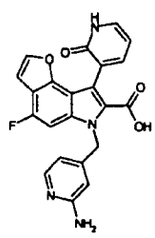
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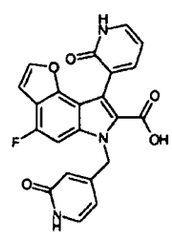
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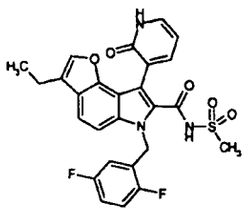
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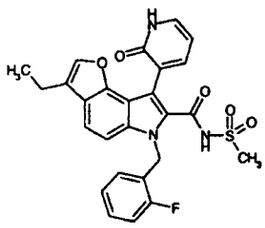
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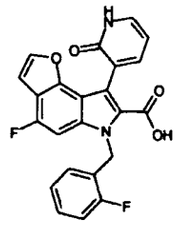
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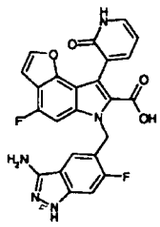
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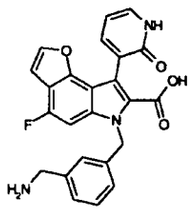
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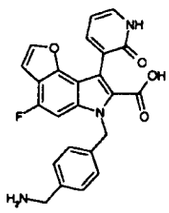
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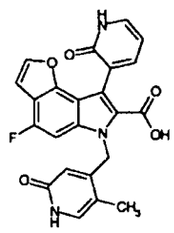
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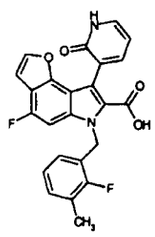
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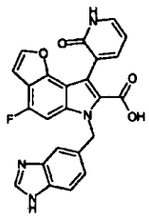
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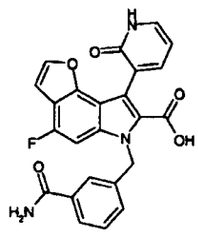
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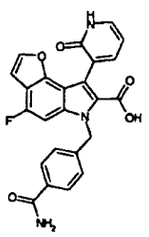
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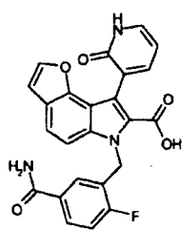
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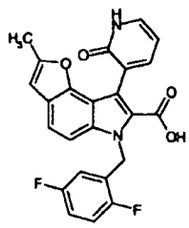
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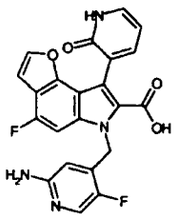
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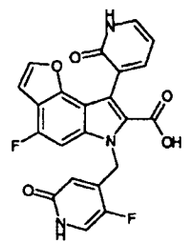
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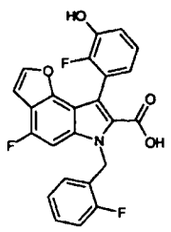
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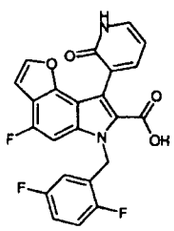
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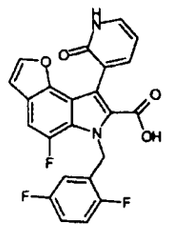
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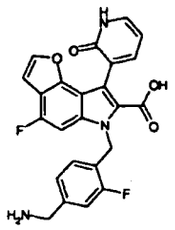
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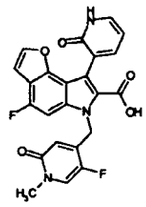
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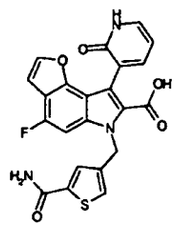
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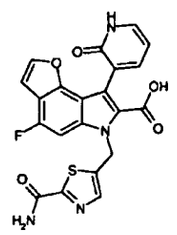
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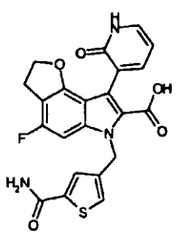
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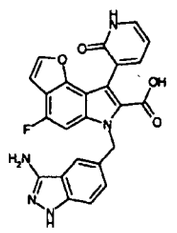
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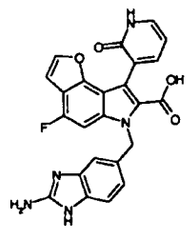
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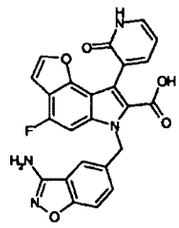
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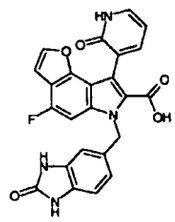
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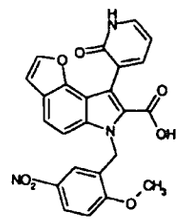
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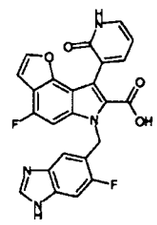
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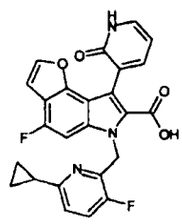
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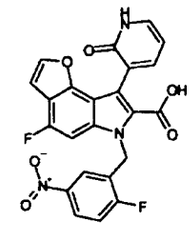
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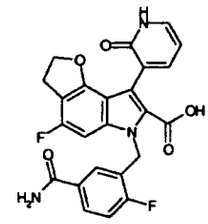
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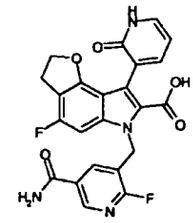
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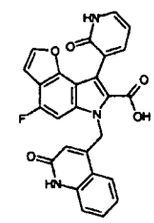
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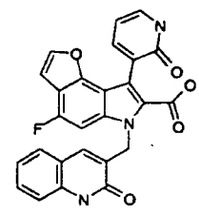
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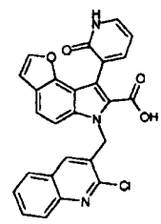
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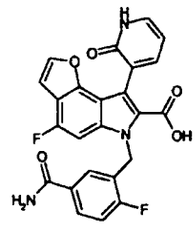
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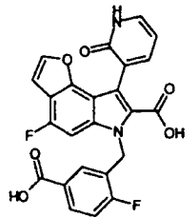
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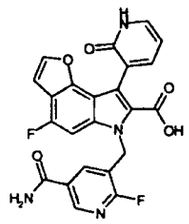
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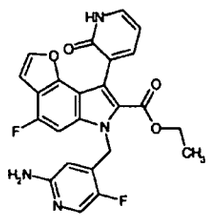
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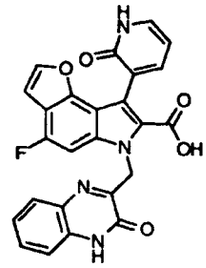
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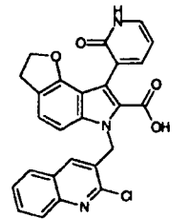
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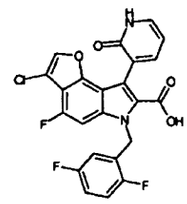
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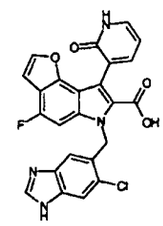
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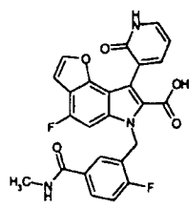
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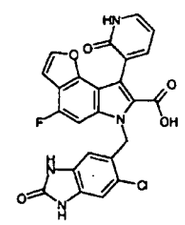
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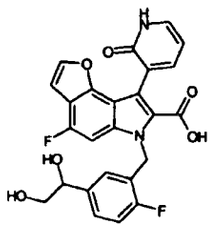
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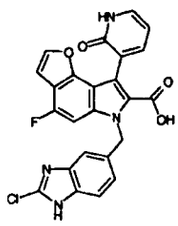
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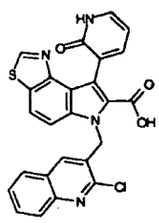
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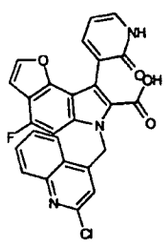
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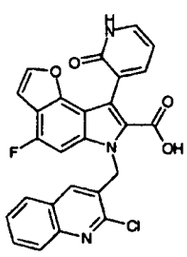
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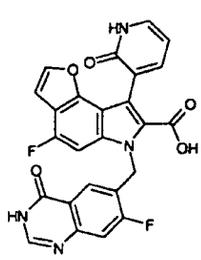
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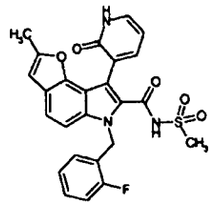
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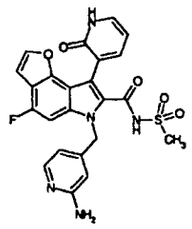
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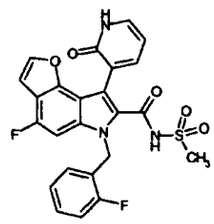
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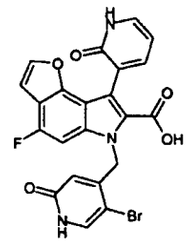
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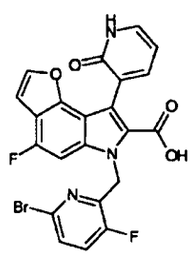
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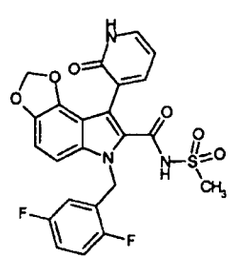
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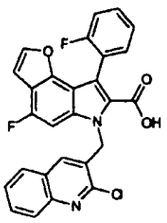
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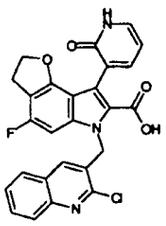
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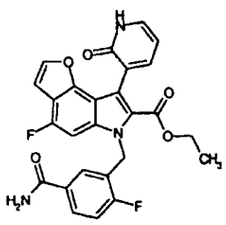
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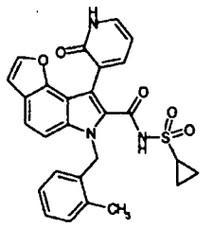
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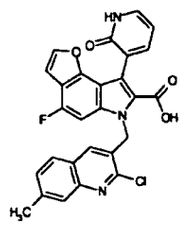
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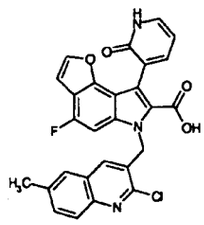
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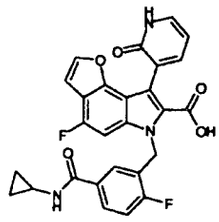


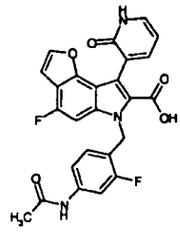
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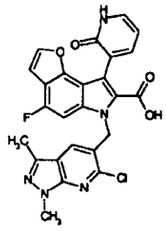


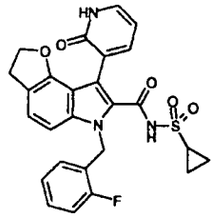
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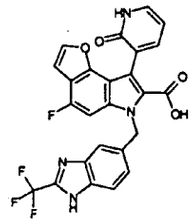


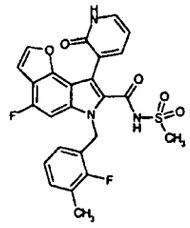
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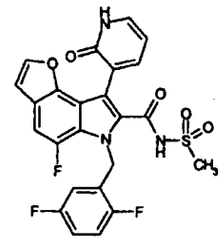
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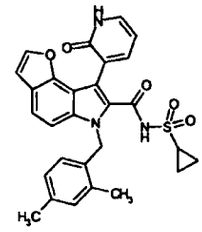
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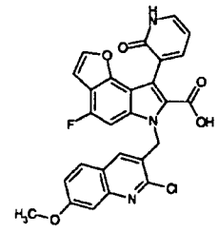
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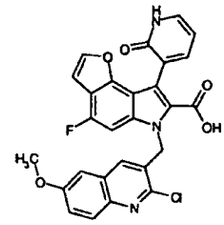
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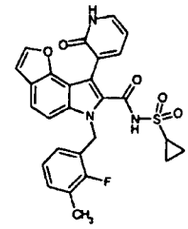
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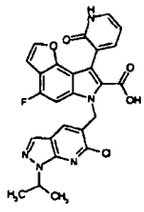
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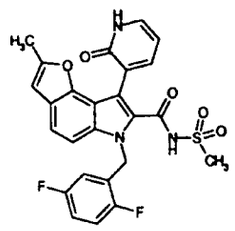
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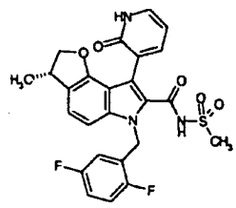
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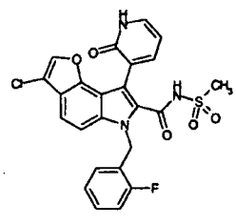
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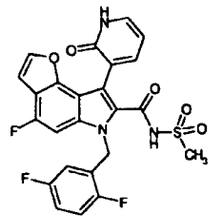
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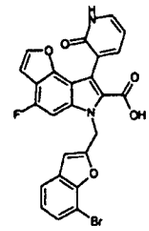
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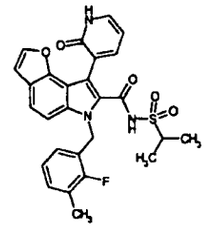
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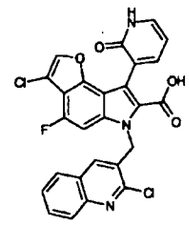
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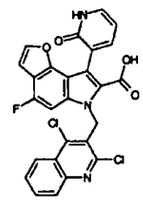
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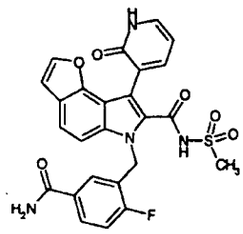
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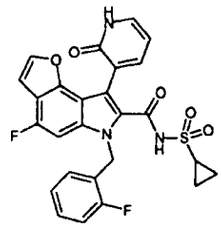
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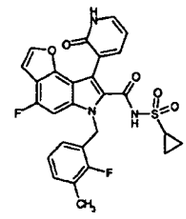
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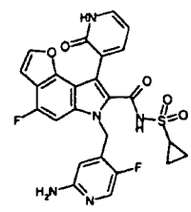
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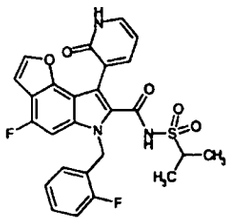
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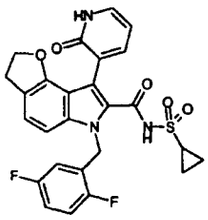
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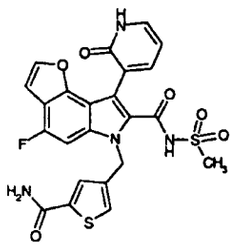
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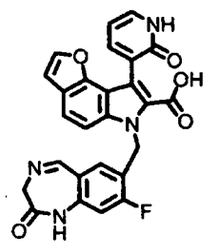
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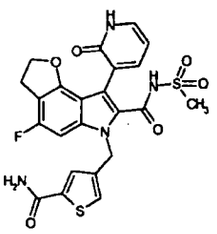
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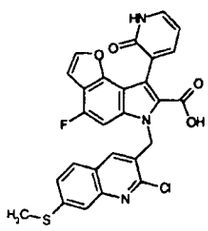
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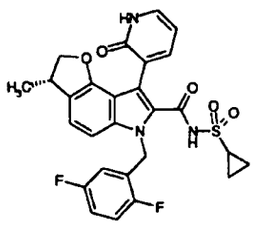
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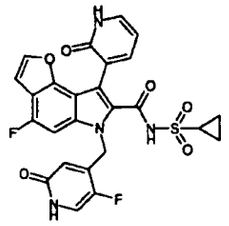
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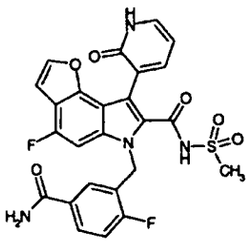
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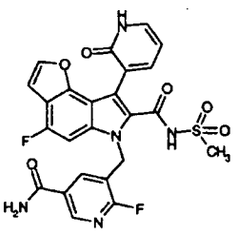
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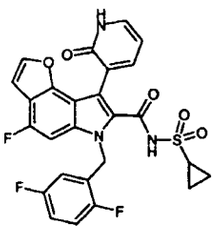
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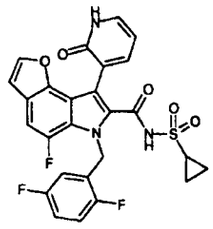
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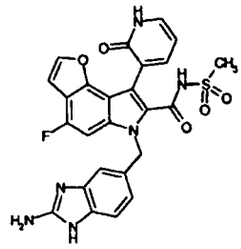
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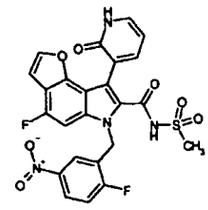
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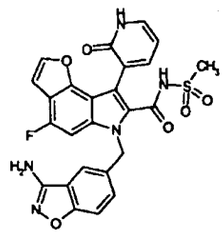
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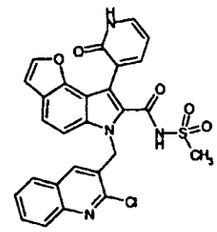
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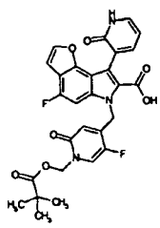
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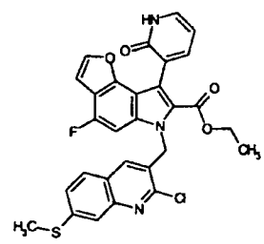
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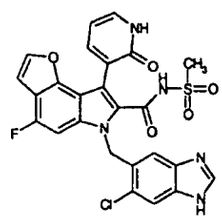
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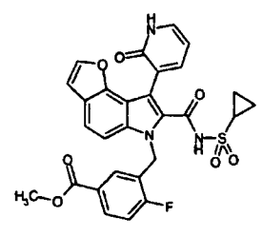
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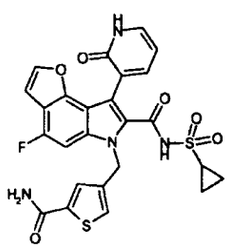
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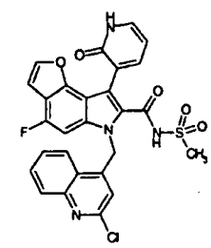
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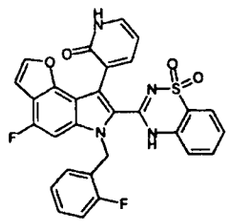
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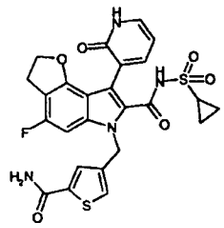
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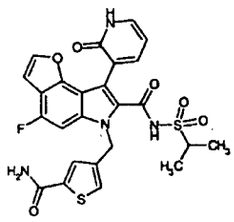
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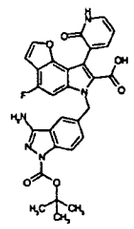
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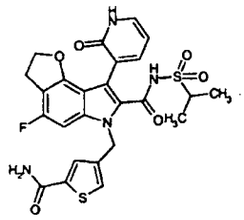
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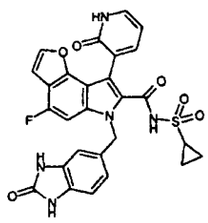
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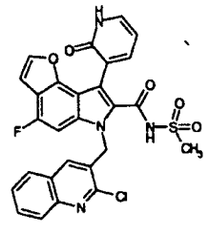
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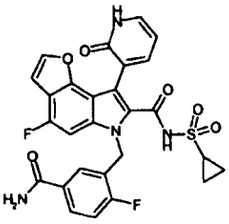
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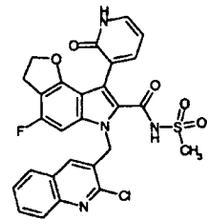
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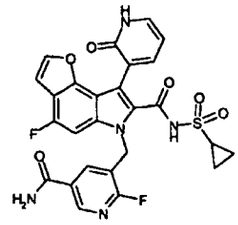
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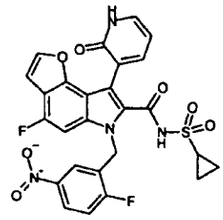
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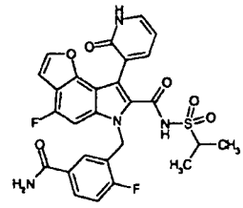
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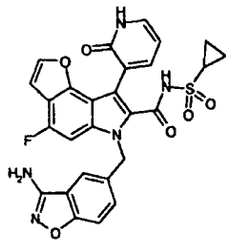
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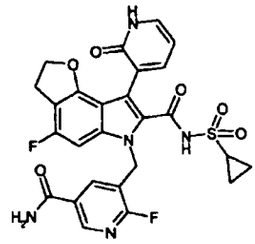
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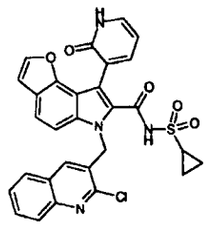
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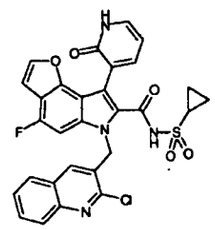
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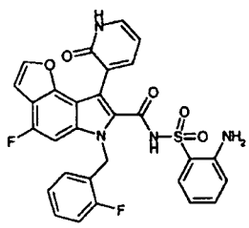
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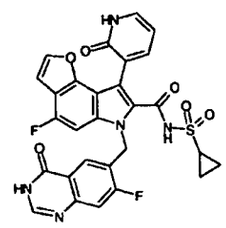
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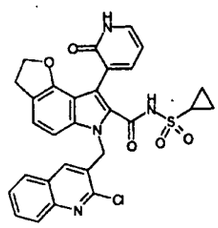
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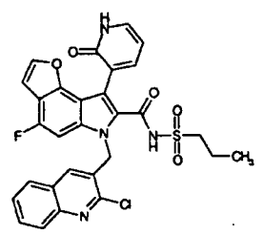
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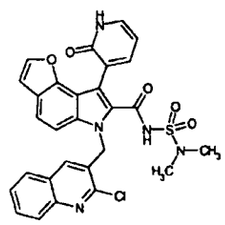
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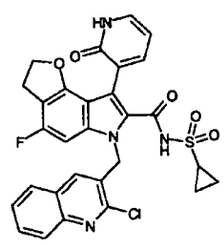
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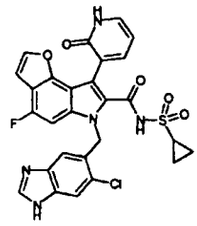
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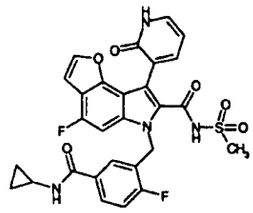
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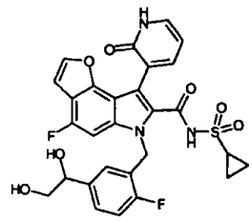
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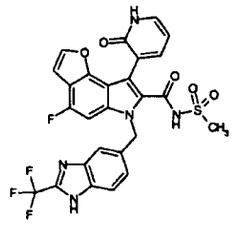
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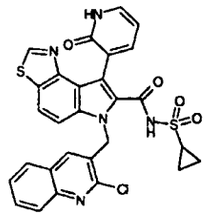
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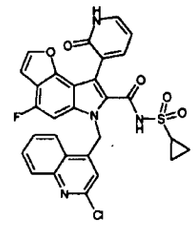
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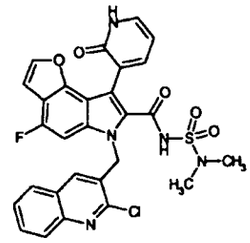
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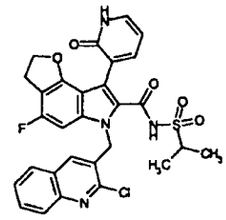
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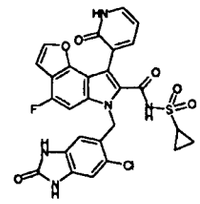
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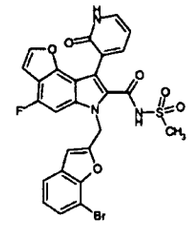
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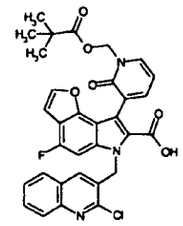
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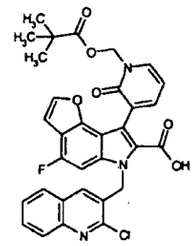
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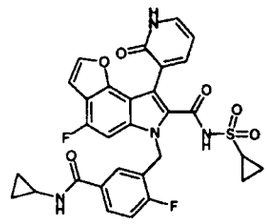
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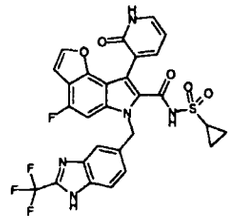
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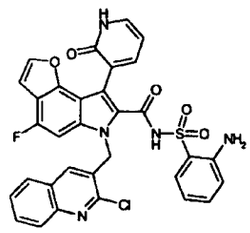
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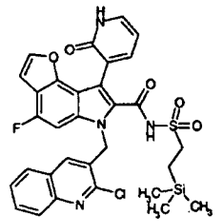
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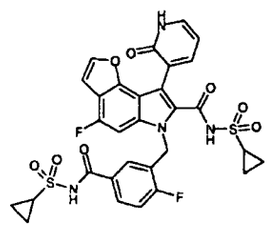
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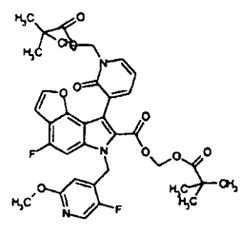
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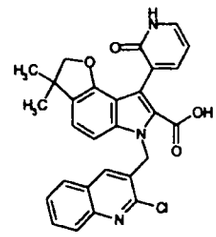
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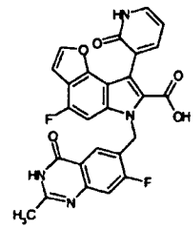
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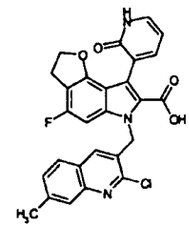
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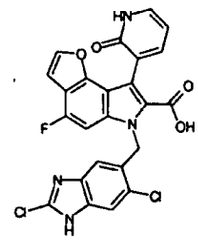
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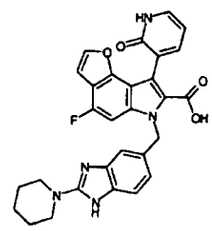
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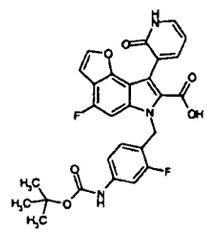
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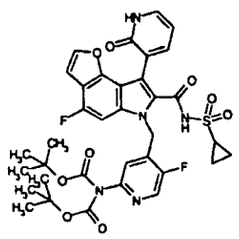
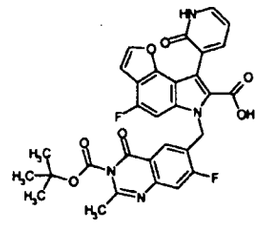
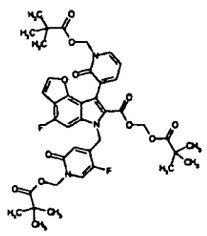
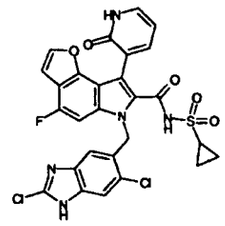
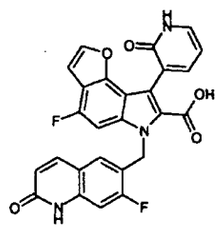
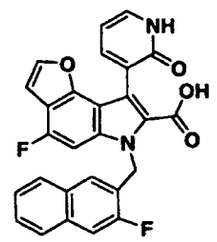
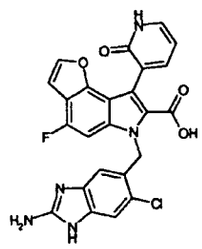
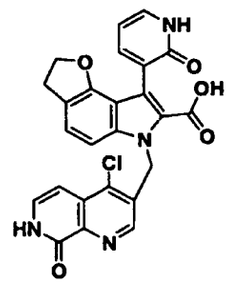
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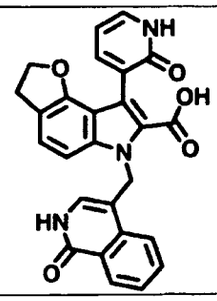
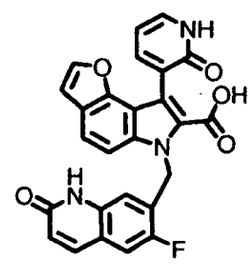
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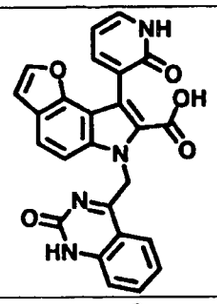
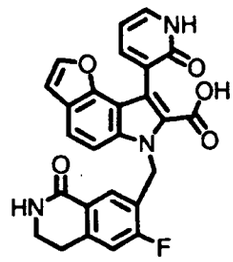
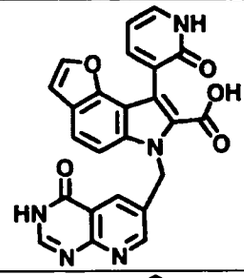
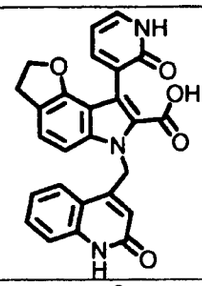
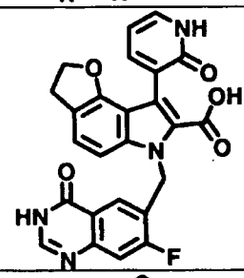
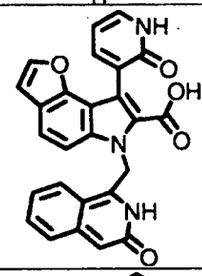
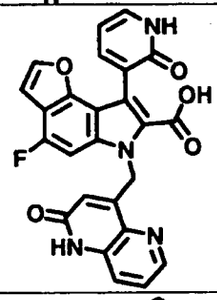
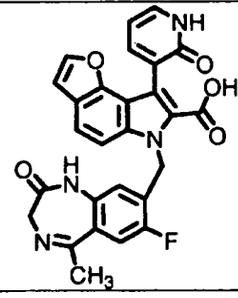
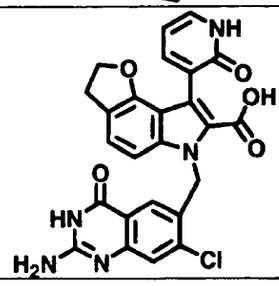
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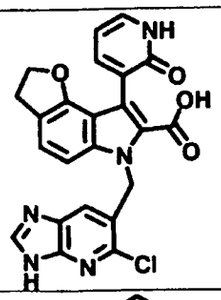
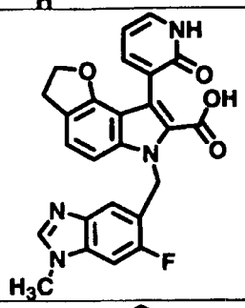
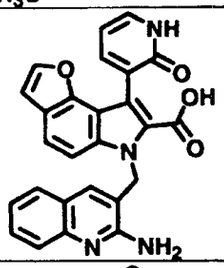
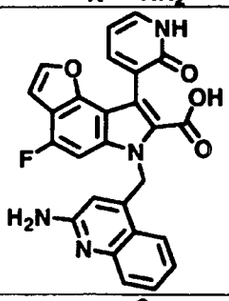
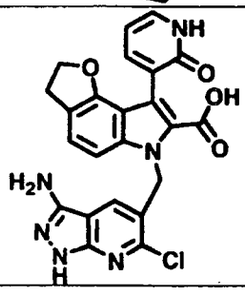
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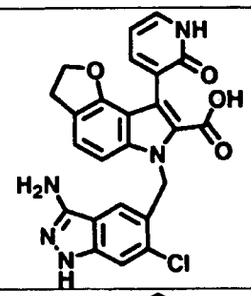
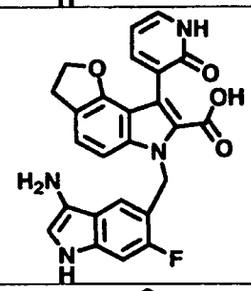
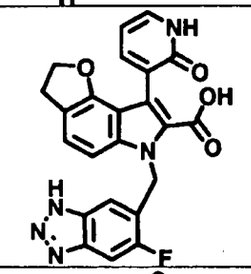
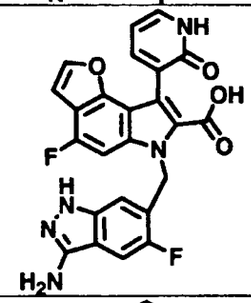
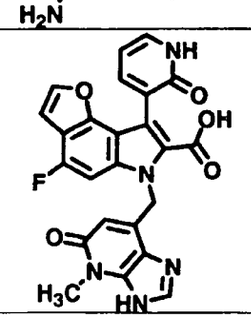
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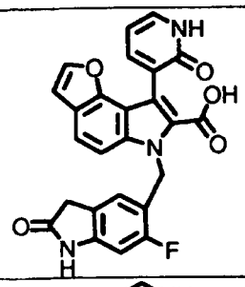
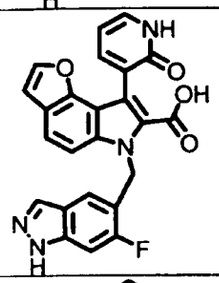
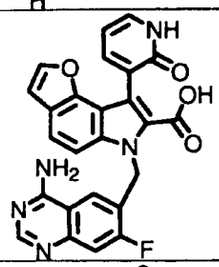
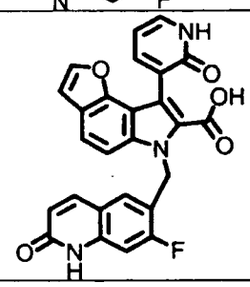
227		**237**	
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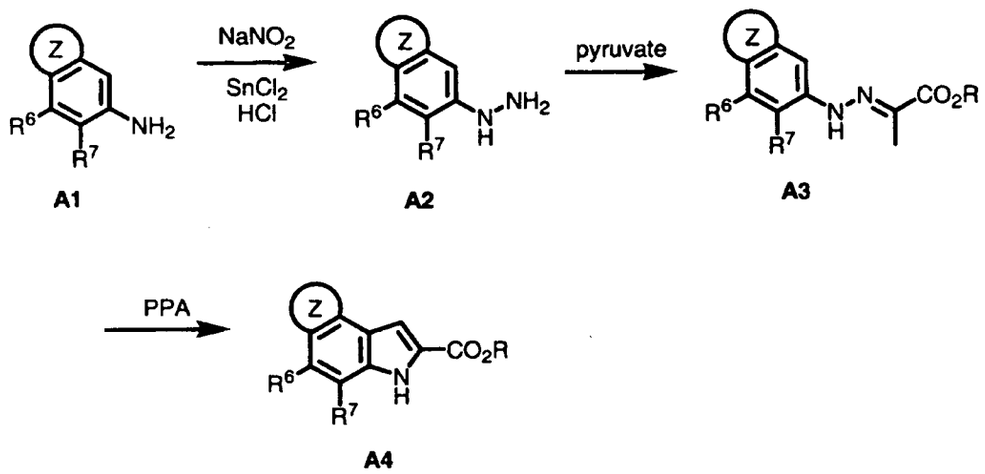
and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof.

Methods For Making the Compounds of Formula (I)

Methods useful for making the Compounds of Formula (I) are set forth in the Examples below and generalized in Schemes 1-9.

Scheme 1 shows one method for preparing compounds of formula **A4**, which are useful intermediates for making of the Compounds of Formula (I).

Scheme 1



A1 **A2** **A3**

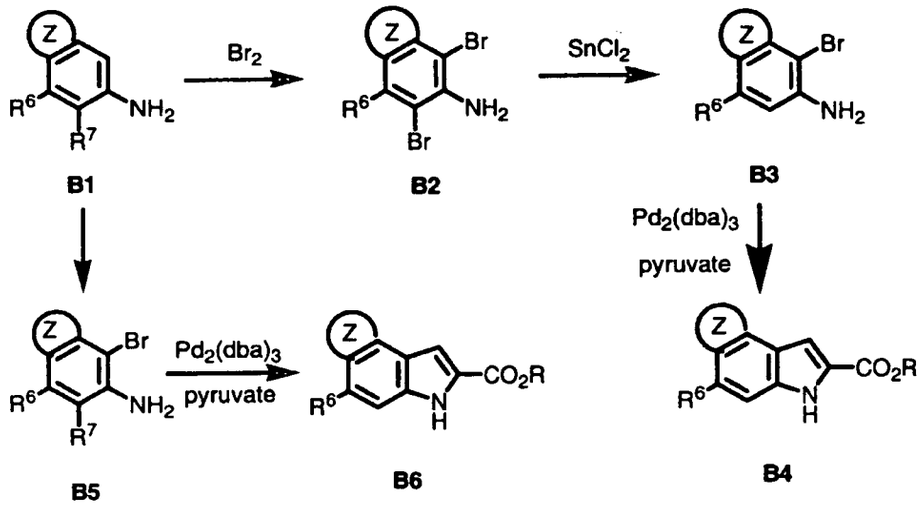
A4

wherein R^6, R^7 and Z are defined above for the Compounds of Formula (I), and R is any carbonyl substituent that is encompassed by R^2, as defined above for the compounds of formula (I).

A 3,4-ring fused aniline compound of formula **A1** can be converted to an indole compound of formula **A4** using various indole syntheses that are well-known to those skilled in the art of organic synthesis, including but not limited to, a Fischer indole synthesis through intermediates of type **A2** and **A3**, the method set forth in Nazare *et al.*, *Angew. Chem.*, 116:4626-4629 (2004).

Scheme 2 shows methods useful for making compounds **B4** and **B6**, which are useful intermediates for making of the Compounds of Formula (I).

Scheme 2

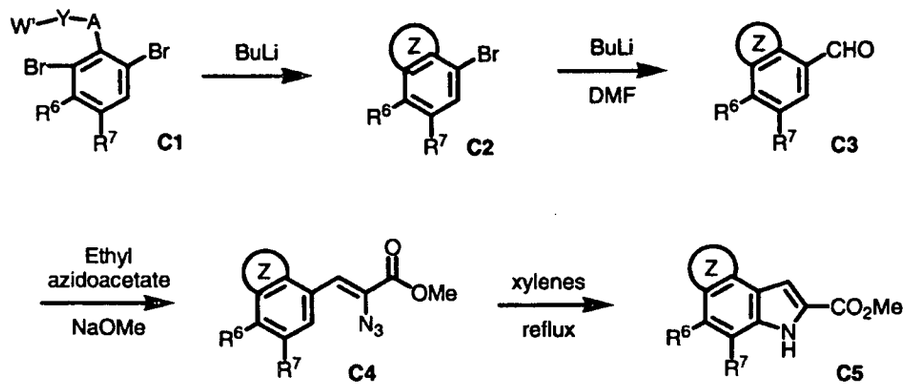


wherein R^6, R^7 and Z are defined above for the Compounds of Formula (I), and R is any carbonyl substituent that is encompassed by R^2, as defined above for the compounds of formula (I).

A bicyclic benzene derivative of formula **B1**, wherein R^7 is H, can be di-brominated to give compound **B2**. Selective de-bromination provides the corresponding monobromo analog **B3**, which under palladium catalyzed cyclization conditions provides the desired intermediate **B4**, wherein R^7 is H. Alternatively a compound of formula **B1**, wherein R^7 is other than H, can be monobrominated to give compound **B5**. Compound **B5** can then undergo under palladium catalyzed cyclization conditions provides the desired intermediate **B6**, wherein R^7 is other than H.

Scheme 3 shows an alternative method to make compounds of formula **C5**, which are analogous to compounds **B4** and **B6** and are also useful intermediates for making of the Compounds of Formula (I).

Scheme 3

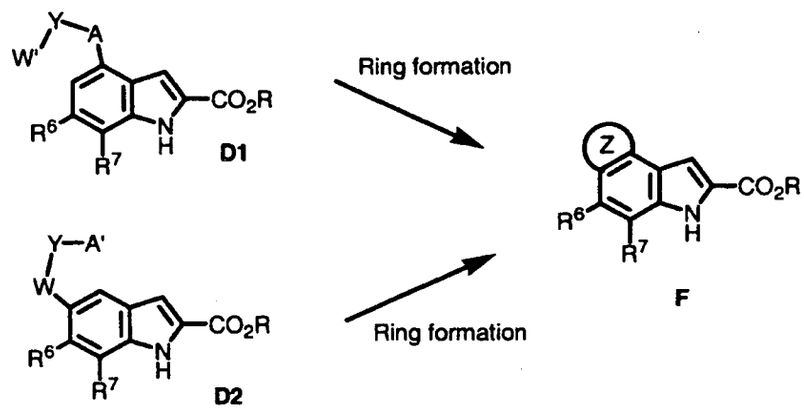


wherein R^6, R^7 and Z are defined above for the Compounds of Formula (I), and W', Y and A are defined below.

A 2,6-dibromophenol compound of formula **C1**, having a group –A-Y-W', wherein A and Y are atoms of ring Z and W' is a group capable of undergoing a ring formation reaction with the aryl bromide group in the presence of n-butyllithium, can be ring closed using ring formation reactions that are well-known to one skilled in the art of organic synthesis to provide compounds of formula **C2**. The bicyclic bromide **C2** can in turn be converted to an aromatic aldehyde of formula **C3**. The aromatic aldehyde **C3** can undergo a condensation reaction in the presence of an alkyl azido acetate to provide the azido compounds of formula **C4** which can be converted to tricyclic indoles of formula **C5** using methods well-known to those skilled in the art of synthetic organic chemistry.

Scheme 4 shows methods useful for making compounds of formula **F**, which are useful intermediates for making of the Compounds of Formula (I)

Scheme 4

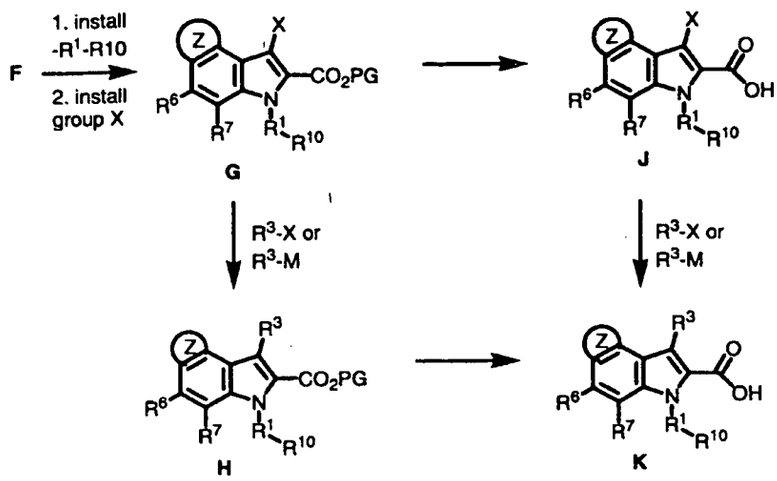


wherein R^6, R^7 and Z are defined above for the Compounds of Formula (I); R is any carbonyl substituent that is encompassed by R^2, as defined above for the compounds of formula (I); and W, W', Y, A and A' are defined below.

A compound of formula **D1**, having a group –A-Y-W', wherein A and Y are atoms of ring Z and W' is a group capable of undergoing a ring formation reaction with the benzene ring to which –A-Y-W' is attached, can undergo numerous ring formation reactions that are well-known to one skilled in the art of organic synthesis to form the tricyclic compounds of formula **F**. Similarly, a compound of formula **D2**, having a group –W-Y-A', wherein W and Y are atoms of ring Z and A' is a group capable of undergoing a ring formation reaction with the benzene ring to which –W-Y-A' is attached, can undergo numerous ring formation reactions that are well-known to one skilled in the art of organic synthesis to form the tricyclic compounds of formula **F**. Examples of ring formation methods include, but are not limited to, those disclosed in as *Comprehensive Heterocyclic Synthesis* (Pergamon Press); John *et al.*, *J. Org. Chem*, 47:2196 (1982); Maria *et al.*, *Synthesis*, 1814 (2000); Martin *et al.*, *J. Med. Chem.*, 44:1561 (2001); Morsy et al., *Pak. J. Sci. Ind. Res*, 43:208 (2000); Koguro *et al.*, *Synthesis*, 911 (1998); Cowden *et al.*, *Tet. Lett.*, 8661 (2000); Norton *et al.*, *Synthesis*, 1406 (1994); Carl *et al.*, *Tet. Lett.*, 2935 (1996); Gunter *et al.*, *J. Org. Chem*, 46:2824 (1981).

Scheme 5 illustrates methods by which intermediate compounds of formula **F** can be further derivatized to provide the Compounds of Formula (I), wherein R^2 is –C(O)OH.

Scheme 5



wherein R^1, R^3 R^6 R^7, R^{10} and Z are defined above for the Compounds of Formula (I); PG is a carboxy protecting group; and X is halo, -O-triflate, $-B(OH)_2$, $-Sn(alkyl)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, or any metal which can participate in an organometallic cross-coupling reaction.

An intermediate compound of formula **F** can be converted to a 3-substituted indole of formula **G** using methods well-known to one skilled in the art of organic synthesis. A compound of formula **G**, wherein X is halo or –O-triflate can then be coupled with an appropriate compound of formula R^3-M (wherein M is $-B(OH)_2$, $-Sn(alkyl)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, or any metal which can participate in an organometallic cross-coupling reaction) using an organometallic cross-coupling method. Alternatively, a compound of formula **G**, wherein X is $-B(OH)_2$, $-Sn(alkyl)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, or any metal which can participate in an organometallic cross-coupling reaction, can then be coupled with an appropriate compound of formula R^3-M (wherein M is halo or -O-triflate) using an organometallic cross-coupling method. Suitable cross-coupling methods include, but not limited to, a Stille coupling (see Choshi *et al.*, *J. Org. Chem.*, 62:2535-2543 (1997), and Scott *et al.*, *J. Am. Chem. Soc.*, 106:4630 (1984)), a Suzuki coupling (see Miyaura *et al.*, *Chem. Rev.*, 95:2457 (1995)), a Negishi coupling (see Zhou *et al.*, *J. Am. Chem. Soc.*, 127:12537-12530 (2003)), and a Kumada coupling (see Kumada, *Pure Appl. Chem.*, 52:669 (1980) and Fu *et al.*, *Angew. Chem.* 114:4363 (2002)) to provide a compound of formula **H**. The carboxy protecting group, PG, can then be removed from the compound of formula **H** and the resulting carboxylic acid can be derivatized using the methods described below in Schemes 6-8 in order to make the appropriate R^2 groups and make the compounds of formula **K**, which correspond to the

compounds formula (I), wherein R^2 is –C(O)OH. Alternatively, a compound of formula **F** can first be deprotected and the R^2 group attached using the above methods to provide a compound of formula **J**. A compound of formula **J** can then be cross-coupled with a compound of R^3-X or R^3-M as described above to provide make the compounds of formula **K**.

Scheme 6 shows a method useful for making the Compounds of Formula (I), wherein R^2 is -C(O)N(R^9)SO_2R^{11}.

Scheme 6

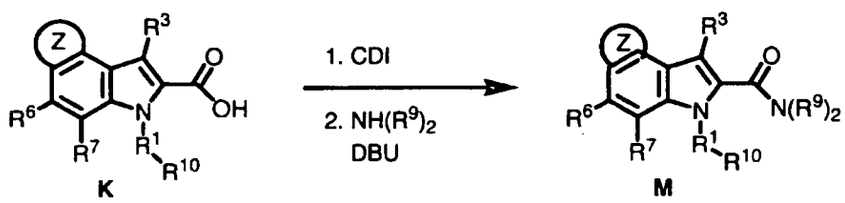


wherein R^1, R^3, R^6, R^7, R^9, R^{10}, R^{11} and Z are as defined for the Compounds of Formula (I).

A 2-carboxy indole compound of formula **K** can be coupled with a compound of formula $R^{11}SO_2NH_2$ in the presence of carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide the compounds of formula **L**, which correspond to the Compounds of Formula (I) wherein R^2 is –C(O)NHSO_2R^{11}.

Scheme 7 shows a method useful for making the Compounds of Formula (I), wherein R^2 is -C(O)N(R^9)$_2$.

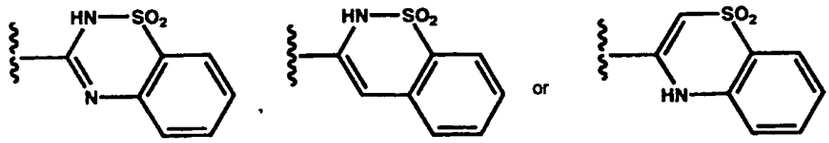
Scheme 7



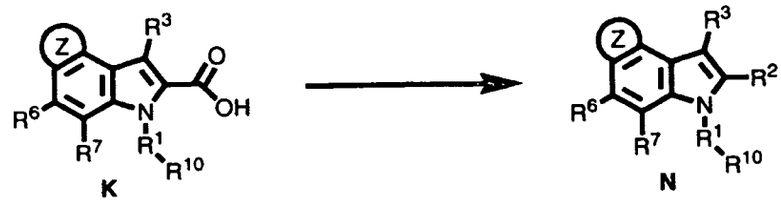
wherein R^1, R^3, R^6, R^7, R^9, R^{10} and Z are as defined for the Compounds of Formula (I).

A 2-carboxy indole compound of formula **K** can be coupled with an amine of formula NH(R^9)$_2$ in the presence of carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide the compounds of formula **M**, which correspond to the Compounds of Formula (I) wherein R^2 is –C(O)N(R^9)$_2$.

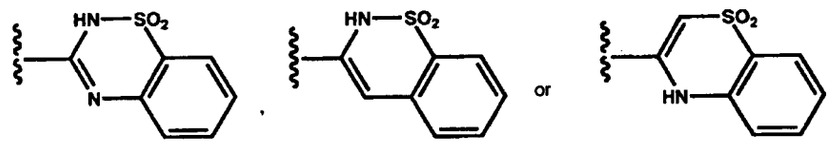
Scheme 8 shows a method useful for making the Compounds of Formula (I), wherein R^2 is:



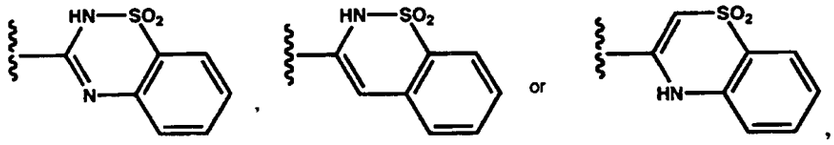
Scheme 8



wherein R^1, R^3, R^6, R^7, R^{10} and Z are as defined for the Compounds of Formula (I) and R^2 is:



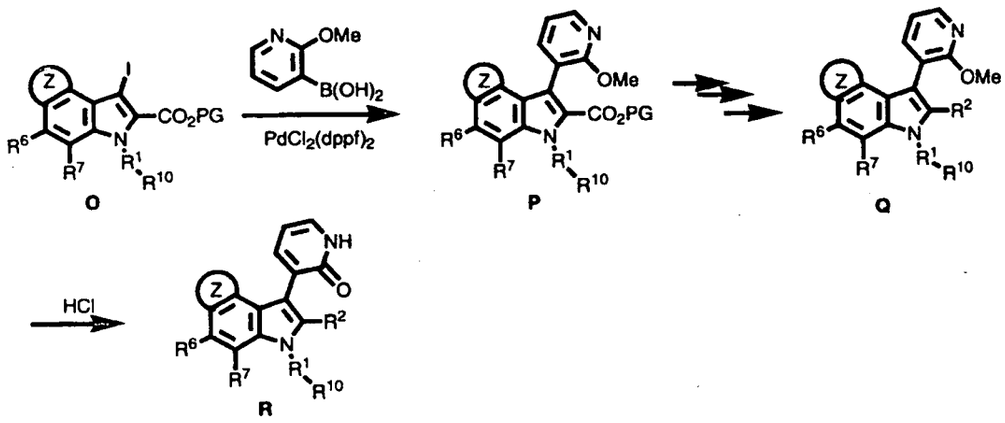
A 2-carboxy indole compound of formula **K** can be converted to the compounds of formula **N**, which correspond to the Compounds of Formula (I) wherein R^2 is:



using the methods set forth in U.S. Patent Application No. US2005/0075331.

Scheme 9 shows a method useful for making the Compounds of Formula (I), wherein R^3 is 1*H*-pyridin-2-one-3-yl.

Scheme 9



wherein R^1, R^2, R^6, R^7, R^{10} and Z are as defined for the Compounds of Formula (I), and PG is a carboxy protecting group.

A 3-iodoindole compound of formula **O** can be coupled with 2-hydroxypyridine-3-boronic acid using a Suzuki coupling reaction to provide the R^3-substituted indole compounds of formula **P**. A compound of formula **P** can be further elaborated using methods set forth above to provide the compounds of formula **Q**. The 2-hydroxypyridyl moiety of a compound of formula **Q** can then be reacted with hydrochloric acid to provide a compound of formula **R**, which corresponds to the Compounds of Formula (I), wherein R^3 is 1*H*-pyridin-2-one-3-yl.

The starting material and reagents depicted in Schemes 1-9 are either available from commercial suppliers such as Sigma-Aldrich (St. Louis, MO) and Acros Organics Co. (Fair Lawn, NJ), or can be prepared using methods well-known to those of skill in the art of organic synthesis.

One skilled in the art will recognize that the synthesis of Compounds of Formula (I) may require the need for the protection of certain functional groups (*i.e.*, derivatization for the purpose of chemical compatibility with a particular reaction condition). Suitable protecting groups for the various functional groups of the Compounds of Formula (I) and methods for their installation and removal can be found in Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

One skilled in the art will also recognize that one route will be optimal depending on the choice of appendage substituents. Additionally, one skilled in the art will recognize that in some cases the order of steps may differ from that presented herein to avoid functional group incompatibilities and amend the synthetic route accordingly.

One skilled in the art will recognize that the synthesis of certain compounds of Formula 1 require the construction of an amide bond. Methods useful for making such amide bonds, include but are not limited to, the use of a reactive carboxy derivative (e.g. acid halide, or ester at elevated temperatures) or the use of an acid with a coupling reagent (e.g. DECI, DCC) with an amine.

The starting materials used and the intermediates prepared using the methods set forth in Schemes 1-9 may be isolated and purified if desired using conventional techniques, including but not limited to filtration, distillation, crystallization, chromatography and the like. Such materials can be characterized using conventional means, including physical constants and spectral data.

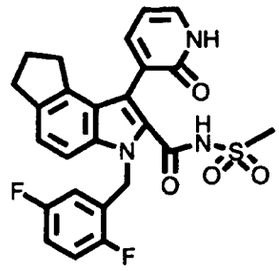
EXAMPLES

General Methods

Solvents, reagents, and intermediates that are commercially available were used as received. Reagents and intermediates that are not commercially available were prepared in the manner as described below. ^{1}H NMR spectra were obtained on a Bruker Avance 500 (500 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33 mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 5-7 min – 95% CH_3CN, 7 min – stop. The retention time and observed parent ion are given. Flash column chromatography was performed using pre-packed normal phase silica from Biotage, Inc. or bulk silica from Fisher Scientific. Unless otherwise indicated, column chromatography was performed using a gradient elution of hexanes/ethyl acetate, from 100% hexanes to 100% ethyl acetate.

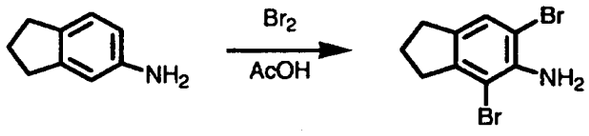
Example 1

Preparation of Compound **12**



12

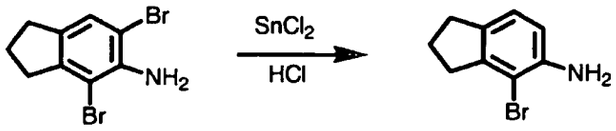
Step A – Synthesis of Compound 12A



12A

To a solution of 5-aminoindane (5.00 g, 37.55 mmol) in acetic acid (200 mL) was added bromine (15 mL). The resulting mixture was allowed to stirfor 1 hour and then concentrated to ~ 100 mL. Chloroform was added to give a precipitate. The solid was isolated by filtration, and washed with chloroform to provide compound **12A** as a lightly tinted solid (12.63 g). mp 220-221° C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.07 (m, 2H), 2.90 (m, 4H), 7.33 (s, 1H).

Step B – Synthesis of Compound 12B

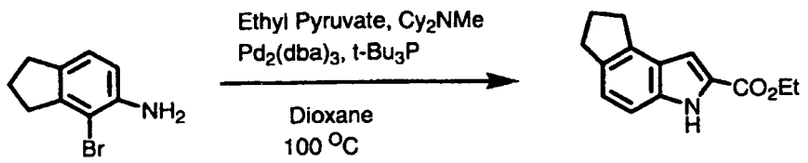


12A **12B**

Stannous chloride (0.89 g) was added to a solution of compound **12A** (1.0g, 3.5 mmol) in acetic acid (5 mL) and aqueous concentrate HCl (4 mL). The resulting mixture was heated at reflux for 30 minutes, then cooled to room temperature. The solvents were then removed *in vacuo* and the resulting residue was partitioned between aqueous NaOH and CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined

organic phases were dried with $MgSO_4$ and concentrated to provide a crude residue that was purified using silica gel chromatography (EtOAc:Hexane=1:20) to provide compound **12B** (0.501 g) as a white solid. ^1H NMR (400MHz, CDCl3) δ 6.95 & 6.93 (d, J = 8.05 Hz, 1H), 6.59 & 6.57 (d, J = 7.32 Hz, 1H), 3.96 (s, 2H), 2.91 (q, J = 7.32 & 15.38 Hz, 4H), 2.07 (qintet, J = 7.32 Hz, 2H).

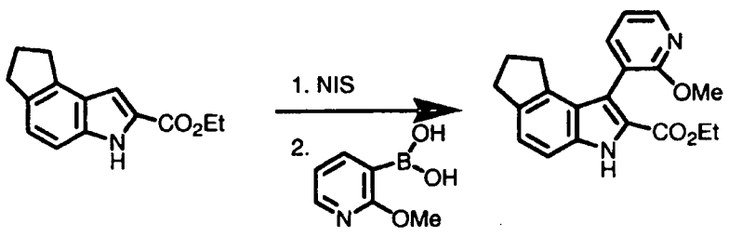
Step C – Synthesis of Compound 12C



12B **12C**

$Pd_2(dba)_3$ (185 mg) was added to a dioxane (20 mL) solution of compound **12B** (0.455 g, 2.1 mmol), tri-tert-butylphosphine (0.81 mL of a 1.0 M solution in toluene), dicyclohexylmethylamine (2.92 mL) and ethyl pyruvate (0.9 mL).The mixture was heated at 100° C under an atmosphere of nitrogen overnight. After cooling, the reaction mixture was partitioned between CH_2Cl_2 and diluted with aqueous HCl (1N). The organic phase was separated and extracted with CH_2Cl_2 (2X). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The crude reaction product was purified using flash column chromatography on silica gel (EtOAc/Hexane=1:10) to provide compound **12C** (0.263 g). MS found for $C_{14}H_{15}NO_2$ = 230.07 (M+H).

Step D – Synthesis of Compound 12D

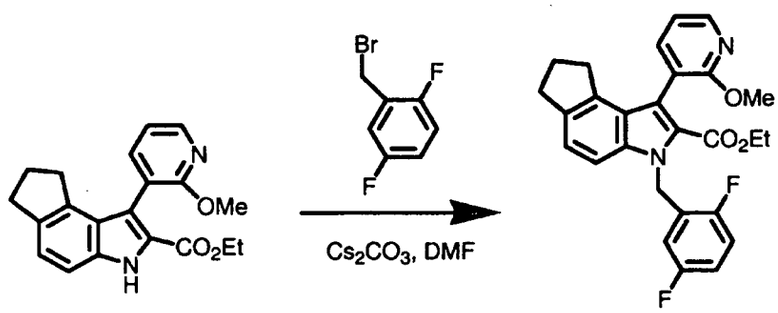


12C **12D**

N-iodosuccinimide (0.402 g, 2.05 mmol) was added to a allowed to stirsolution of solution of compound **12C** (0.47 g, 2.05 mmol) in CH_2Cl_2 (15 mL) at 4° C. The reaction was monitored by TLC until no starting materials remained (about 1 hour). The reaction was

partitioned between EtOAc and diluted with aqueous sodium thiosulfate (5 %). The organic phase was separated, washed with sat. aqueous sodium bicarbonate and water. The crude product was used directly in the next step without purification. The SME (30 mL) solution of the above crude indole and $PdCl_2$ $(DPPF)_2$ (0.141 g, 0.1 eq) was heated to 90 °C (oil bath temperature) for a period of 0.5 hour and a solution of the boronic acid (0.318 g, 1.2 eq) and potassium carbonate (1.197 g, 5 eq) in H_2O/DME (6 mL/6mL) was added dropwise. When the addition was complete the reaction mixture was heated to 150 °C (oil bath) for 2 hours. After cooling, 3% aqueous sodium sulfate was added followed by EtOAc and filtered through celite. The filtrate was partitioned between water and CH_2Cl_2. The organic phase was separated and the aqueous phase was further extracted with CH_2Cl_2. The combined organic phase was dried ($MgSO_4$) and concentrated. The residue was purified using silica gel chromatography (EtOAc:Hexane=1:10) to provide compound **12D**. MS found for $C_{20}H_{20}N_2O_3$ = 337.18 (M+H).

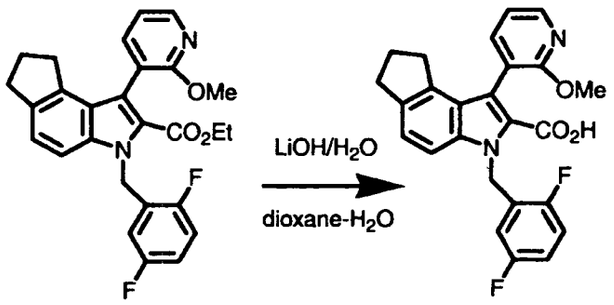
Step E – Synthesis of Compound 12E



12D **12E**

2,4-difluorobenzylbromide (0.187 g, 1.5 eq) was added dropwise to a allowed to stirsolution of compound **12D** (202 mg, 0.6 mmol) and Cs_2CO_3 in DMF at room temperature under an atmosphere of nitrogen. After 16 hours, the reaction mixture was partitioned between EtOAc and water. The aqueous phase was separated, washed with water three times, dried ($MgSO_4$) and concentrated. The residue was purified using flash column chromatography on silica gel (EtOAc:Hexane=1:20) to provide compound **12E** (0.263 g) as a white solid. MS found for $C_{27}H_{24}N_2O_3$ = 463.18 (M+H).

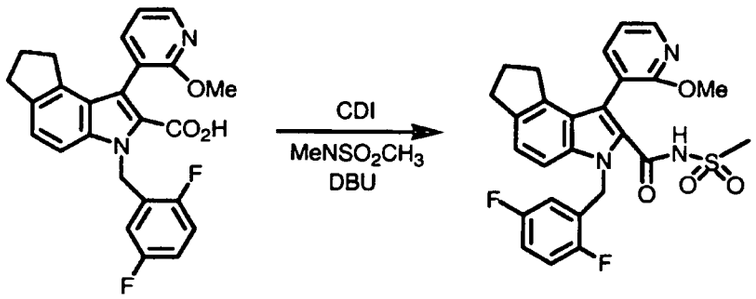
Step F – Synthesis of Compound 12F



12E **12F**

Lithium hydroxide (53 mg, 3 eq) was added to a allowed to stirsolution of the ethylester **12E** (196 mg, 0.42 mmol) in aqueous THF/H_2O (3 mL /1 mL) under an atmosphere of nitrogen. The resulting reaction mixture was heated to 100 °C for 4 hours (oil bath). After cooling, the reaction was partitioned between CH_2Cl_2 and diluted with aqueous HCl (1N). The organic phases were separated and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to provide a crude residue that was purified using flash column chromatography on silica gel (EtOAc/Hexane=1:10) followed by EtOAc as eluent to provide compound **12F** as a white solid (95.2 mg). MS found for $C_{25}H_{20}F_2N_2O_3$ = 435.11 (M+H).

Step G – Synthesis of Compound 12G

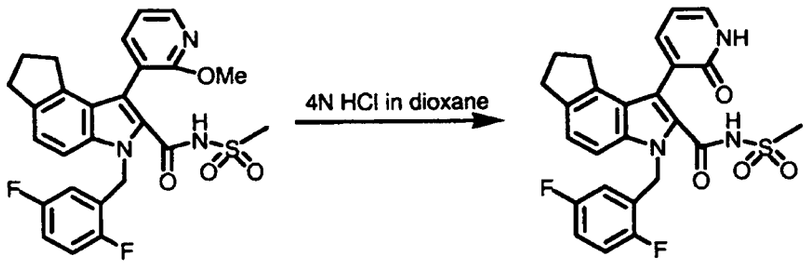


12F **12G**

CDI (35 mg, 1 eq) was added to a allowed to stirsolution of the acid **12F** (95 mg) in THF and the reaction mixture was heated at reflux under an atmosphere of nitrogen for a period of 2 hours. After cooling, methane sulfonamide (31 mg, 1.5 eq) followed by DBU (0.26 mmol) were added. After 6 hours the mixture was partitioned between EtOAc and diluted with aqueous HCl (1N), the organic phase was separated and the aqueous phase was further

extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to provide a crude residue that was purified using flash column chromatography on silica gel (CH_2Cl_2:MeOH=20:1) to provide compound **12G** (20.6 mg). MS found for $C_{26}H_{23}F_2N_3O_4S$ = 517.12

Step H – Synthesis of Compound 12

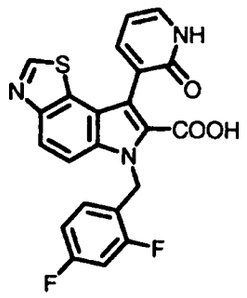


12G **12**

HCl (4N in dioxane, 10 mL) was added to compound **12G** (50 mg) in a sealed tube and the resulting suspension was heated to 80 °C (oil bath) and allowed to stir at this temperature overnight. The reaction mixture was then cooled to room temperature and the solvent was removed *in vacuo* to provide a crude residue which was triturated with ether and the resulting solid was collected to provide compound **12** (35.2 mg). MS found for $C_{25}H_{21}F_2N_3O_4S$: 498.03 $(M+H)^+$. ^1H NMR (500 MHz, d_6-DMSO) δ 12.68 (bs, 1H), 12.50 (bs, 1H), 7.74 (d, J = 6.59 Hz, 1H), 7.67 (m, 1H), 7.37 (d, J = 8.79 Hz, 1H), 7.32-7.26 (m, 1H), 7.24 (d, J = 8.79 Hz, 1H), 7.17-7.12 (m, 1H), 6.59-6.54 (m, 2H), 5.69 (s, 2H), 3.23 (s, 3H), 2.86-2.83 (m, 2H), 2.8-2.0 (bs, 2H), 1.95 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.864, 161.097, 158.974, 157.059, 156.602, 154.687, 144.974, 136.933, 136.884, 135.826, 135.781, 128.571, 127.140, 127.083, 127.004, 126.944, 123.307, 123.155, 122.083, 117.030, 116.962, 116.837, 116.769, 115.700, 115.628, 115.511, 114.911, 114.726, 108.947, 106.806, 106.194, 72.068, 66.255, 41 .665, 41.102, 32.178, 31.747, 24.874.

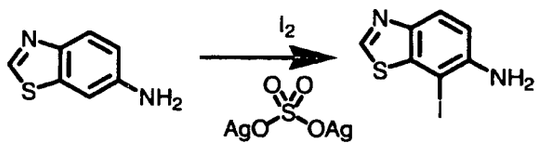
Example 2

Preparation of Compound **16**



16

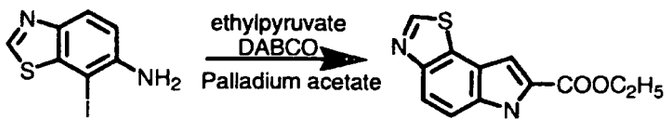
Step A – Synthesis of Compound 16A



16A

To a solution of benzothiazol-6-ylamine (5.00 g, 33.25 mmol) in ethanol (50 mL) was added silver sulfate (10.5 g, 33.25 mmol) and iodine (8.45 g, 33.25 mmol) and the reaction was allowed to stir at room temperature for 48 hours. The reaction mixture was added sodium thiosulfate and allowed to stirfor 1 h and filtered. The reaction mixture was extracted with EtOAc (350 mL), washed with brine, dried($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (EtOAc/Hexanes, 0-100%) to provide compound **16A** as a colorless solid (1.7 g).

Step B– Synthesis of Compound 16B

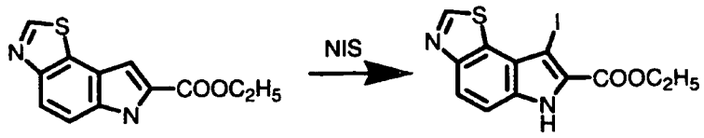


16A **16B**

A solution of compound **16A** (1.7 g, 6.16 mmol) in DMF (15 mL) was extensively degassed and treated with ethyl pyruvate (0.965 g, 8.4 mmol), DABCO and palladium acetate (139 mg, 0.616 mmol) and then heated at 105 °C for 12 hours. The reaction mixture was poured into water and extracted with ethyl acetate and the organic layer was dried ($MgSO_4$),

filtered, concentrated *in vacuo* and purified using flash column chromatography on silica gel (EtOAc/Hexanes 0-70%) to provide compound **16B** (500 mg).

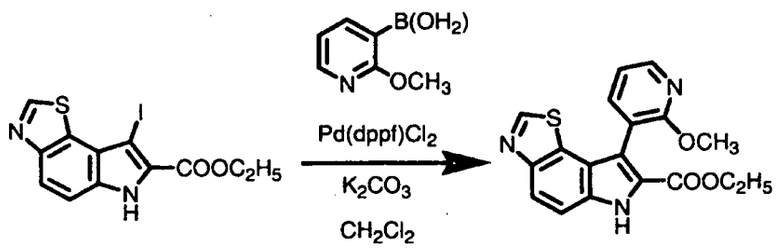
Step C – Synthesis of Compound 16C



16B **16C**

To a solution of compound **16B** (430 mg, 1.75 mmol) in chloroform (30 mL) was added N-iodosuccinimide and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with water, and extracted with ethyl acetate (500 mL). The combined organic layers were extracted with brine, dried ($MgSO_4$), filtered, concentrated under vacuum, pre-absorbed on silica and purified using flash column chromatography (1:1 EtOAc/Hexanes) to provide compound **16C** as a colorless solid.

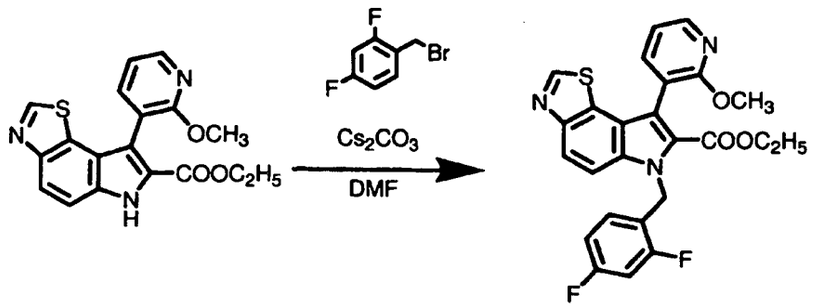
Step D – Synthesis of Compound 16D



16C **16D**

To a solution of compound **16C** (500 mg, 1.35 mmol) in DME (15 mL) was added 2-methoxy-3-pyridyl boronic acid (413 mg, 2.7 mmol) and $Pd(dppf)Cl_2$ (130 mg) and the reaction was allowed to stir at room temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (932 mg, 6.75 mmol) in 10 mL of water and heated at 90 °C for 3 hours. The reaction mixture was diluted with EtOAc (250 mL), concentrated *in vacuo* and purified using flash column chromatography on silica gel using EtOAc/Hexanes (0 to 100% EtOAc) to provide compound **16D**.

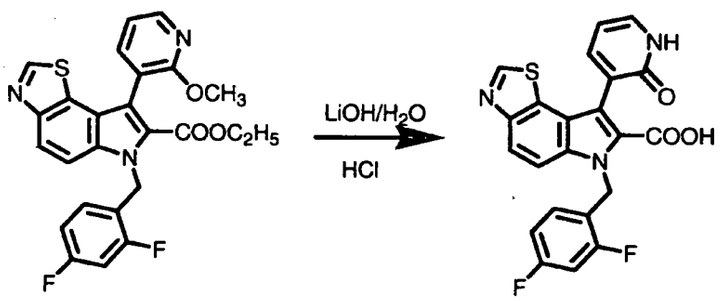
Step E – Synthesis of Compound 16E



16D **16E**

To a solution of compound **16D** (100 mg, 0.29 mmol) in DMF (3 mL) was added cesium carbonate (189 mg, 0.58 mmol) and 2,4-difluorobenzyl bromide and the resulting reaction was allowed to stir at room temperature for 1 hour. The reaction mixture was diluted with EtOAc (300 mL) and washed with brine (2x100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (EtOAc/Hexane, 0 to 100% EtOAc) to provide compound **16E** as a colorless solid.

Step F – Synthesis of Compound 16



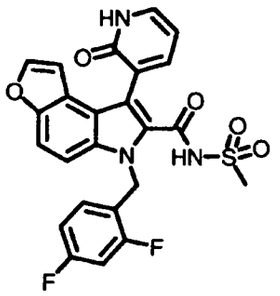
16E **16**

To a solution of compound **16E** (200 mg, 0.041 mmol) in methanol/water/THF (5 mL each) was added lithium hydroxide and the resulting reaction was allowed to stir at reflux overnight. The reaction mixture was diluted with aqueousHCl and extracted into ethyl acetate (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and used as it is in the next step. The residue was taken up in methanol (1 mL) and treated with aqueous HCl (4M) and heated for 1h at 80 °C. A large amount of white solid separated out which was filtered and dried to provide compound **16**. MS found for $C_{22}H_{13}F_2N_3O_3S$: 438.00

$(M+H)^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 9.15 (s, 1H), 8.01 + 7.98 (d, J = 9.52 Hz, 1H), 7.79 & 7.77 (d, J = 8.79 Hz, 1H), 7.59 & 7.57 (d, J = 6.59 Hz, 1H), 7.497 & 7.48 (d, J = 5.86 Hz, 1H), 7.29 (t, J = 9.52 Hz, 1H), 6.96 (t, J = 9.50 Hz, 1H), 6.70 (q, J = 8.79 & 15.38 Hz, 1H), 6.34 (t, J = 7.32 Hz, 1H), 5.98 (q, J = 16.11 & 46.87 Hz, 2H).

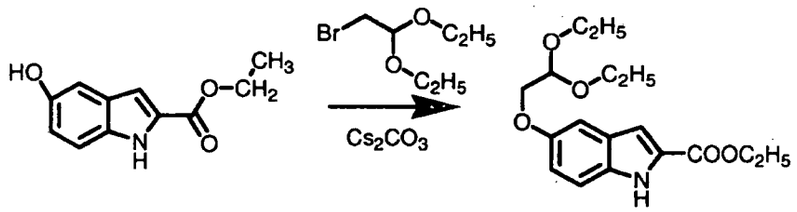
Example 3

Preparation of Compound **9**



9

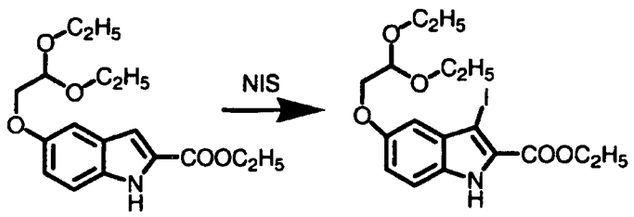
Step A – Synthesis of Compound 9A



9A

To a solution of 5-hydroxy-1*H*-indole-2-carboxylic acid ethyl ester (5.00 g, 25.00 mmol) in DMF (30 mL) was added Cs_2CO_3 (9.00 g, 1.1 mmol) and bromoacetaldehyde-diethylacetal (20 g, 5.00 mmol) and the resulting reaction was allowed to stir at reflux for 2 hours. The reaction mixture was cooled to room temperature, treated with aqueous NaOH (1M, 500 mL) and extracted into EtOAc (500 mL). The organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* (high vacuo to distill out DMF and bromoacetaldehyde) and purified using flash column chromatography (Hexanes/EtOAc, 0 to 100%) to provide compound **9A** as a colorless solid.

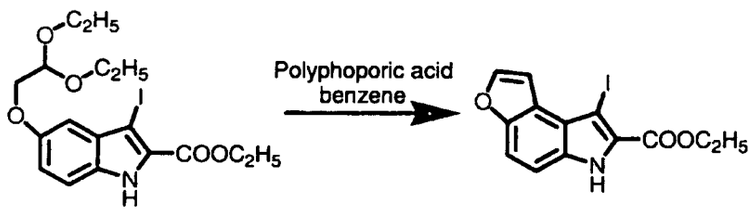
Step B – Synthesis of Compound 9B



9A **9B**

To a solution of compound **9A** (2.3 g, 7.1 mmol) in chloroform (20 mL) was added N-iodosuccinimide (1.77 g, 7.8 mmol) and the reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (200 mL) and washed three times with water. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography (eluent: EtOAc/Hexanes, 0 to 50% EtOAc) to provide compound **9B** as a colorless solid (2.7 g).

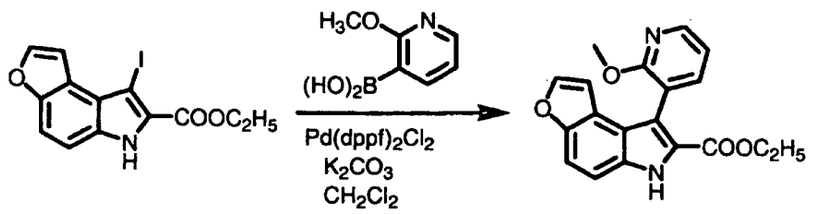
Step C – Synthesis of Compound 9C



9B **9C**

To a solution of compound **9B** (2.7 g, 6.00 mmol) in benzene (30 mL) was added polyphosporic acid (3 g) and the resulting reaction was allowed to stir at reflux for about 1 hour. The reaction was then quenched using cold water and the resulting solution was extracted into EtOAc. The organic layer were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography (Hexane:EtOAc, 1:1) to provide compound **9C**.

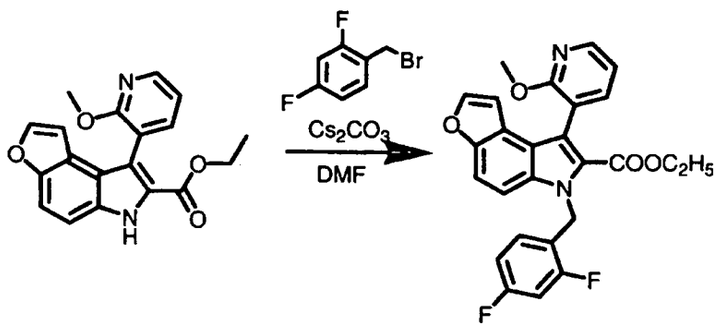
Step D – Synthesis of Compound 9D



9C **9D**

To a solution of compound **9C** (1.5 g, 4.33 mmol) in DME (20 mL) was added 2-methoxy-3-pyridyl boronic acid (795 mg, 5.2 mmol) and $Pd(dppf)_2Cl_2$ (408 mg) and the reaction was allowed to stir at room temperature under nitrogen for 30 minutes. The reaction mixture was added a solution of potassium carbonate (2.4 g, 17.3 mmol) in 10 mL of water and heated at 90 °C for 1 hour. The reaction mixture was diluted with EtOAc (250 mL), concentrated *in vacuo*, and purified using flash column chromatography (EtOAc/Hexanes, 1:1) to provide compound **9D** as a colorless solid (620 mg).

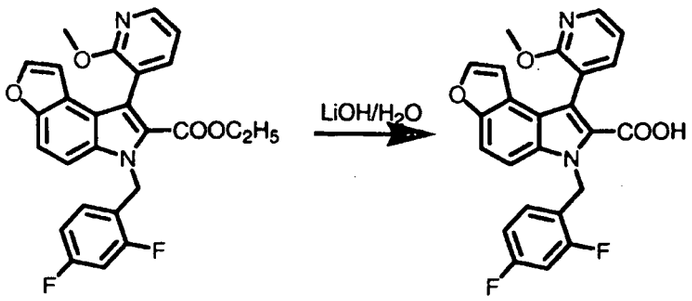
Step E – Synthesis of Compound 9E



9D **9E**

To a solution of compound **9D** (620 mg, 1.86 mmol) in DMF (5.00 mL) was added Cs_2CO_3 (1.21 g, 3.72 mmol) and 2,4-difluorobenzylbromide (577, 2.79 mmol) and the resulting reaction was allowed to stir overnight. The reaction mixture was then diluted with water (250 mL) and extracted into EtOAc (300 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography (EtOAc/Hexanes, 1:1) to provide compound **9E** (900 mg).

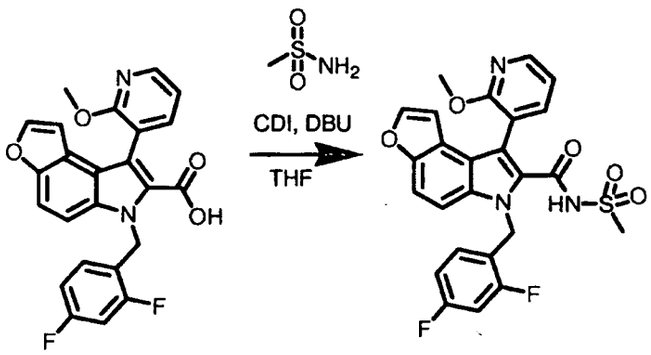
Step F – Synthesis of Compound 9F



9E **9F**

To a solution of compound **9E** (1.95 mmol) in methanol/water/THF (15 mL, 1:1:1) was added lithium hydroxide (10 mmol) and the resulting reaction was allowed to stir for 4 hours at reflux. The reaction mixture was acidified with aqueous HCl (1N, 20 mL) and extracted into EtOAc (250 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide compound **9F**, which was used without further purification.

Step G – Synthesis of Compound 9G

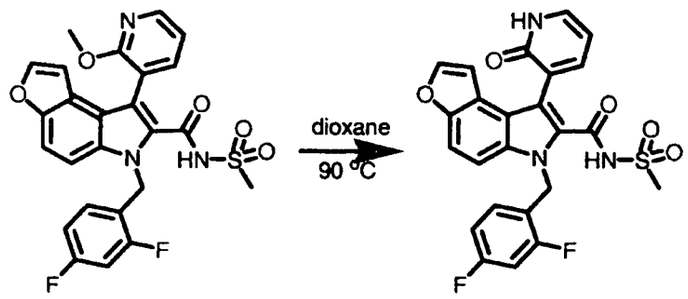


9F **9G**

To a solution of compound **9F** (0.34 mmol) in 3 mL of THF was added CDI (0.5 mmol) and the resulting reaction was heated to reflux and allowed to stir at this temperature for 3 hours. The reaction mixture was then cooled to 0 °C and treated with methane sulfonamide and DBU. The resulting reaction mixture was allowed to stir at room temperature for 48 hours, then diluted with EtOAc (100 mL) and the resulting solution was washed with water and aqueous HCl (1N). The combined organic layers were dried ($MgSO_4$), filtered, and

concentrated *in vacuo* and ther resulting residue was purified using flash column chromatography on silica gel (acetone/CH_2Cl_2, 0 to 70% acetone) to provide compound **9G** (100 mg).

Step H – Synthesis of Compound 9

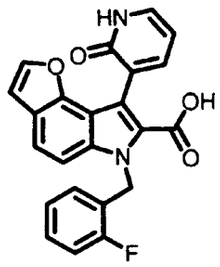


9G **9**

A solution of compound **9G** (100 mg, 0.2 mmol) in 4M solution of dioxane (5mL) was heated to 90 °C and allowed to stir at this temperature for 3 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was diluted with EtOAc. The solid product was filtered and washed with EtOAc, then diethyl ether, to provide compound **9**. MS found for $C_{24}H_{17}F_2N_3O_5S$: 498.05 $(M+H)^+$. ^1H NMR (400 MHz, d_6-DMSO) δ 12.77 (s, 1H), 12.70 (s, 1H), 7.97 & 7.966 (d, J = 2.14 Hz, 1H), 7.87 (q, J = 2.14 & 7.26 Hz, 1H), 7.76-7.72 (m, 1H), 7.66 & 7.63 (d, J = 8.97 Hz, 1H), 7.56 & 7.54 (d, J = 9.40 Hz, 1H), 7.30-7.25 (m, 1H), 6.99-6.86 (m, 2H), 6.65 (t, J = 6.41 Hz, 1H), 6.468 & 6.464 (d, J = 1.71 Hz, 1H), 5.78 (s, 2H), 3.26 (s, 3H).

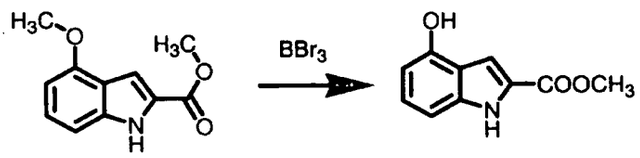
Example 4

Preparation of Compound **1**



1

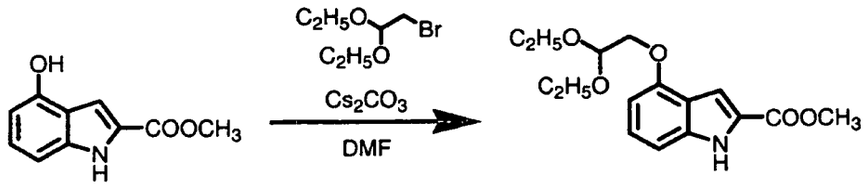
Step A – Synthesis of Compound 1A



1A

A solution of 4-methoxy-1*H*-indole-2-carboxylic acid methyl ester (410 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was cooled to -78 °C and BBr_3 (6mL solution, 1M) was added. The resulting reaction was then allowed to stir at 0 °C for 3 hours. The reaction mixture was then quenched using water and the resulting solution was extracted with EtOAc (200 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography to provide compound **1A**.

Step B – Synthesis of Compound 1B

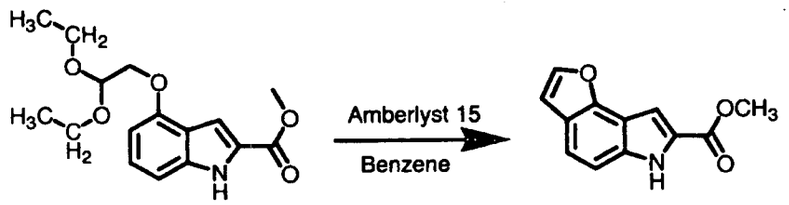


1A **1B**

To a solution of compound **1A** (2.5 g, 13.10 mmol) in DMF (50 mL) was added Cs_2CO_3 (5.12 g, 15.72 mmol), then bromoacetaldehyde-diethylacetal (12.90 g, 65.6 mmol), and the resulting reaction was allowed to stir at reflux for 2 hours. The reaction mixture was

cooled to room temperature, treated with aqueous NaOH (1M, 50 mL) and extracted into EtOAc (250 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography (Hexanes/EtOAc 0 to 100%) to provide compound **1B** as a colorless solid.

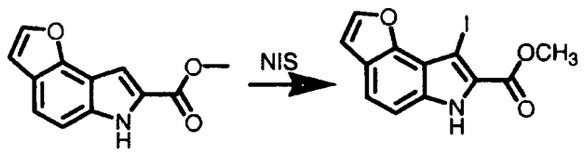
Step C – Synthesis of Compound 1C



1B **1C**

To a solution of compound **1B** in benzene (60 mL) was added Amberlyst-15 strongly acidic resin (4.5 g) and the resulting reaction was heated to 70 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was then cooled to room temperature, diluted with EtOAc (300 mL) and washed with aqueous $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography on silica gel (EtOAc/Hexanes, 0-30% EtOAc) to provide compound **1C** (1.2 g).

Step D – Synthesis of Compound 1D

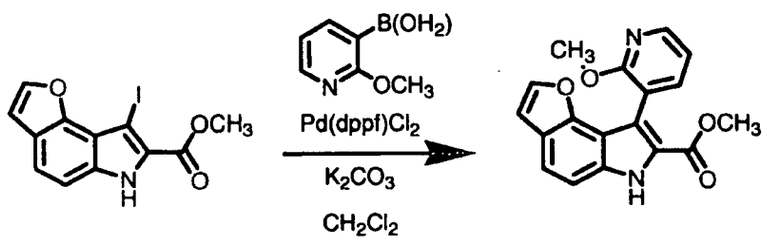


1C **1D**

To a solution of compound **1C** (2.00 g, 9.3 mmol) in DMF (20 mL) was added N-iodosuccinimide (2.29 g, 10.2 mmol) and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was then concentrated *in vacuo*, diluted with water and extracted into EtOAc (300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The resulting brown residue was diluted with a minimum

amount of CH_2Cl_2 and triturated using hexanes. Compound **1D** separated out as a brown solid, which was filtered, then dried *in vacuo*. (Yield 2.6 g, 84%).

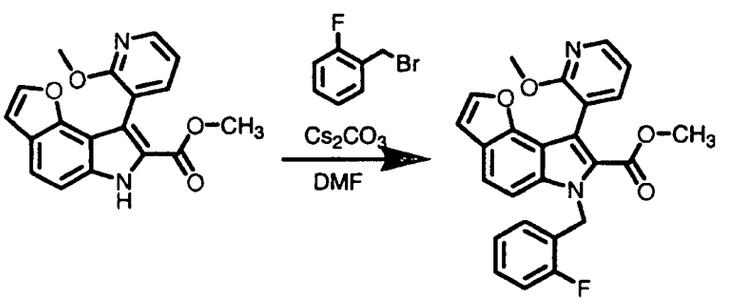
Step E – Synthesis of Compound 1E



1D **1E**

To a solution of compound **1D** (2.6 g, 7.6 mmol) in DME (40 mL) under nitrogen atmosphere was added with 2-methoxy-3-pyridyl boronic acid (3.5 g, 22.8 mmol) and Pd $(dppf)_2Cl_2$ (616 mg) and the resulting reaction was allowed to stir at room temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (6.3 g, 45.6 mmol) in water (40 mL) and the resulting solution was heated to 90 °C and allowed to stir at this temperature for 1 hour. The reaction mixture was then diluted with EtOAc (300 mL) and the resulting solution was concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography (EtOAc/Hexanes, 0 to 50% EtOAc) to provide compound **1E** as a solid (2.0 g).

Step F – Synthesis of Compound 1F

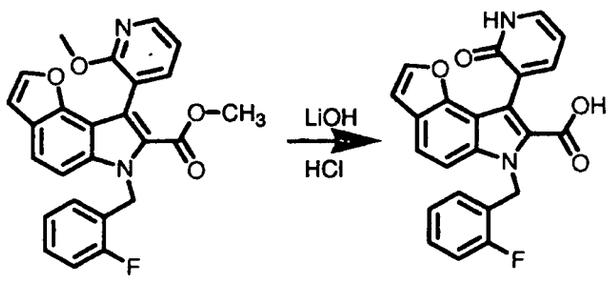


1E **1F**

To a solution of indole **1E** (300 mg, 0.93 mmol) in DMF (10 mL) was added cesium carbonate (604 mg, 1.86 mmol) and 2-fluorobenzyl bromide (351 mg, 1.86 mmol) and allowed

to stir at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (250 mL) and washed with brine (2x100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* and purified using flash column chromatography on silica gel to provide compound **1F** as a colorless solid.

Step G – Synthesis of Compound 1



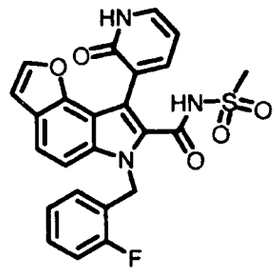
1F **1**

To a solution of compound **1F** (100 mg, 0.23 mmol) in THF/water/methanol (4 mL each) was added lithium hydroxide (40 mg, 1 mmol) and the resulting reaction was allowed to stir at reflux for 4 hours. The reaction mixture was diluted with acid and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$), concentrated *in vacuo* and used as it is in next step. A solution of crude acid (80 mg) in 4 M HCl in dioxane (5mL) and methanol (1mL) was heated at 80 °C for 3 hours. The reaction mixture was concentrated *in vacuo* and the crude was purified using reverse-phase HPLC using the following conditions, to provide compound **1**: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15mM, 300 A, 343K16006 (W): Flow Rate: 30 mL/min; Mobile Phase: 30-70% ramp acetonitrile, water; 0--> 40 minutes.

For compound **1**: MS found for $C_{23}H_{15}FN_2O_4$: 403.08 $(M+H)^+$. ^1H NMR (300 MHz, d_6-DMSO) δ 11.72 (bs, 1H), 7.84 & 7.83 (d, J = 2.20 Hz, 1H), 7.68 & 7.66 (dd, J = 6.59 & 2.20 Hz, 1H), 7.55 & 7.53 (d, J = 8.79 Hz, 1H), 7.45 & 7.43 (d, J = 8.79 Hz, 1H), 7.41-7.39 (m, 1H), 7.30-7.19 (m, 2H), 7.02 (t, J = 7.32 Hz, 1H), 6.963 & 6.957 (d, J = 2.20 Hz, 1H), 6.60 (t, J = 7.32 Hz, 1H), 6.33 (t, J = 7.32 Hz, 1H), 5.95 (s, 2H).

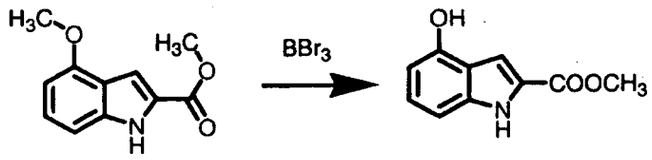
Example 5

Preparation of Compound **4**



4

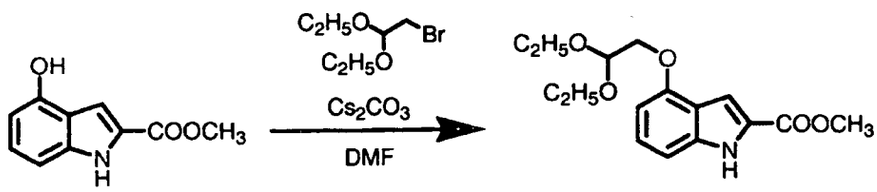
Step A –Synthesis of Compound 4A



4A

To a solution of 3-methoxy-1*H*-indole-2-carboxylic acid methyl ester (410 mg, 2.00 mmol) in CH_2Cl_2 (5 mL) was added BBr_3 (6mL solution, 1M) at -78 °C and the reaction was allowed to stir at 0 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc (200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* and purified using flash column chromatography to provide compound **4A**.

Step B - Synthesis of Compound 4B

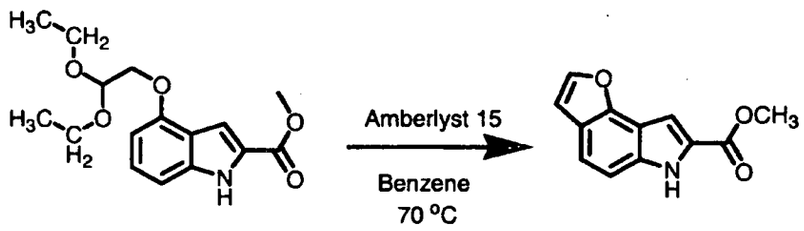


4A **4B**

To a solution of compound **4A** (2.5 g, 13.10 mmol) in DMF (50 mL) was added Cs_2CO_3 (5.12 g, 15.72 mmol) and bromoacetaldehyde-diethylacetal (12.90 g, 65.6 mmol) and the resulting reaction was allowed to stir at reflux for 2 hours. The reaction mixture was

cooled to room temperature, dilutedtreated with aqueous NaOH (1M, 50 mL) and extracted into EtOAc (250 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography (Hexane/EtOAc 0 to 100%) to provide compound **4B** as a colorless solid.

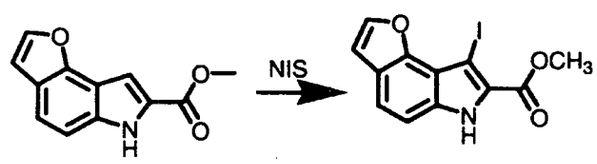
Step C – Synthesis of Compound 4C



4B **4C**

To a solution of compound **4B** in benzene (60 mL) was added Amberlyst-15 strongly acidic resin (4.5 g) and th reaction was heated at 70 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was cooled diluted with EtOAc (300 mL) and washed with aqueous $NaHCO_3$. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* and purified using flash column chromatography (SiO_2) EtOAc/Hexanes (0-30%) to provide compound **4C** (1.2 g).

Step D – Synthesis of Compound 4D

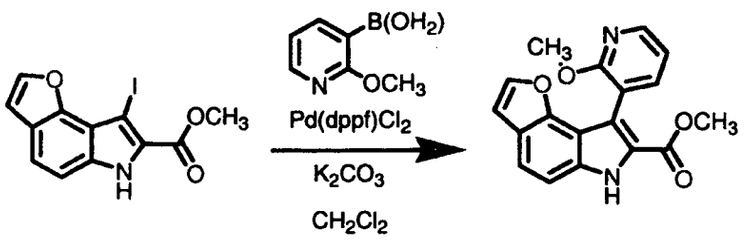


4C **4D**

To a solution of compound **4C** (2.00 g, 9.3 mmol) in DMF (20 mL) was added N-iodosuccinimide (2.29 g, 10.2 mmol) and the reaction allowed to stir at room temperature for 12 hours. The reaction mixture concentrated *in vacuo* and diluted with water and extracted in EtOAc (300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The brown residue was taken in minimum amount of CH_2Cl_2 and triturated with

hexanes. Compound **4D** separated out as a brown solid which was filtered, and dried *in vacuo*. (Yield 2.6 g, 84%)

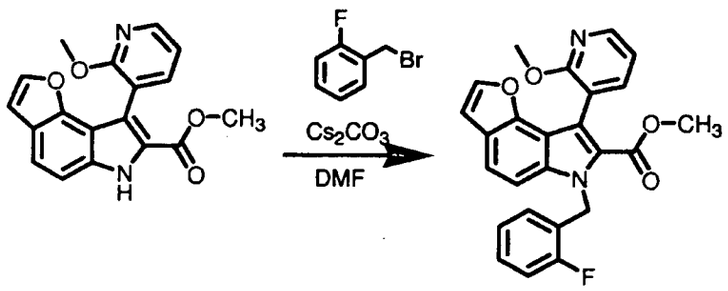
Step E – Synthesis of Compound 4E



4D **4E**

To a solution of compound **4D** (2.6 g, 7.6 mmol) in DME (40 mL) was added 2-methoxypyridyl boronic acid (3.5 g, 22.8 mmol) and $Pd(dppf)_2Cl_2$ (616 mg) was allowed to stir at room temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (6.3 g, 45.6 mmol) in 40 mL of water and the resulting solution was heated to 90 °C and allowed to stir at this temperature for 1 hour. The reaction mixture was diluted with EtOAc (300 mL), concentrated *in vacuo* and purified using flash column chromatography on silica gel (EtOAc/Hexanes, 0 to 50%) to provide compound **4E** (2.00 g).

Step F – Synthesis of Compound 4F

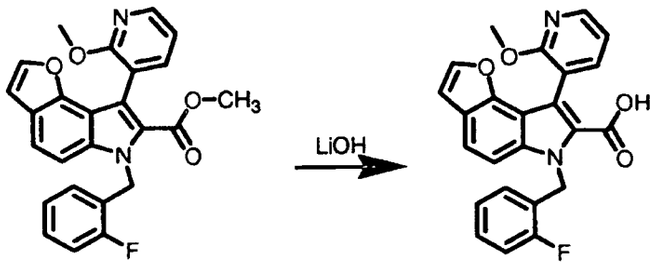


4E **4F**

To a solution of compound **4E** (300 mg, 0.93 mmol) in DMF (10 mL) was added cesium carbonate (604 mg, 1.86 mmol) and 2-fluorobenzyl bromide (351 mg, 1.86 mmol) and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (250 mL) and washed with brine (2x100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* and the resulting

residue was purified using flash column chromatography on silica gel to provide compound **4F** as a colorless solid.

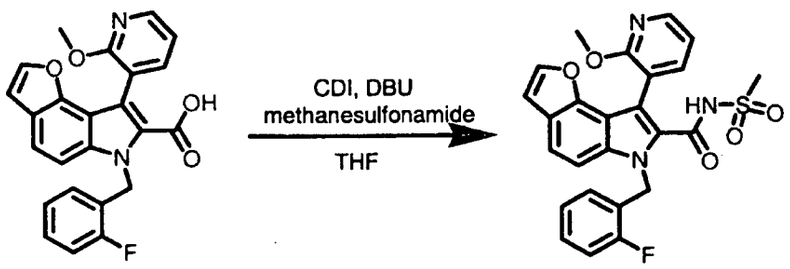
Step G – Synthesis of Compound 4G



4F **4G**

To a solution of compound **4F** (100 mg, 0. 23 mmol) in THF/water/methanol (4 mL each) was added lithium hydroxide (40 mg, 1 mmol) and the resulting reaction was heated to reflux and allowed to stir at this temperature for 4 hours. The reaction mixture was diluted with aqueous HCl (1N) and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to provide compound **4G** which was used without further purification.

Step H – Synthesis of Compound 4H

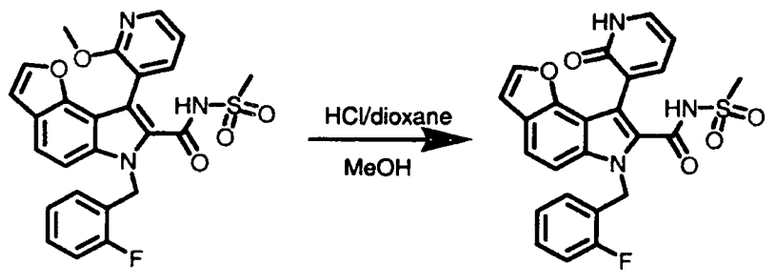


4G **4H**

To a solution of compound **4G** (150 mg, 0.36 mmol) in 5 mL of THF was added CDI (70 mg, 0.43 mmol) and the resulting reaction was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and methanesulfonamide (40 mg, 0.43 mmol) and DBU (100 mg, 0.65 mmol) were added. The resulting reaction mixture was allowed to stir at 65 °C for 48 hours, diluted with EtOAc (150 mL) and washed with water and aqueous HCl

(1N). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography on silica gel (acetone/CH_2Cl_2, 0 to 70% acetone) to provide compound **4H** as a colorless solid.

Step I – Synthesis of Compound 4

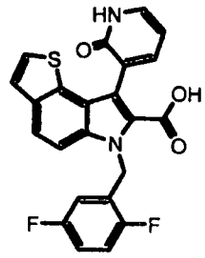


4H **4**

To a solution of compound **4H** (80 mg, 0.16 mmol) in 4 M HCl in dioxane (5mL) and methanol (1.5 mL) was heated at 80 °C and allowed to stir at this temperature for 4 hours. The reaction mixture was concentrated *in vacuo* and the resulting crude residue was purified using HPLC (reverse phase) using following conditions: Column: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15mM, 300 A, 343K16006 (W): 30 mL/min flow; 30-70% ramp acetonitrile, water; 0--> 40 minutes, to provide compound **4** as colorless solid (60 mg). MS found for $C_{24}H_{18}FN_3O_5S$: 480.05 $(M+H)^+$. ^1H NMR (300 MHz, d_6-DMSO) δ 12.77 (bs, 1H), 12.61 (bs, 1H), 7.98 + 7.96 (d, J = 6.04 Hz, 1H), 7.86-7.83 (m, 1H), 7.67 (s, 1H), 7.60 & 7.58 (d, J = 7.69 Hz, 1H), 7.51 & 7.49 (d, J = 8.24 Hz, 1H), 7.32-7.27 (m, 1H), 7.21 (t, J = 8.79 Hz, 1H), 7.05 (t, J = 7.69 Hz, 1H), 6.82 (t, J = 7.69 Hz, 1H), 6.67-6.60 (m, 1H), 5.81 (s, 2H), 3.22 (s, 3H).

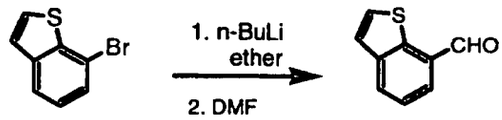
Example 6

Preparation of Compound **49**



49

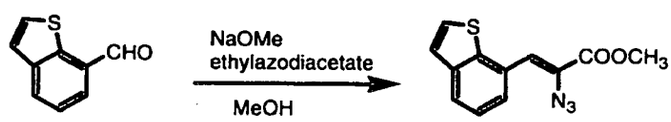
Step A – Synthesis of Compound 49A



49A

A solution of 7-bromothiophene (8.0 g, 37.5 mmol) in ether (50 mL) was cooled to -78 °C and treated dropwise with n-BuLi (1.6 M solution in hexanes, 1.0 eq.) and the resulting reaction was allowed to stir at -78 °C for 20 minutes. The reaction mixture was then diluted with DMF (dry 5.4 g, 67.4 mmol) and allowed to stirat -78 °C for 1 hour. The reaction mixture was then diluted with water and extracted into ether. The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified using flash column chromatography on silica gel to provide compound **49A** as a colorless liquid.

Step B – Synthesis of Compound 49B

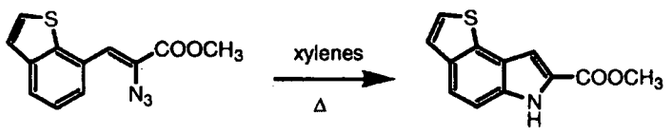


49A **49B**

To a solution of freshly made sodium methoxide (prepared by dissolving (1.42 g, 62.0 mmol) in methanol (30 mL)) was added dropwise to a solution of ethylazidoacetate (7.99 g, 62 mmol) and compound **49A** (5.1 g, 31 mmol) in methanol (30 mL) which was precooled to -20 °C. The reaction mixture was allowed to stir at room temperature for 3 hours, then diluted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel to

provide a crude yellow residue which was recrystallized from ether and hexanes to provide compound **49B** (1.95 g).

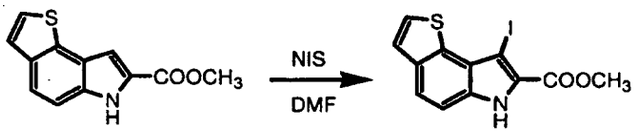
Step C – Synthesis of Compound 49C



49B **49C**

A solution of compound **49B** (1.95 g) in xylenes (20 mL) was heated at reflux for 30 minutes, then cooled to room temperature. The reaction mixture was then concentrated *in vacuo* until a solid precipitate appeared and was collected to provide compound **49C** as a colorless solid (1.1 g).

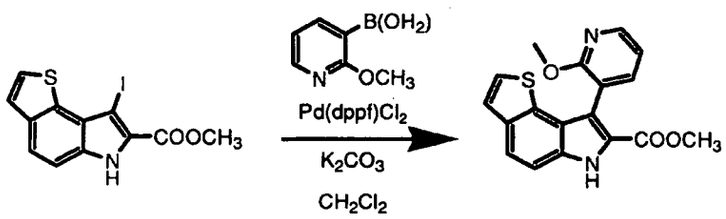
Step D – Synthesis of Compound 49D



49C **49D**

To a solution of compound **49C** (1.00 g, 4.33 mmol) in DMF (20 mL) was added *N*-iodosuccinimide and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with water and extracted into EtOAc (300 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel to provide compound **49D** as a colorless solid.

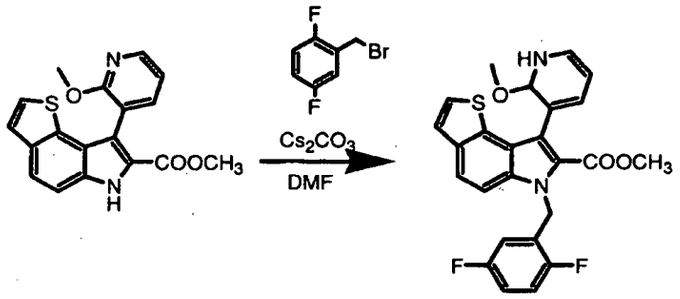
Step E – Synthesis of Compound 49E



49D **49E**

To a solution of compound **49D** (1.2 g, 3.35 mmol) in DME (25 mL) was added 2-methoxy-3-pyridyl boronic acid (1.52 g, 10 mmol) and $Pd(pddf)_2Cl_2$ (324 mg) was allowed to stir at room temperature under nitrogen for 15 minutes. The reaction mixture was then treated with a solution of potassium carbonate (2.77 g, 20.1 mmol) in 25 mL of water and the resulting reaction was heated at 90 °C and allowed to stir at this temperature for 1 hour. The reaction mixture was diluted with EtOAc (300 mL), concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (EtOAc/Hexanes, 0 to 70% EtOAc) to provide compound **49E**.

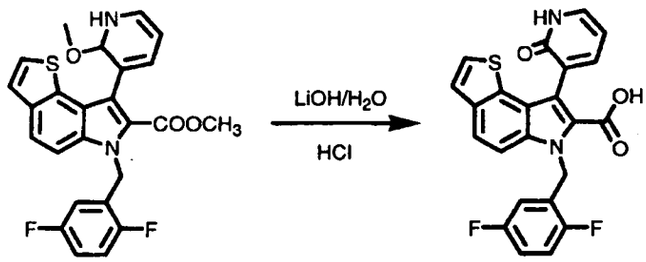
Step F – Synthesis of Compound 49F



49E **49F**

To a solution of compound **49E** (300 mg, 0.90 mmol) in DMF (10 mL) was added cesium carbonate (585 mg, 1.80 mmol) and 2,4-difluorobenzyl bromide (372 mg, 1.80 mmol) and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and the organic layer was washed with brine (2x100 mL), then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Theresulting residue was purified a first time using flash column chromatography on silica gel (EtOAc/Hexanes, 0 to 70% EtOAc) and a second time using acetone/CH_2Cl_2 (0 to 50% acetone) as eluent to provide compound **49F** as a colorless solid.

Step G – Synthesis of Compound 49



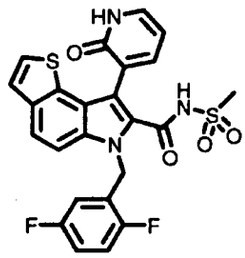
49F **49**

To a solution of compound **49F** (100 mg, 0.23 mmol) in THF/water/methanol (4 mL each) was added lithium hydroxide (40 mg, 1 mmol) and the resulting reaction was allowed to stir at reflux for 4 hours. The reaction mixture was diluted with aqueous HCl (1N) and extracted with EtOAc (200 mL). The organic layer was dried ($MgSO_4$) then concentrated *in vacuo*, and the crude residue was diluted with hydrochloric acid (4M solution in dioxane). To the resulting acidic solution was added 1 mL of methanol and the resulting mixture was allowed to stir at 90 °C for 3 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc. To resulting solution was added hexanes, until compound **49** separated out and was filtered and used as it is (45 mg). MS found for $C_{23}H_{14}F_2N_2O_3S$: 437.10 $(M+H)^+$. ^1H NMR (300 MHz, d_6-DMSO)

δ 11.76 (bs, 1H), 7.81 + 7.87 (d, J = 8.79Hz, 1H), 7.62 (s, 1H), 7.61-7.58 (m, 1H), 7.50-7.46 (m, 1H), 7.33-7.28 (m, 1H), 7.16-7.10 (m, 1H), 6.35-6.31 (m, 2H), 5.98 (q, J = 16.84 & 40.27 Hz, 2H).

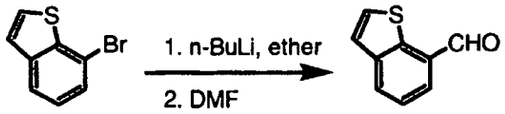
Example 7

Preparation of Compound **52**



52

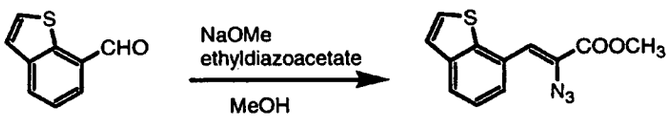
Step A – Synthesis of Compound 52A



52A

A solution of 7-bromothiophene (8.0 g, 37.5 mmol) in ether (50 mL) was cooled to -78 °C, then n-BuLi (1.6 M soln in hexanes, 1.0 eq.) was added dropwise and the resulting reaction was allowed to stir at -78 °C for 20 minutes. The reaction mixture was diluted with DMF (dry 5.4 g, 67.4 mmol) and allowed to stir at -78 °C for 1 hour. The reaction mixture was then quenched with water and the resulting solution was extracted into ether. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography on silica gel to provide compound **52A** as a colorless liquid.

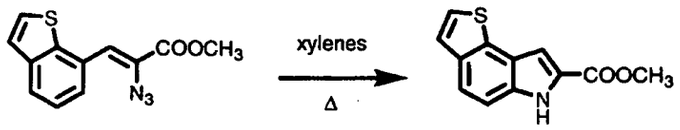
Step B – Synthesis of Compound 52B



52A **52B**

A solution of freshly made sodium methoxide (prepared by dissolving (1.42 g, 62.0 mmol) in methanol (30 mL)) was added dropwise to a solution of ethylazidoacetate (7.99 g, 62 mmol) and 5.1 g (31 mmol) of compound **52A** in methanol (30 mL) which was precooled to -20 °C. The resulting reaction was allowed to stir at room temperature for 3 hours and was then diluted with EtOAc (200 mL). The organic layer were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography on silica gel to provide a yellow solid which was recrystallized from ether and hexanes to provide compound **52B** (1.95 g).

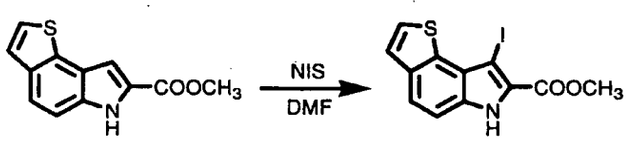
Step C – Synthesis of Compound 52C



52B **52C**

A solution of compound **52B** in xylene was heated at reflux for 30 minutes, then cooled to room temperature and concentrated *in vacuo* until a solid precipitate appeared. The solid was collected to provide compound **52C** (1.1 g) as a colorless solid which was used without further purification.

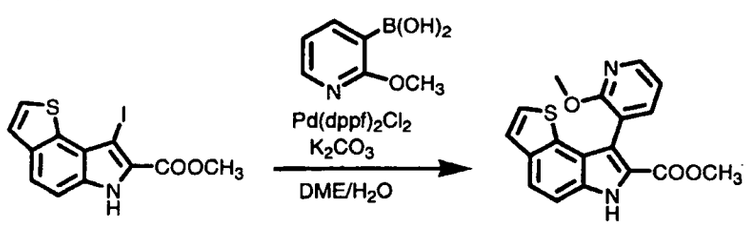
Step D – Synthesis of Compound 52D



52C **52D**

To a solution of compound **52C** (1.00 g, 4.33 mmol) in DMF (20 mL) was added *N*-iodosuccinimide and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was then concentrated *in vacuo* and the resulting residue was diluted with water and extracted into EtOAc (300 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (EtOAc/Hexanes, 0 to 50% EtOAc) to provide compound **52D** as a colorless solid.

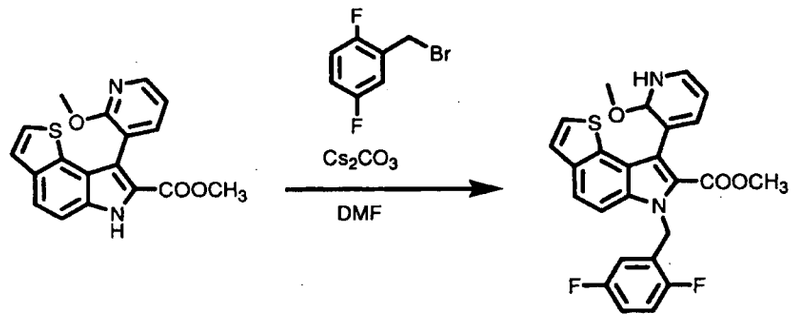
Step E – Synthesis of Compound 52E



52D **52E**

To a solution of compound **52D** (1.2 g, 3.35 mmol) in DME (25 mL) was added 2-methoxy-3-pyridyl boronic acid (1.52 g, 10 mmol) and $Pd(dppf)_2Cl_2$ (324 mg) and the resulting reaction was allowed to stir under a nitrogen atmosphere at room temperature for 15 minutes. The reaction mixture was then treated with a solution of potassium carbonate (2.77 g, 20.1 mmol) in 25 mL of water and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for 1 hour. The reaction mixture was then diluted with EtOAc (300 mL), concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel using EtOAc/Hexanes (0-70% EtOAc) to provide compound **52E**.

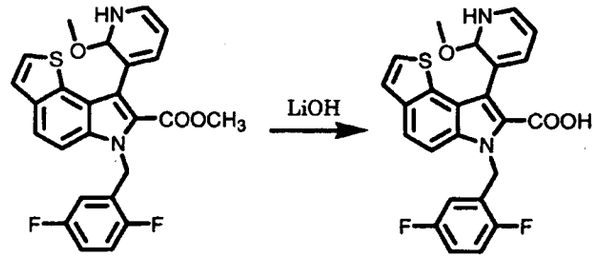
Step F – Synthesis of Compound 52F



52E **52F**

To a solution of compound **52E** (300 mg, 0.90 mmol) in DMF (10 mL) was added cesium carbonate (585 mg, 1.80 mmol) and 2,4-difluorobenzyl bromide (372 mg, 1.80 mmol) and the resulting reaction was allowed to stir at room temperature for 12 hours. The reaction mixture was then diluted with EtOAc (250 mL) and washed with brine (2x100 mL). The organic layer were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide a crude residue which was purified first using flash column chromatography on silica gel (EtOAc/Hexanes, 0 to 70% EtOAc) and once again using (acetone/CH_2Cl_2, 0 to 50% acetone) to provide compound **52F** as a colorless solid.

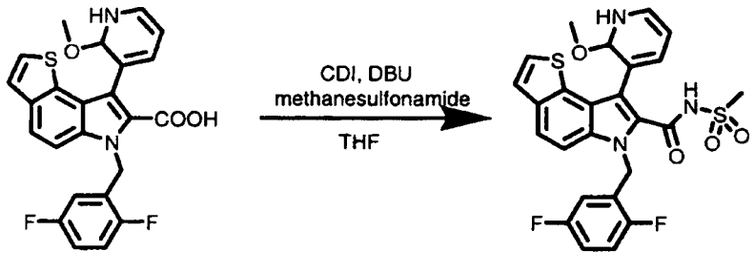
Step G – Synthesis of Compound 52G



52F **52G**

To a solution of compound **52F** (100 mg, 0.23 mmol) in THF/water/methanol (4 mL each) was added lithium hydroxide (40 mg, 1 mmol) and the resulting reaction was heated to refluxed and allowed to stir at this temperature for 4 hours. The reaction mixture was diluted with aqueous HCl (1N) and extracted into EtOAc (200 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide compound **52G** which was used without further purification.

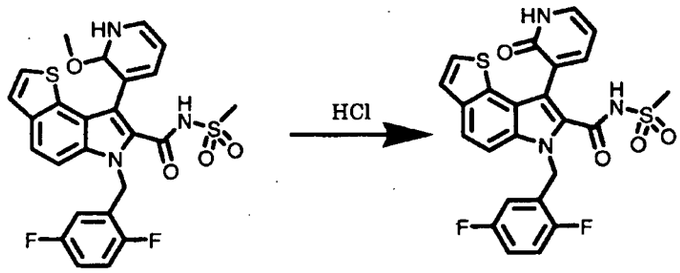
Step H – Synthesis of Compound 52H



52G **52H**

To a solution of compound **52G** (170 mg, 0.37 mmol) in 5 mL of THF was added CDI (74 mg, 0.45 mmol) and the resulting reaction was heated to reflux and allowed to stir at this temperature for 2 hours. The reaction mixture was then cooled to room temperature and treated with methanesulfonamide (43 mg, 0.45 mmol) and DBU (100 mg, 0.65 mmol). The resulting reaction was heated to 65 °C and allowed to stir at this temperature for 12 hours, after which time it was diluted with EtOAc (150 mL) and washed with water and aqueous HCl (1N). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to provide a crude residue which was purified using flash column chromatography on silica gel (acetone/CH_2Cl_2, 0 to 50% acetone) to provide compound **52H**.

Step I – Synthesis of Compound 52



52H **52**

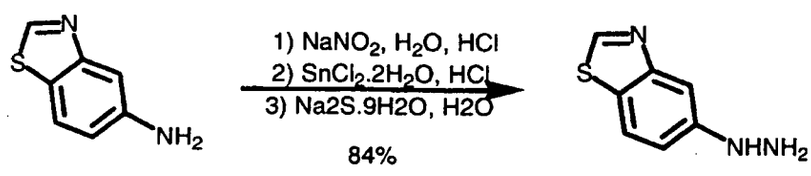
To a solution of compound **52H** (110 mg, 0.21 mmol) in HCl (4M in dioxane) was added 1 mL of methanol and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc, then purified using HPLC (reverse phase) using following conditions to provide compound **52**:Column: Waters Delta Pk, P/No 11805, Watman 011805, 300x30 mm (L/ID) C18, 15mM, 300 A, 343K16006 (W); Flow Rate: 30 mL/min; Mobile Phase: 30-70% ramp acetonitrile/water over 40 minutes.

For compound **52**: MS found for $C_{24}H_{17}F_2N_3O_4S_2$: 513.97 $(M+H)^+$. ^1H NMR (300 MHz, d_6-DMSO) δ 12.77 (bs, 1H), 12.50 (bs, 1H), 7.97 & 7.95 (d, J = 6.59 Hz, 1H), 7.84 & 7.82 (d, J = 8.79 Hz,1H), 7.76 (s, 1H), 7.65 & 7.63 (d, J = 8.79 Hz, 1H), 7.52-7.47 (m, 2H), 7.34-7.28 (m, 1H), 7.19-7.13 (m, 1H), 6.66-6.59 (m, 2H), 5.82 (s, 2H), 3.25 (s, 3H).

Example 8

Preparation of Compound **51**

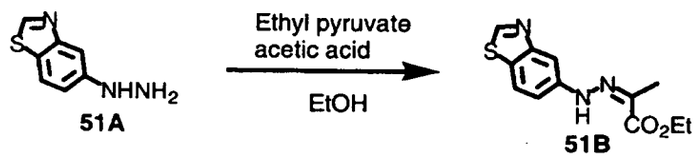
Step A – Synthesis of Compound 51A



51A

To a suspension of 1,3-benzothiazol-5-amine (16 g, 107 mmol) in concentrated HCl (180 mL) at -10 °C was added very slowly a solution of sodium nitrite (7.66 g,111 mmol) in water (35 mL). After addition, the mixture was vigorously allowed to stirat -5 °C to 0 °C for 0.5 hours. To the reaction mixture was then added dropwise a solution of tin(II) chloride (81.0 g, 359 mmol) in concentrated HCl (60 mL). The internal temperature was maintained at or below -5 °C during the addition and the resulting suspension was allowed to stir at -10 °C to 20 °C for about 1.5 hours. The precipitate was filtered off and the flask was rinsed with a small amount of water. The collected solids were dissolved into water (100 mL), and to the resulting solution was added $Na_2S.9H_2O$ (39 g). The aqueous layer was adjusted to pH 11 using 50% aqueous sodium hydroxide solution (4 mL). The solids were removed by filtration and washed with water. The aqueous layer was extracted with THF/ethyl acetate (1:2) (2 X 200 mL). The combined organic layer was dried (magnesium sulfate), filtered, and concentrated *in vacuo* to provide compound **51A** (14.8 g, 84%), which was used without further purification.

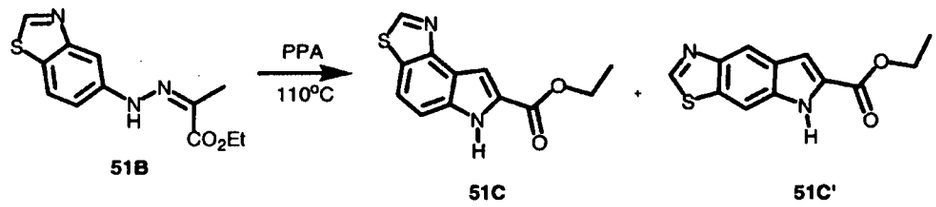
Step B – Synthesis of Compound 51B



51A **51B**

To a solution of compound **51A** (14.8 g, 89.6 mmol) in ethanol (300 mL) at room temperature, was added ethyl pyruvate (15 mL, 137 mmol) and acetic acid (1.35 mL). The reaction was heated to reflux and allowed to stir at this temperature for 2.5 hours. After being cooled to room temperature, the reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with ethyl acetate (300 mL) and 0.1 N aqueous sodium carbonate solution (300 mL). The separated organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide a crude residue which was purified using flash chromatography on silica gel (EtOAc:Hexanes, 0 to 50% EtOAc) to provide compound **51B** (22.7 g, 96%).

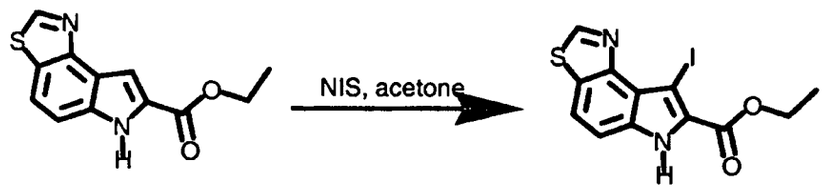
Step C – Synthesis of Compound 51C



51B 51C 51C'

Compound **51B** (22 g, 83.6 mmol) was ground into a powder, then was mixed with polyphosphoric acid (180 g). The bi-phasic mixture was vigorously allowed to stirat 110 °C for 1.5 h, then cooled to room temperature and poured into ice water. The aqueous layer of the mixutre was basified to pH 11 using aqueous ammonium hydroxide (37 N). The resulting mixture was extracted with 300 mL of ethyl acetate/THF (2:1) four times. The combined organics were dried (magnesium sulfate), filtered, and concentrated *in vacuo* to provide a crude residue which contained compounds **51C** and **51C'**. The crude residue was purified using flash chromatography on silica gel (EtOAc:Hexanes, 0 to 50% EtOAc) to provide compound **51C** (2.55 g, 12%). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.28 (s, 1H), 7.86 (d, J= 8.8 Hz, 1H), 7.52 & 7.50 (dd, J=0.6 Hz & 8.5 Hz, 1H), 7.40 & 7.39 (dd, J= 0.9 Hz & 2.2 Hz, 1H), 4.37 (q, J= 6.9 Hz & 7.3 Hz, 2H), 2.85 (s, 3H), 1.36 (t, J= 6.9 Hz, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 166.4, 161.0, 136.3, 126.9, 126.7, 120.5, 117.8, 110.8, 109.1, 105.1, 60.4, 19.6, 14.2. HRMS calcd for $C_{13}H_{12}N_2O_2S$: 261.0698 $(M+H)^+$. Found: 261.0701.

Step D – Synthesis of Compound 51D

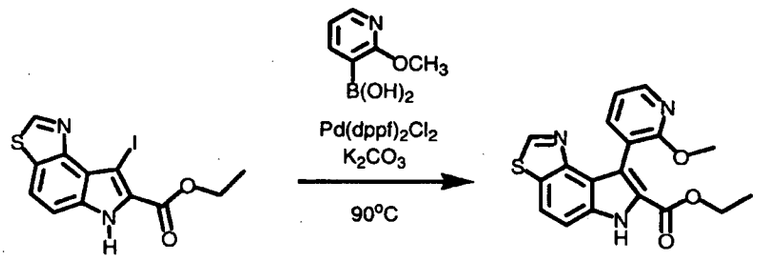


51C 51D

To a solution of compound **51C** (2.55 g, 10.4 mmol) in acetone (400 mL) at room temperature, was added *N*-iodosuccinimide (15.8 mmol). The resulting reaction was allowed to stir at room temperature for 18 hours, then concentrated *in vacuo*, and the resulting residue was dissolved with ethyl acetate (150 mL). The organic layer was collected and washed with

saturated aqueous sodium thiosulfate solution (80 mL). The aqueous layer was then extracted with ethyl acetate (2 X 100 mL) and the combined organic layers were dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide compound **51D** (quant.), which was used without further purification. ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.66 (s, 1H), 9.49 (s, 1H), 8.06 & 8.04 (dd, J= 3.47 Hz & 8.83 Hz, 1H), 7.66 & 7.65 (dd, J= 3.15 Hz & 8.51 Hz, 1H), 4.40 (q, J= 4.42 Hz & 4.39 Hz, 2H), 1.40 (dt, J= 3.47 Hz & 7.09 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO): δ 160.25, 154.74, 146.47, 146.25, 135.83, 127.14, 126.49, 125.64, 119.00, 111.86, 60.71, 14.19. M.S. found for $C_{12}H_9IN_2O_2S$: 373.17 $(M+H)^+$.

Step E – Synthesis of Compound 51E

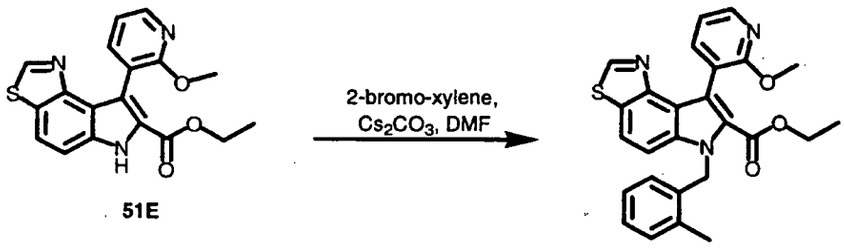


51D **51E**

To a solution of compound **51D** (10.4 mmol) in 1,2-dimethoxyethane (225 mL) was added $Pd(dppf)_2Cl_2$ (1.05 mmol) and the resulting solution was degassed using argon bubbling for 5 minutes. The degassed solution was then heated to 90 °C and allowed to stirfor 0.5 hours. In a second flask, 2-methoxy-3-pyridine boronic acid (14.6 mmol) and potassium carbonate (52.1 mmol) were dissolved into dimethoxyethane (75 mL) and water (75 mL) and the resulting solution was degassed with argon bubbling for 5 minutes, then the contents of the second flask were added to the solution containing compound **51D**. The resulting bi-phasic mixture was heated to 90 °C and vigorously allowed to stirat this temperature. After 4 hours the reaction was cooled to room temperature and quenched by addition of a solution of sodium sulfite (3.6 g) in water (80 mL) at room temperature. Ethyl acetate (200 mL) and water (100 mL) were added to the quenched reaction and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 200 mL) and the combined organic layers was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide compound **51E** (100%). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.41 (s, 1H), 9.21 (s, 1H), 8.19 & 8.18 (ddd, J= 0.63 Hz, 1.89 Hz & 5.04 Hz, 1H), 7.99 (d, J= 8.83 Hz, 1H), 7.72 (s, 1H), 7.66 (d, J= 8.83 Hz, 1H), 7.04 (q,

J= 5.04 Hz & 2.21 Hz, 1H), 4.17 (q, J= 7.25 Hz & 6.94 Hz, 2H), 3.69 (s, 3H), 1.09 (t, J= 7.09 Hz, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 161.42, 160.80, 154.43, 152.61, 146.80, 145.17, 140.71, 135.05, 126.34, 123.64, 120.32, 118.25, 116.36, 116.02, 111.75, 60.10, 39.00, 13.78. M.S. found for $C_{18}H_{15}N_3O_3S$: 354.04 $(M+H)^+$.

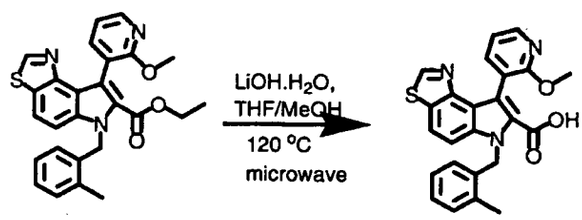
Step F – Synthesis of Compound 51F



51E 51F

To a solution of compound **51E** (0.71 mmol) in DMF (25 mL) at room temperature, was added 2-bromo-xylene (1.00 mmol) and cesium carbonate (1.23 mmol). The resulting suspension was allowed to stir at room temperature for 18 hours, then ethyl acetate (200 mL) and water (100 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layer was washed with water (2 X 100 mL). The separated organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide a crude residue which was purified using flash chromatography to provide compound **51F** (0.21 g, 65%). M.S. found for $C_{26}H_{23}N_3O_3S$: 458.11 $(M+H)^+$.

Step G – Synthesis of Compound 51G

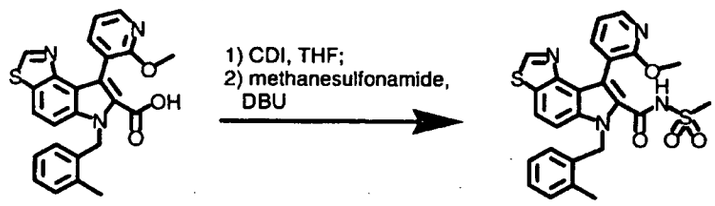


51F 51G

To a solution of compound **51F** (0.21 g, 0.45 mmol) in tetrahydrofuran (2 mL) and methanol (3 mL) was added lithium hydroxide monohydrate (60 mg, 1.43 mmol). The

resulting suspension was allowed to stir at room temperature for 5 minutes before being placed in microwave reactor for 20 minutes (120 °C, high power). The reaction was then concentrated *in vacuo* and ethyl acetate (50 mL) and tetrahydrofuran (50 mL) were added to the residue. The aqueous layer was acidified to pH=1 by adding 5% phosphoric acid, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried (magnesium sulfate) and filtered and concentrated *in vacuo* to provide compound **51G** (100%). M.S. found for $C_{24}H_{19}N_3O_3S$: 430.10 $(M+H)^+$.

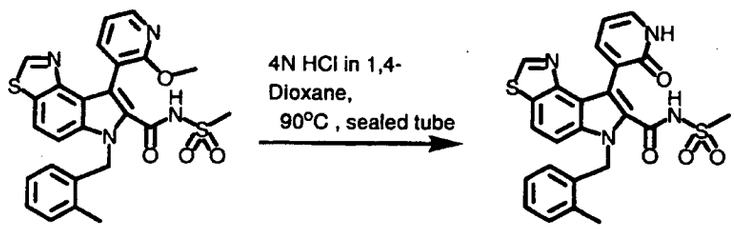
Step H – Synthesis of Compound 51H



51G **51H**

To a solution of compound **51G** (132 mg, 0.31 mmol) in tetrahydrofuran (5 mL) was added carbonyl diimidazole (60 mg). The resulting suspension was refluxed at 75 °C for 1 hour, and then cooled to room temperature before adding methanesulfonamide (70 mg, 0.74 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.11 mL). The resulting reaction mixture was allowed to stir at room temperature for 48 hours. Ethyl acetate (80 mL), tetrahydrofuran (10 mL) and 1% aqueous phosphoric acid (50 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel to provide compound **51H** (106 mg, 68%).

Step I – Synthesis of Compound 51



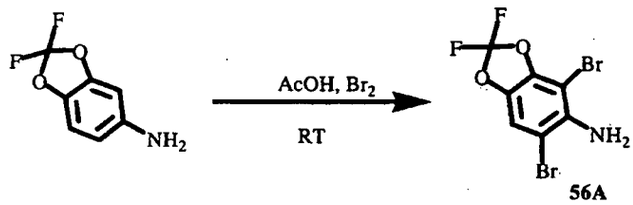
51H **51**

A solution of compound **51H** (103 mg, 0.20 mmol) in 4N HCl (4.5 mL in 1,4-dioxane) was placed in a sealed tube, heated to 90 °C, and allowed to stir at this temperature for 3 hours. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The crude product was purified using reverse phase HPLC to provide compound **51** (35 mg, 35%). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.72 (s,1H), 12.57 (s, 1H), 9.32 (s, 1H), 8.04 (d, J= 8.83 Hz, 1H), 7.98 (d, J= 6.62 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.21 (d, J= 7.57 Hz, 1H), 7.12 (t, J= 7.41 Hz, 1H), 6.98 (t, J= 7.57 Hz, 1H), 6.59 (t, J= 6.62 Hz, 1H), 6.23 (d, J= 7.88 Hz, 1H), 5.79 (s, 2H), 3.09 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 163.64, 162.74, 160.88, 155.03, 146.60, 142.59, 136.12, 135.32, 134.60, 132.27, 129.89, 129.01, 127.38, 127.07, 126.72, 125.92, 124.64, 119.03, 114.42, 110.27, 106.96, 73.69, 45.91, 18.71. M.S. found for $C_{24}H_{20}N_4O_4S_2$: 493.06 $(M+H)^+$.

Example 9

Preparation of Compound **56**

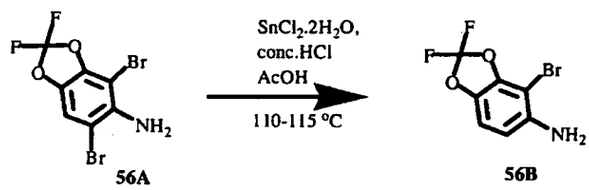
Step A – Synthesis of Compound 56A



56A

Bromine (11.3 mL) was added into a solution of 5-amino-2,2-difluorobenzodioxole (Maybridge, 5.0 g, 28.9 mmol) in acetic acid (150 mL). The mixture was allowed to stir at room temperature for 1 hour, then concentrated *in vacuo*. The resulting residue was diluted with methylene chloride (50 mL) and the solid was filtered, washed with methylene chloride (4 x 15 mL) and dried under vacuum to provide compound **56A** (8.2 g, 86%) as a yellow solid. M.S. found for $C_7H_3Br_2F_2NO_2$: 331.93 $(M+H)^+$.

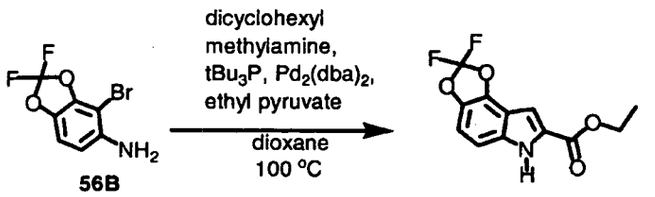
Step B – Synthesis of Compound 56B



56A **56B**

To a suspension of compound **56A** (4.48 g,13.5 mmol) in acetic acid (glacial, 20 mL) and concentrated HCl (16.0 mL) was added stannous chloride (3.36 g, 14.9 mmol). The resulting suspension was heated to 110 - 115 °C and allowed to stirat this temperature for 30 minutes. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. To the residue were added methylene chloride (80 mL) and aqueous 1N sodium hydroxide (80 mL), and the layers were seperated. The aqueous layer was extracted with methylene chloride (2 X 80 mL). The combined organic layer was dried (magnesium sulfate), filtered, and concentrated *in vacuo* to provide compound **56B** (2.68 g, 79%) as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO): δ 7.12 (d, J= 8.5 Hz, 1H), 6.54 (d, J= 8.8 Hz, 1H), 5.48 (s, 2H) .^{13}C NMR (125 MHz, d_6-DMSO): δ 143.7, 141.6, 133.1, 130.7, 109.5, 108.4, 87.5. M.S. found for $C_7H_4BrF_2NO_2$: 254.00 $(M+H)^+$.

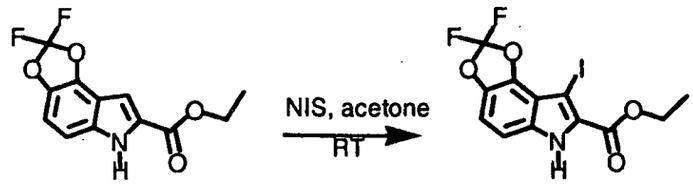
Step C – Synthesis of Compound 56C



56B **56C**

Compound **56B** (2.66 g,10.6 mmol) was dissolved into anhydrous dioxane (100 mL). To the solution was added dicyclohexyl methylamine (14.8 mL, 69.1 mmol), tri-tert-butyl phosphine (0.83 g, 4.10 mmol), $Pd_2(dba)_3$ (971 mg, 1.06 mmol) and ethyl pyruvate (4.60 mL, 42.0 mmol). The mixture was heated to 100 °C and allowed to stirfor 18 hours. The reaction mixture was cooled to room temperature, and was diluted with methylene chloride (300 mL) and aqueous 1N HCl solution (300 mL). The layers were separated, and the aqueous layer was extracted with methylene chloride (2 X 150 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography on silica gel to provide compound **56C** (1.79 g, 62%).^{1}H NMR (500 MHz, d_6-DMSO): δ 12.40 (s, 1H), 7.38 (d, J=9.1 Hz, 1H), 7.31 & 7.30 (dd, J=0.9 Hz & 8.8 Hz, 1H), 7.17 (d, J= 2.2 Hz, 1H), 4.37 (q, J= 6.9 Hz & 7.3 Hz, 2H), 1.35 (t, J= 7.1 Hz, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 160.5, 136.1, 135.8, 134.4, 133.6, 130.1, 111.6, 108.1, 107.4, 101.6, 60.9, 14.1.

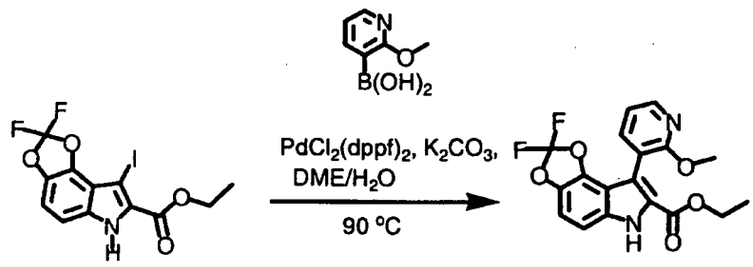
Step D – Synthesis of Compound 56D



56C **56D**

Compound **56C** (1.79 g, 6.62 mmol) was dissolved into acetone (150 mL) at room temperature. To the mixture was added N-iodosuccinimide (1.70 g, 7.18 mmol), and the resulting suspension was allowed to stir at room temperature for 3 hours. The mixture was concentrated *in vacuo*. Residue was dissolved into ethyl acetate (100 mL) and washed with saturated aqueous sodium thiosulfate solution (50 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried (magnesium sulfate), filtered, and concentrated *in vacuo* to provide compound **56D** (2.47 g, 94%).

Step E – Synthesis of Compound 56E

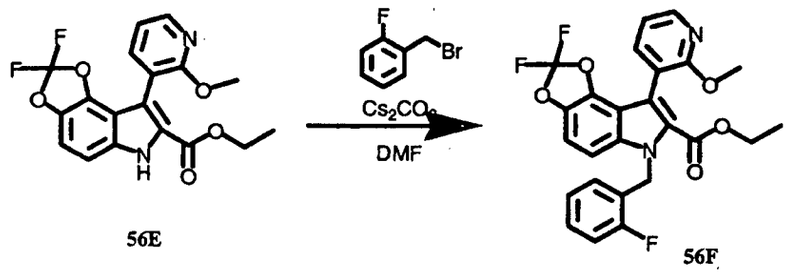


56D **56E**

Compound **56D** (2.46 g, 6.21 mmol) was dissolved into 1,2-dimethoxyethane (75 mL). To the mixture was added $PdCl_2(dppf)_2$ (510 mg, 0.63 mmol). The resulting suspension was heated to 90 °C and was de-gassed with nitrogen bubbling for 15 minutes. In a second flask, 2-methoxy-3-pyridine boronic acid (1.15 g, 7.52 mmol) and potassium carbonate (4.30 g, 31.1 mmol) were dissolved into dimethoxyethane (25 mL) and water (25 mL). The mixture was de-gassed with nitrogen bubbling for 5 minutes before being transferred to the first flask. The resulting mixture was vigorously allowed to stirat 90 °C for 3.5 h, then cooled to room temperature. A solution of sodium sulfite (4.3 g) in water (57 mL) was thn added to the mixture, followed by ethyl acetate (150 mL), and the layers were seperated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were dried

(magnesium sulfate), filtered, and concentrated *in vacuo*. The resulting residue was purified using flash chromatography on silica gel to provide compound **56E** (0.96 g, 41%). M.S. found for $C_{18}H_{14}F_2N_2O_5$: 377.02 $(M+H)^+$.

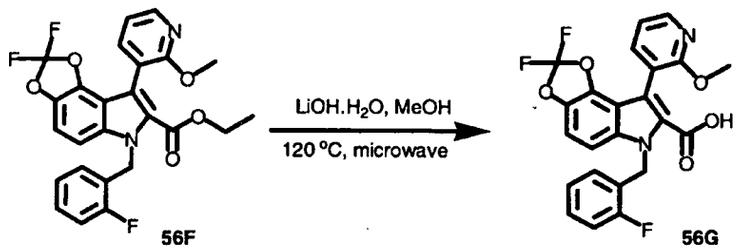
Step F – Synthesis of Compound 56F



56E **56F**

Compound **56E** (250 mg, 0.66 mmol) was dissolved into N,N-dimethyl formamide (20 mL) at room temperature. To the mixture were added 2-fluorobenzyl bromide (175 mg, 0.92 mmol) and cesium carbonate (325 mg, 1.00 mmol). The resulting suspension was allowed to stir at room temperature for 18 hours. Ethyl acetate (200 mL) and water (100 mL) were added to the reaction mixture, and then the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layer was washed with water (2 X 50 mL), and then was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide compound **56F** (0.27 g, 84%). M.S. found for $C_{25}H_{19}F_3N_2O_5$: 485.10 $(M+H)^+$.

Step G – Synthesis of Compound 56G

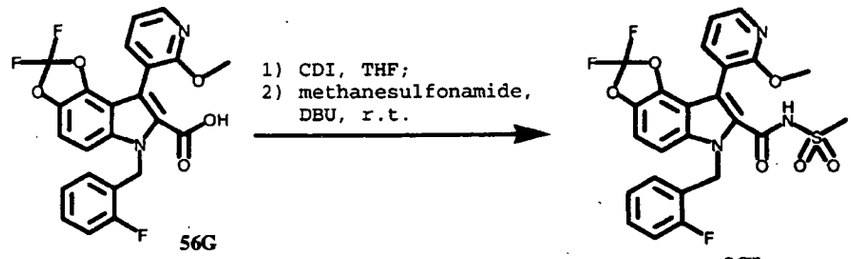


56F **56G**

To a solution of compound **56F** (0.55 mmol) in methanol (5 mL) was added lithium hydroxide monohydrate (2.19 mmol) and the resulting suspension was allowed to stir at room temperature for 5 minutes before being placed in a microwave reactor for 20 min (120 °C, high power). The mixture was then concentrated *in vacuo* and the resulting residue was diluted with ethyl acetate (50 mL) and tetrahydrofuran (50 mL). The aqueous layer was acidified to pH 1 using 1N HCl solution, and the layers were seperated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL), and the combined organic layer was dried (magnesium sulfate),

filtered and concentrated *in vacuo* to provide compound **56G** (100%). M.S. found for $C_{23}H_{15}F_3N_2O_5$: 457.09 $(M+H)^+$.

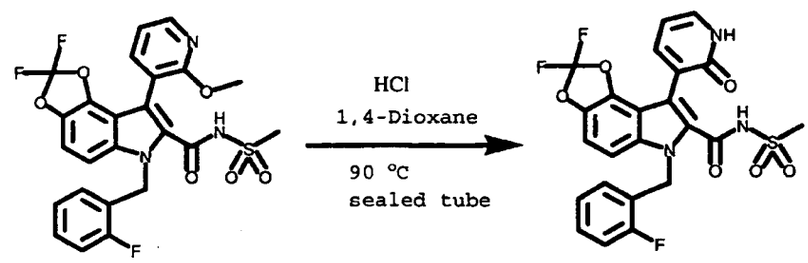
Step H – Synthesis of Compound 56H



56G **56H**

Compound **56G** (143 mg, 0.31 mmol) was dissolved into tetrahydrofuran (5.0 mL) at room temperature. To the mixture was added carbonyl diimidazole (65 mg, 0.40 mmol). The suspension was refluxed at 75 °C for 1 h, and then cooled to room temperature before adding methanesulfonamide (60 mg, 0.63 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (1.00 mmol). The resulting reaction mixture was allowed to stir at room temperature for 68 hours. Ethyl acetate (80 mL), tetrahydrofuran (10 mL) and 1% aqueous phosphoric acid (50 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide compound **56H** (113 mg, 68%). M.S. found for $C_{24}H_{18}F_3N_3O_6S$: 534.04 $(M+H)^+$.

Step I – Synthesis of Compound 56



56H **56**

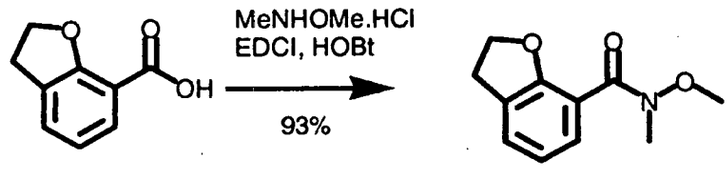
A solution of Compound **56H** (65 mg, 0.12 mmol) in HCl (4N in dioxane, 5.0 mL) in a sealed tube was heated to 90 °C and allowed to stirat this temperature for 2 hours. The reaction mixture was then cooled to room temperature, then concentrated *in vacuo* to provide a crude residue which was purified using reverse phase HPLC to provide compound **56** (44 mg, 69%). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.77 (s, 1H), 12.49 (s, 1H), 7.82 & 7.81 (dd, J= 1.58 Hz &

6.94 Hz, 1H), 7.61 (t, J= 5.20 Hz, 1H), 7.50 (d, J= 8.83 Hz, 1H), 7.45 (d, J= 9.14 Hz, 1H), 7.33 (q, J= 6.31 Hz & 7.57 Hz, 1H), 7.22 (t, J= 9.46 Hz, 1H), 7.09 (t, J= 7.57 Hz, 1H), 6.89 (t, J= 7.72 Hz, 1H), 6.56 (t, J= 6.62 Hz, 1H), 5.76 (s, 2H), 3.23 (s, 3H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 161.81, 160.59, 158.65, 157.27, 145.62, 143.33, 137.17, 135.62, 135.24, 134.57, 129.54, 128.67, 127.17, 124.10, 123.99, 123.79, 115.23, 111.32, 107.34, 106.68, 106.45, 42.10, 40.95. M.S. found for $C_{23}H_{16}F_3N_3O_6S$: 520.04 $(M+H)^+$.

Example 10

Preparation of Compound **59**

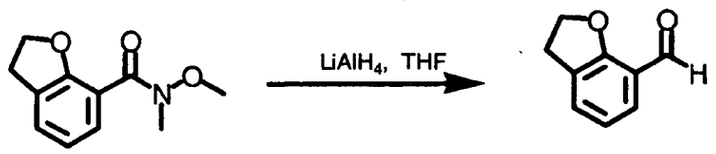
Step A – Synthesis of Compound 59A



59A

A suspension of 2,3-dihydro-benzofuran-7-carboxylic acid, (TCI, 20.0 g, 121.8 mmol) in 600 mL of dry acetonitrile was cooled to 0 °C and treated with N,O-dimethylhydroxylamine hydrochloride (14.25 g, 146.1 mmol). The reaction was allowed to stirfor 10 minutes and EDCI (24.6 g, 158.3 mmol) was added, followed by HOBT (3.2 g, 24.2 mmol) and the resulting mixture was allowed to stirfor 5 minutes. Triethylamine (365.4 mmol) was then added and the reaction mixture was allowed to stirfor 18 hours at room temperature, then diluted with aqueous 1N HCl (250 mL) and extracted with ethyl acetate (1.0 L). The organic layer was sequentially washed with aqueous 10% potassium carbonate (200 mL), aqueous 1N HCl (200 mL), and brine (200 mL). The organic layer was then dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide compound **59A** (23.37 g, 93 %) as a colorless oil. M.S. found for $C_{11}H_{13}NO_3$: 230.11 $(M+Na)^+$.

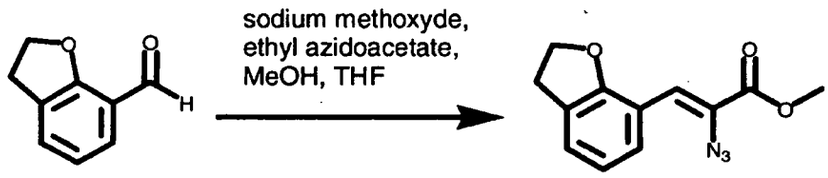
Step B – Synthesis of Compound 59B



59A **59B**

A suspension of lithium aluminum hydride (pellets, 5.56 g, 146.5 mmol) in 500 mL of dry THF was allowed to stir at 55 °C for 18 hours under anhydrous atmosphere, then cooled to 0 °C, and a solution of compound **59A** (23.37 g, 112.7 mmol) in 500 mL of dry THF was added over 45 minutes. The reaction mixture was allowed to stir at 0 °C for 30 minutes, then quenched by careful addition of aqueous 20% sodium hydrogen sulfate until gas evolution stopped. Additional aqueous 20% sodium hydrogen sulfate (approx. 5 mL) was added, and the resulting solution was vigorously allowed to stirfor 15 minutes. The reaction mixture wsa diluted with ether (500 mL) and hexanes (500 mL) and filtered through a short path of celite. The filtrate was concentrated *in vacuo* to afford a crude residue which was purified using medium pressure liquid chromatography (Biotage 75-M silica gel column, gradient: 0 to 30 % ethyl acetate in hexanes) to provide compound **59B** (9.00 g, 54 %) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ10.10 (s, 1H), 7.51 (q, J= 7.32 Hz & 5.13 Hz, 2H), 6.95 (t, J= 7.69 Hz, 1H), 4.69 (t, J= 8.79 Hz, 2H), 3.22 (t, J= 8.42 Hz, 2H).

Step C – Synthesis of Compound 59C

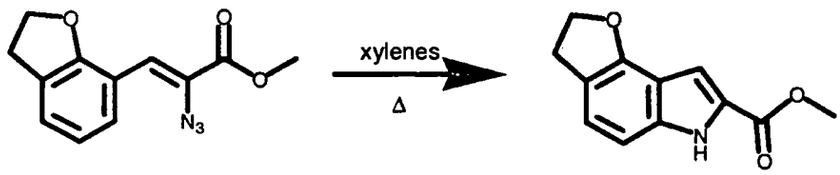


59B **59C**

A solution of freshly prepared sodium methoxyde in methanol (2.5 eq, prepared by dissolving 1.94 g of sodium in 80 mL of methanol) was added dropwise (over 20 minutes) to a cooled (-20 °C, internal temperature) solution of compound **59B** (5.0 g, 33.74 mmol) and ethyl azidoacetate (10.9 g, 84.36 mmol) in 20 mL of dry methanol and 20 mL of dry THF. The addition was carried such that the internal reaction temperature was not permitted to rise above -10 °C. The reaction was then allowed to stirat -10 °C for 1 hour, then allowed to warm to room temperature over 1 hour. The reaction mixture was then allowed to stir at room temperature for 1 hour (a white precipitate formed), and was then quenched with aqueous saturated ammonium chloride solution (10 mL). The resulting solution mixture was partitioned between ethyl acetate (500 mL) and water (100 mL). The organic layer was washed with brine (80 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (Biotage 75-M column;

gradient: 0 to 25% ethyl acetate in hexanes) to provide compound **59C** (4.20 g, 52 %) as a slightly yellow solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.96 (d, J= 8.06 Hz, 1H), 7.24 (d, J= 6.59 Hz, 1H), 7.01 (s, 1H), 6.88 (t, J= 7.69 Hz, 1H), 4.58 (t, J= 8.79 Hz, 2H), 3.84 (s, 3H), 3.21 (t, J= 8.79 Hz, 2H).

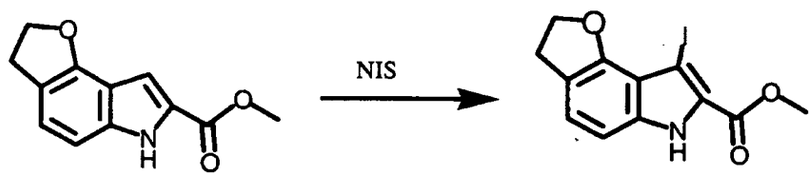
Step D – Synthesis of Compound 59D



59C **59D**

A solution of compound **59C** (4.0 g, 16.31 mmol) in 60 mL of xylenes was heated to 150 °C and allowed to stir at this temperature for 10 minutes, then was cooled to room temperature, during which time a white solid formed. The suspension was stored as -20 °C in freezer for 1 hour, then filtered to provide compound **59D** as a white solid (1.0 g). The filtrate was concentrated *in vacuo*, and the resulting residue was purified using column chromatography on silica gel (Biotage 40-S column; gradient: 0 to 35% ethyl acetate in hexanes) to provide an additional amount of compound **59D** (290 mg). (Total yield = 1.29 g, 37%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.91 (s, 1H), 7.12 (d, J= 8.06 Hz, 1H), 6.96 (s, 1H), 6.95 (d, J= 8.06 Hz, 1H), 4.65 (t, J= 8.79 Hz, 2H), 3.85 (s, 3H), 3.22 (t, J= 8.79 Hz, 2H).

Step E– Synthesis of Compound 59E

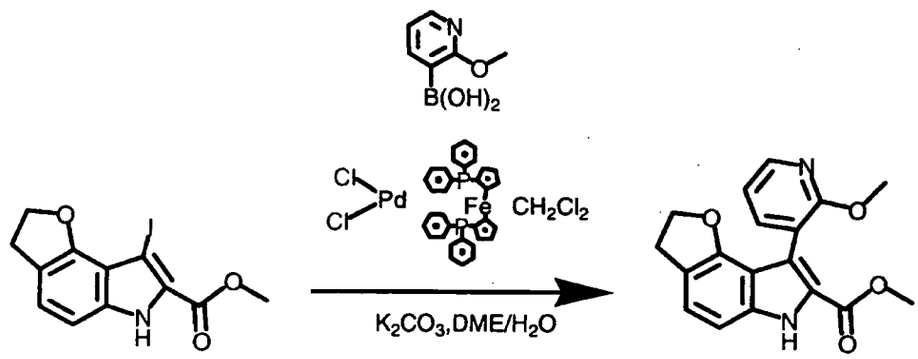


59D **59E**

To a solution of compound **59D** (1.45 g, 6.67 mmol) in 50 mL of chloroform and 20 mL of THF at 0 °C was added N-iodosuccinimide (1.65 g, 7.34 mmol). The resulting reaction was allowed to stir at 0 °C for 30 minutes, then warmed to room temperature and allowed to stir at this temperature for 30 minutes. The reaction mixture was then diluted with ethyl acetate (100 mL), and the resulting solution was sequentially washed with aqueous saturated

sodium thiosulfate (20 mL), aqueous saturated sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified using column chromatography on silica gel (Biotage 40-S column; gradient: 0 to 40 % ethyl acetate in hexanes) to provide compound **59E** (190 mg, 10 %) as a white solid. M.S. found for $C_{12}H_{10}INO_3$: 343.87 $(M+H)^+$.

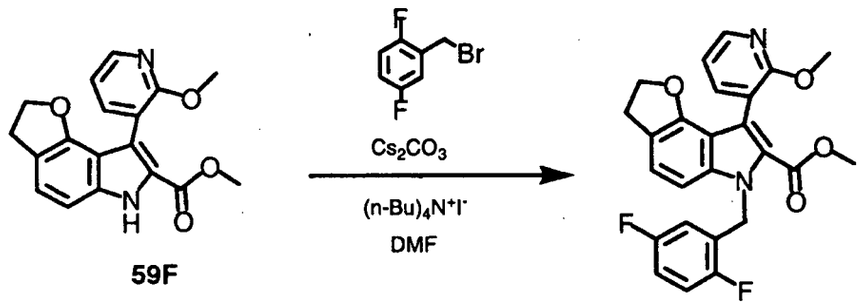
Step F – Synthesis of Compound 59F



59E **59F**

To a solution of of compound **59E** (180 mg, 0.524 mmol) in 10 mL of 1,2-dimethoxyethane was added 2-methoxy-3-pyridine boronic acid (240 mg, 1.573 mmol) and the resulting mixture was de-gassed (vacuum/argon flush), and $PdCl_2(dppf)_2$ (10 mol%, 42 mg) was added. The resulting mixture was allowed to stirfor 15 minutes at room temperature and a solution of potassium carbonate (434 mg, 3.144 mmol) was added. The resulting brown reaction was heated to 90 °C and allowed to stir at this temperature for 45 minutes. The reaction mixture was then cooled to room temperature, and diluted with ethyl acetate (80 mL). The organic layer was washed sequentially with aqueous saturated sodium bicarbonate (10 mL) and brine (10 mL), then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was purified using column chromatography on silica gel (Biotage 25-S column; gradient: 10 to 50 % ethyl acetate in hexanes) to provide compound **59F** (140 mg, 83 %) as a white solid. M.S. found for $C_{18}H_{16}N_2O_4$: 325.07 $(M+H)^+$.

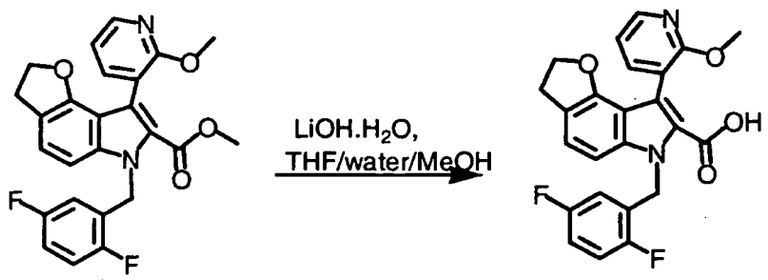
Step G – Synthesis of Compound 59G



59F **59G**

To a solution of compound **59F** (130 mg, 0.400 mmol) in 5 mL of dry DMF at 0 °C were added 2,5-drifluorobenzyl bromide (99 mg, 0.480 mmol), cesium carbonate (391 mg, 1.200 mmol) and tetrabutylammonium iodide (10 mg, catalytic). The resulting reaction was allowed to stir at 0 °C for 45 minutes, then warmed to room temperature. The mixture was then diluted with ethyl acetate (80 mL), and the resulting solution was sequentially washed with water (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo* to provide a crude residue which was purified using column chromatography on silica gel (Biotage 25-S column; gradient: 0 to 25% ethyl acetate in hexanes) to provide compound **59G**(140 mg, 78 %) as a white solid. M.S. found for $C_{25}H_{20}F_2N_2O_4$: 451.12 $(M+H)^+$.

Step H – Synthesis of Compound 59H

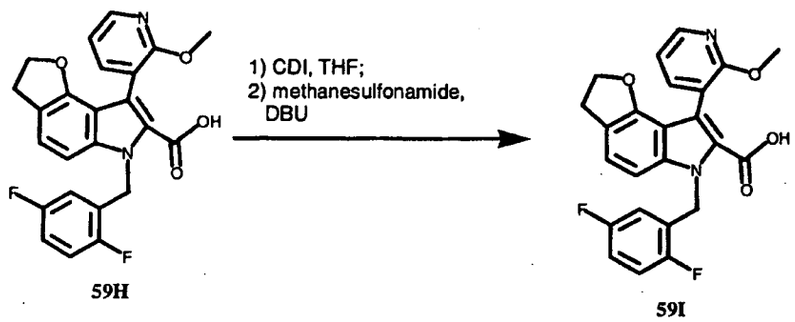


59G **59H**

To a solution of compound **59G** (140 mg, 0.310 mmol) in 8 mL of a solution of tetrahydrofuran/ water/methanol (2:1:1) was added lithium hydroxide monohydrate (65 mg, 1.554 mmol). The reaction was heated to 50 °C for and allowed to stir at this temperature for 5 hours. The mixture was diluted with aqueous 1N HCl solution (40 mL), and then was extracted with dichloromethane (3 X 25 mL). The combined organic layers were dried

(magnesium sulfite), filtered and concentrated *in vacuo* to provide compound **59H** (135 mg, 99%) as a white solid, which was used without further purification.

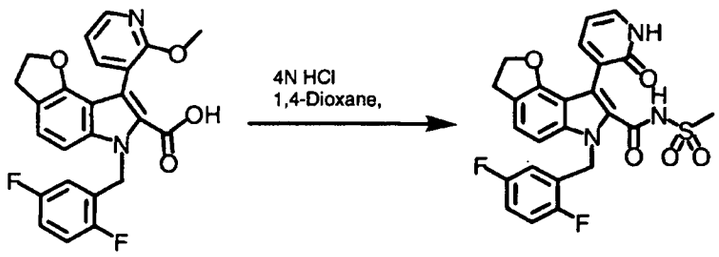
Step I – Synthesis of Compound 59I



59H **59I**

To a solution of compound **59H** (150 mg, 0.343 mmol) in tetrahydrofuran (4.0 mL) was added carbonyl diimidazole (69 mg, 0.429 mmol). The resulting mixture was refluxed at 70 °C for 2 h and then cooled to room temperature. Methanesulfonamide (41 mg, 0.429 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (78 mg, 0.514 mmol) were added to the reaction and the resulting reaction mixture was heated to 40 °C and allowed to stir at this tempearature for 48 hours. The reaction mixture was diluted with ethyl acetate (60 mL), and sequentially washed with aqueous 1N HCl (10 mL) and brine (10 mL). The organic layer was dried (magnesium sulfate), filtered, and concentrated *in vacuo* to provide compound **59I** (103 mg, 60%), which was used without further purification. ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.71 (s, 1H), 8.14 & 8.13 (dd, J= 2.20 Hz & 5.13 Hz, 1H), 7.79 & 7.77 (dd, J= 2.20 Hz & 7.32 Hz, 1H), 7.34 – 7.26 (m, 1H), 7.20 (d, J= 8.79 Hz, 1H), 7.19 – 7.12 (m, 1H), 7.10 – 7.07 (m, 2H), 6.58 – 6.53 (m, 1H), 5.65 (s, 2H), 4.55 (d, J= 8.79 Hz, 2H), 3.75 (s, 3H), 3.19 – 3.14 (m, 2H), 3.06 (s, 3H).

Step J – Synthesis of Compound 59



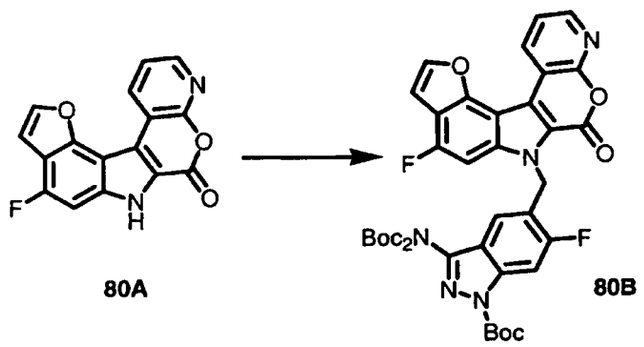
59I **59**

A solution of Compound **59I** (100 mg, 0.194 mmol) in 3 mL of HCl (4M in dioxane) and methanol (1 mL) was placed in a sealed tube, heated at 90 °C and allowed to stir at this temperature for 3 hours. The reaction mixture was concentrated *in vacuo* to provide a yellow solid residue which was purified using reverse phase HPLC (Delta Pak, C18, 5 micrometer, 300A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; Gradient: 40% acetonitrile in water for 20 min then increase to 80% over 30 min and stay there for 10 min) to provide compound **59** (62 mg, 65%) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.78 & 7.76 (dd, J= 2.20 Hz & 7.32 Hz, 1H), 7.62 (d, J= 5.86 Hz, 1H), 7.55 & 7.53 (dd, J= 1.47 Hz & 6.59 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.23 -7.13 (m, 3H), 7.04 (q, J= 4.39 Hz & 3.66 Hz, 1H), 6.57 (q, J= 6.59 Hz, 1H), 5.66 (s, 2H), 3.25 (s, 3H), 3.20-3.15 (m, 4H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 162.46, 161.32, 161.00, 153.15, 145.25, 140.18, 138.92, 135.30, 128.30, 125.89, 122.76, 122.25, 121.98, 117.41, 117.06, 115.69, 113.19, 112.00, 106.96, 102.46, 72.11, 51.40, 41.06, 28.66. M.S. found for $C_{24}H_{19}F_2N_3O_5S$: 500.14 $(M+H)^+$.

Example 11

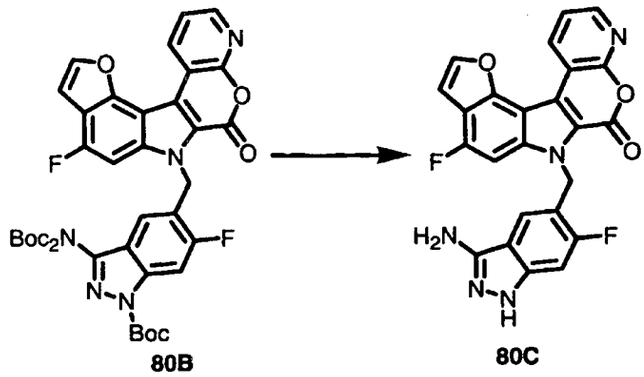
Preparation of Compound **80**

Step A – Synthesis of Compound 80B



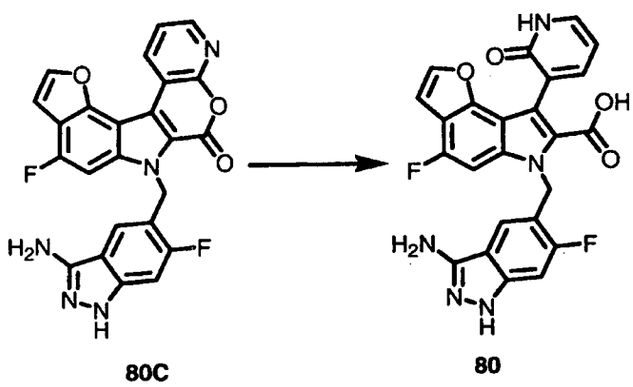
A solution of compound **80A** (294.2 mg, 0.99 mmol), Cesium carbonate (488.67 mg, 1.4998 mmol) in DMF (10 mL) was stirred at room temperature for 12 hours, the concentrated *in vacuo*. The residue obtained was dissolved in EtOAc (200 mL) washed with brine (100 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified using flash column chromatography (SiO_2, Acetone/Hexanes) to provide compound **80B** (490 mg; Yield = 65%)

Step B – Synthesis of Compound 80C



A solution of **80B** (490.00 mg, 0.646 mmol) in HCl (4 M in dioxane, 25 mL, Supplier = Aldrich) was stirred at room temperature for 4 h and concentrated *in vacuo*. The residue obtained was dried under vacuum and used without further purification.

Step C – Synthesis of Compound 80

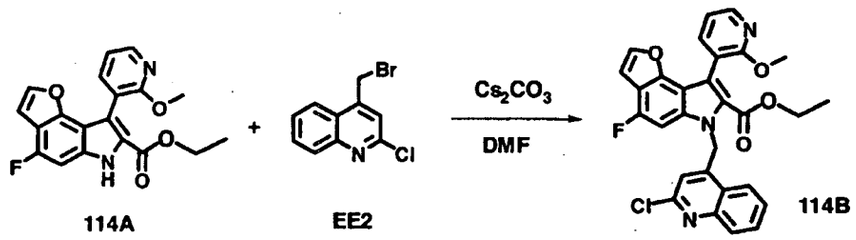


To a solution of compound **80C** (100 mg, 0.219 mmol), in THF (4 mL) and water (4 mL) was added lithium hydroxide monohydrate (64.2 mg, 1.53 mmol) and the reaction was strirred at room temperature for 12 hours. The reaction mixture was concetrated *in vacuo* and the resulting residue was purified using HPLC (reverse phase) using following conditions: Coloumn: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15µM, 300Å, 343K16006 (W): 30 mL/min flow; 10-100% ramp THF, water containing 0.01% TFA; Ramp = 0--> 60 minutes, to provide compound **80** as colorless solid. ^{1}H NMR (D6-dmso, 400 MHz),

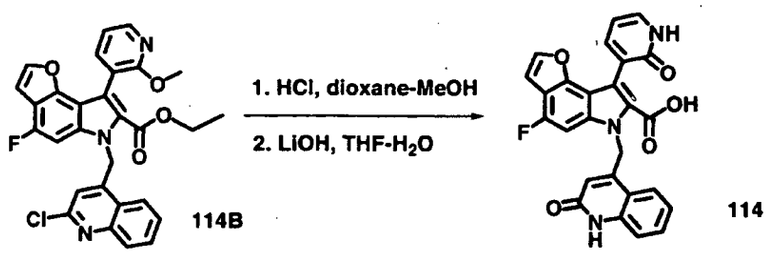
δ 12.48 (s, 1 H), 11.74 (b, 2 H), 7.90 (d, 1 H, J = 2.4 Hz), 7.67 (dd, 1 H, J = 1.8 & 6.7 Hz), 7.42 (d, 1 H, J = 10.8 Hz), 7.42 (d, 1 H, J = 2.4 Hz), 7.01 (d, 1 H, J = 11.0 Hz), 6.33 (t, 1 H, J = 6.7 Hz), 5.90 (s, 2 H), 6.00-4.4 (b, 2 H).

Example 12

Preparation of Compound **114**



To a suspension of compound **114A** (200 mg, 0.564 mmol) and cesium carbonate (600 mg, 1.85 mmol) in DMF (3 mL) was added compound **EE2** (520 mg, ~50% purity, ~1 mmol) and the resulting mixture was allowed to stir at room temperature for about 15 hours. The reaction mixture was diluted with ethyl acetate (100 mL), then washed with water (3 x 40 mL), dried over sodium sulfate, and concentrated *in vacuo*. The residue obtained was purified using Combi-flash chromatography (12 g silica column) with 0-25% ethyl acetate in hexanes as the eluent to provide compound **114B** as a white solid (210 mg, 70%).

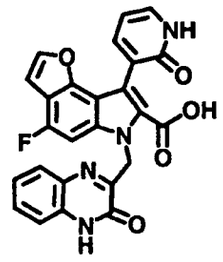


A 15 mL pressure vessel was charged with a solution of compound **114B** (210 mg, 0.40 mmol), HCl in dioxane (4M, 5 mL, 20 mmol), and methanol (2 mL) and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for about 15 hours. After cooling to room temperature, the reaction mixture was concentrated *in vacuo*. The residue obtained was suspended with MeOH (~10 mL) and concentrated again *in vacuo* to remove excess HCl. The resulting residue was washed with methanol (3 x 3 mL) and dried under vacuum to provide a white solid (160 mg, 76%), which was diluted with solid THF (8 mL) and aqueous LiOH solution (2.0 mL, 1.0 M, 2.0 mmol). The resulting reaction was heated to reflux and allowed

to stir at this temperature for about 7 hours, then cooled to room temperature. The reaction mixture was neutralized using HCl (2.0 mL, 1.0 M, 2.0 mmol) and the resulting suspension was concentrated in vacuo. The resulting residue was washed with water (2 x 20 mL) and methanol (3 mL), then dried under vacuum to provide compound **114** as a white solid (112 mg, 75%). M.S. found for C26H17FN3O5: 470.3 $(M+H)^+$; ^{1}H NMR (500 MHz, CD3OD, Na salt): δ 7.85 (1H, dd, J = 6.9, 2.2 Hz), 7.64-7.60 (2H, m), 7.44-7.37 (3H, m), 6.97 (1H, d, J = 10.4 Hz), 6.91 (1H, d, J = 2.2 Hz), 6.51-6.49 (1H, m), 6.34 (2H, s), 5.65 (1H, s).

Example 13

Preparation of Compound **117**



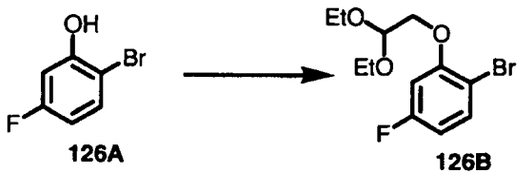
117

Compound **117** was synthesized using the method described above in Example 12 and utilizing the appropriate coupling partners. M.S. found for C25H16FN4O5: 471.3 $(M+H)^+$; ^{1}H NMR (500 MHz, CD3OD, Na salt): δ 7.94 (1H, d, J = 1.89 Hz), 7.69 (1H, dd, J = 6.94, 1.89Hz), 7.53-7.40 (4 H, m), 7.32 (1H, d, J = 8.2 Hz), 7.19 (1 H, t, J = 7.57 Hz), 7.09 (1H, d, J = 1.89 Hz), 6.38 (1H, t, J = 6.3 Hz), 5.97 (2H, s).

Example 14

Preparation of Compound **126**

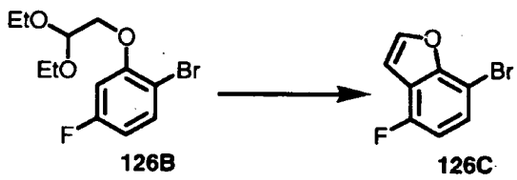
Step A – Synthesis of Compound 126B



126A **126B**

A solution of compound **126A**, (228.00 g, 1.19 mmol), Potassium carbonate (247.47 g, 1.79 mol) in DMF (3.00 L) was treated with 2-Bromo-1,1-diethoxyethane (197.54 mL, 1.31 mol) and heated at 135 °C for 7 hours. The reaction mixture was concentrated in *vacuo* and extracted with EtOAc (3x 2L). The combined organic layers were washed with aqueous NaOH (2M, 4 L). The organic layer was dried ($MgSO_4$), filtered, concentrated in *vacuo* to provide compound **126B** (362.00 g, 98%) which was used without further purification.

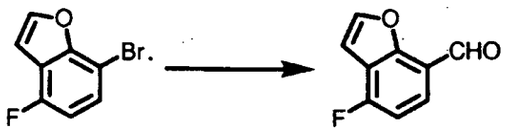
Step B – Synthesis of Compound 126C



126B **126C**

A solution of compound **126B** (352.00 g, 1.15 mol) in toluene (2500 mL, 2.3 mol) was treated with polyphosphoric acid (370.00 g, 3.4 mol) and heated at reflux for 5 hours. The reaction mixture was concentrated in *vacuo* diluted with water (3L) and the extracted with EtOAc (4 L). The organic layer was washed with aqueous NaOH (2L), filtered, concentrated in *vacuo* and purified by distillation at reduced pressure to provide compound **126C** (125.00 g, 50.8%). Bp. 80 °C (1mm/Hg) as a colorless liquid which solidified at room temperature. ^1H NMR (400 MHz,$CDCl_3$) δ 7.67 (d, 1 H, J = 2.2 Hz), 7.39 (dd, 1 H J =5.1 & 3.7 Hz), 6.94 (d, 1 H, J = 2.2 Hz), 6.86 (t, 1 H, J = 8.8 Hz).

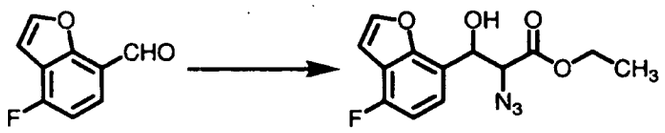
Step C – Synthesis of Compound 126D



126C **126D**

A solution of compound **126C** (124.12 g, 577.25 mmol) in ether (2.0 L) was cooled to -78 °C and treated dropwise with a solution of 2.5 M of n-butyllithium in hexane (235.5 mL) and allowed to stir at -78 °C for 15 minutes. To this reaction mixture was added DMF (89.393 mL, 1.15 mol) and allowed to stir at -78 °C for 30 minutes. The reaction mixture was quenched with methanol (23.383 mL, 577.25 mmol) and warmed to room temperature. The reaction mixture was diluted with ether (300 mL) and the organic layer was washed with water (300 mL). The separated organic layer was dried ($MgSO_4$) filtered, concentrated in *vacuo* to provide compound **126D** (89.00 g, 93.9%).

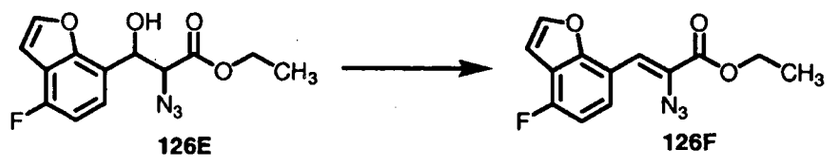
Step D – Synthesis of Compound 126E



126D **126E**

A solution of compound **126D** (12.71 g, 77.45 mmol), lithium chloride (6.567 g, 154.9 mmol) and ethyl azidoacetate (20.00 g, 154.9 mmol; added as a 30% solution in CH_2Cl_2), diazabicyclo[5.4.0]undec-7-ene (23.16 mL, 154.9 mmol) and stirred for 2 hours. The completion of the reaction was followed by TLC (EtOAc/Hexanes 1:4). Upon completion, the reaction mixture was diluted with ethyl acetate (1L) and washed with water and aqueous HCl (400 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo* and the residue obtained was purified using flash column chromatography SiO_2 (EtOAc/Hexanes) to provide compound **126E** (18.3 g, 80.6%) as a colorless oil.

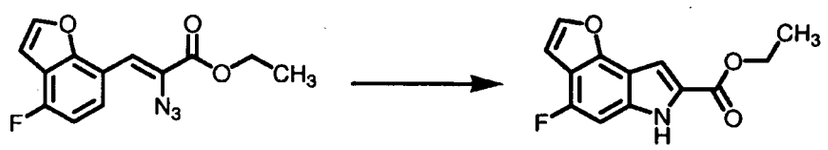
Step E – Synthesis of Compound 126F



126E **126F**

A solution of compound **126E** (15.7 g, 53.5 mmol) and methanesulfonyl chloride (8.29 mL, 107 mmol) in methylene chloride (87.7 mL, 1.37 mmol) at -30 °C was treated dropwise with a solution of triethylamine (52.2 mL, 375.0 mmol) in methylene chloride (100 mL). The reaction mixture was allowed to stir at -30 °C for 3 hours, diluted with aqueous saturated sodium bicarbonate and methylene chloride (400 mL). The organic layer was separated and washed with water, aqueous HCl and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified using flash column chromatography (SiO_2, 10% EtOAc in (1:1) Hexanes/CH_2Cl_2) to provide compound **126F** (12.6 g, 85.5%).

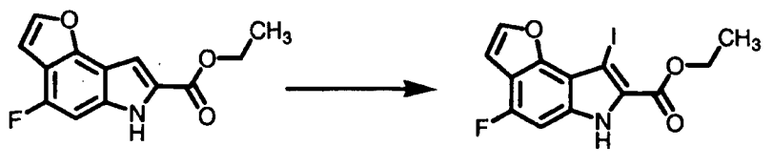
Step F – Synthesis of Compound 126G



126F **126G**

150 mL of xylenes was heated at 165 °C. To this boiling solution was added dropwise a solution of compound **126F** (11.2 g, 40.7 mmol) in Xylenes (70 mL, 189.4 mmol). The reaction mixture was stirred for additional 20.0 minutes and allowed to cool to room temperature to provide compound **126G** as a precipitate (7.00 g, 69.6%), which was filtered, washed with hexanes and dried under vacuum.

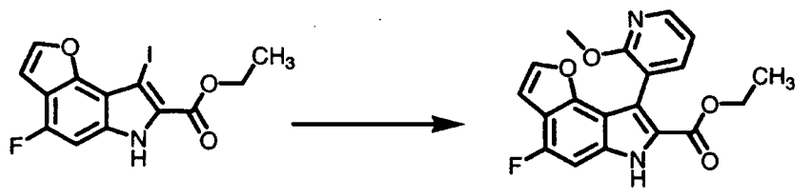
Step G – Synthesis of Compound 126H



126G **126H**

To a solution of compound **126G** (15.88 g, 64.23 mmol) in DMF (100 mL) was added N-iodosuccinimide (15.90 g, 70.66 mmol) and allowed to stir at room temperature. for 2 hours. The reaction mixture was diluted with water (1000 mL) and extracted in EtOAc (1000 mL). The organic layer was washed with water (1000 mL), aqueous sodium thiosulfate (5% aqueous soln. 1L) and dried ($MgSO_4$). The organic layer was dried ($MgSO_4$), filtered, concentrated in *vacuo* to provide compound **126H** (22.30 g, 93.04%) as a solid.

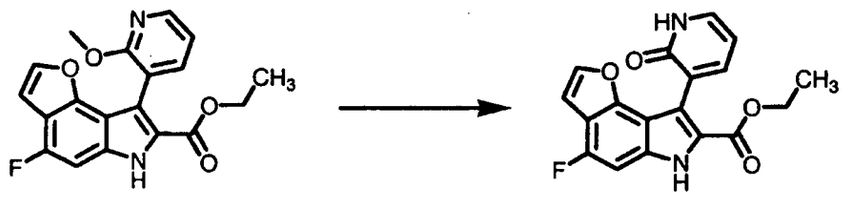
Step H – Synthesis of Compound 126I



126H **126I**

A solution of compound **126H** (22.000 g, 58.962 mmol), 2-methoxypyridin-3-ylboronic acid (13.527 g, 88.444 mmol), $(PPh_3)_2PdCl_2$ (4.13 g, 5.88 mmol) in 1,2-dimethoxyethane (250.0 mL) was degassed for 2 min and allowed to stir at room temperature. for 15 minutes. The orange reaction mixture was treated with a solution of potassium carbonate (30.53 g, 220.9 mmol) in water (250.0 mL) and allowed to stir at 90 °C for 3 hours. The yellow reaction turned orange dark with the disappearance of starting material (TLC). The reaction mixture was diluted with EtOAc (1000 mL) and washed with aqueous NaOH (500 mL, 1M), dried ($MgSO_4$), filtered, concentrated in *vacuo*, and purified using flash column chromatography SiO_2 (THF/Hexanes 0--> 60%) to provide compound **126I** (16.65 g, 79.7%) as pale brown solid.

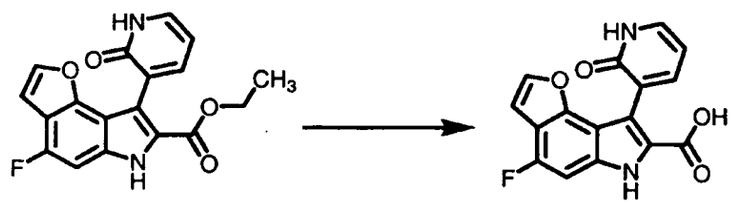
Step I – Synthesis of Compound 126J



126I **126J**

A solution of compound **126I** (4.50 g, 12.7 mmol) in methanol (10 mL, 246.9 mmol) was treated with a solution of 4 M HCl in dioxane (100 mL) and heated at 90 °C for 3 hours in a pressure tube. The reaction mixture was concentrated *in vacuo* and the residue obtained was purified using flash column chromatography (SiO_2, THF/Hexanes 0--> 100%) to provide compound **126J** as a colorless solid.

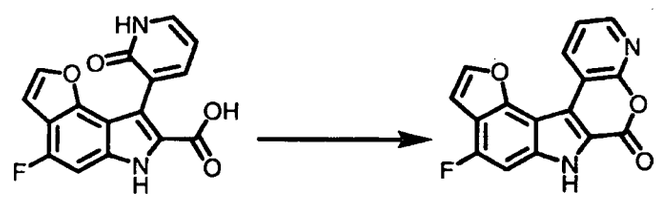
Step J – Synthesis of Compound 126K



126J **126K**

A solution of compound **126J** (810.00 mg, 2.38 mmol) in water (25mL), THF (25mL) and methanol (25mL, 780.2 mmol) was treated with lithium hydroxide monohydrate (499.41 mg, 11.901 mmol) and heated at 80 °C for 1 hour. The reaction mixture was then acidified using 1N HCl, filtered and dried in *vacuo* to provide compound **126K** (627.00 mg, 84.4%) as colorless solid.

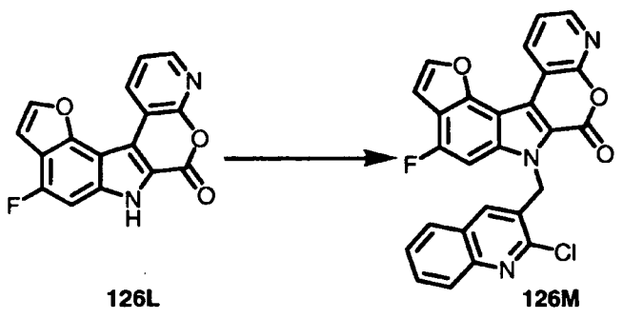
Step K – Synthesis of Compound 126L



126K **126L**

To a suspension of compound **126K** (8.00 g, 25.6 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (9.82 g, 51.2 mmol) in DMF (153.85 mL) was added triethylamine (35.71 mL, 256.2 mmol) and the reaction was stirred overnight at room temperature. The reaction mixture was concentrated *in vacuo* and the resulting residue was diluted with methanol (100 mL). The resulting precipitate was filtered and dried to provide compound **126L** (5.90 g, 78.3%)

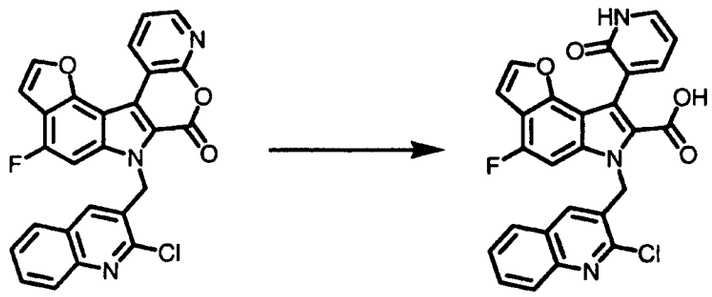
Step L – Synthesis of Compound 126M



126L **126M**

A suspension of compound **126L** (300 mg, 1 mmol), cesium carbonate (664.40 mg, 2.0392 mmol) and 2-chloro-3-(chloromethyl)quinoline (432.46 mg, 2.0392 mmol) in DMF (20 mL, 200 mmol) was allowed to stir at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue obtained was stirred with methanol (20 mL). The resulting precipitate was filtered and dried to provide compound **126M** (410 mg, 80%)

Step M – Synthesis of Compound 126



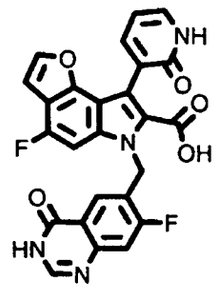
126M **126**

A solution of compound **126M** (130.00 mg, 0.27668 mmol) in water (10 mL) and THF (10 mL) was treated with lithium hydroxide monohydrate (58.05 mg, 1.38 mmol) and the reaction was allowed to stir at room temperature for 3 hours. The reaction mixture was

quenched with aqueous HCl (1M, 3 mL) and mixture was purified by HPLC (reverse phase) using following conditions: Coloumn: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15 µM, 300 A, 343K16006 (W): 30 mL/min flow; 30-70% ramp acetonitrile, water; 0--> 40 minutes, to provide compound **126** (47.00 mg, 34.82%) as colorless solid.

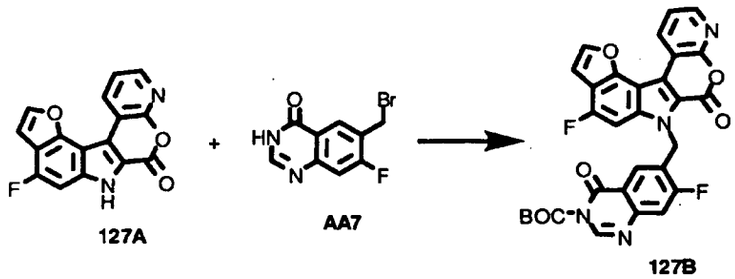
Example 15

Preparation of Compound **127**



127

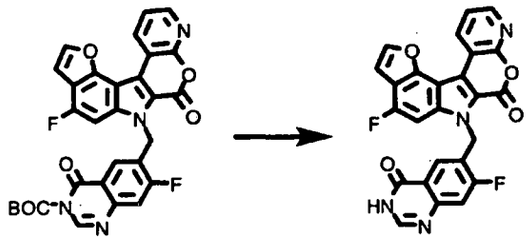
Step A – Synthesis of Compound 127B



127A **AA7** **127B**

To a solution of compound **127A** (130 mg, 0.442) and compound **AA7** (225 mg, < 0.5 mmol) in DMF (10 mL) was added cesium carbonate (330 mg, 1.01 mmol). The resulting reaction was stirred at room temperature for 18 hours, then diluted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (2 x 60 mL), dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide product **127B** (160 mg, 63 %), which was further purified using reverse-phase HPLC on a Waters Sunfire C_{18} column (10 µM, 50 x 250 mm) using 20-100 % acetonitrile/water as eluent. MS found for $C_{30}H_{20}F_2N_4O_6$: 470.9 $(M+H-100)^+$.

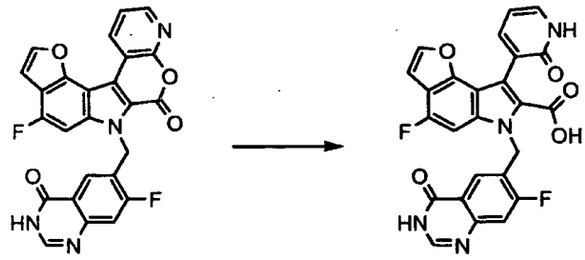
Step B – Synthesis of Compound 127C



127B 127C

Compound **127B** (150 mg, 0.263 mmol) was dissolved in 4 M HCl in 1,4-dioxane (15 mL) and the reaction mixture was stirred for 3 hours, then concentrated in vacuo to provide the crude compound **127C** (165 mg, quant.), which was further purified using reverse-phase HPLC as described above. MS found for $C_{25}H_{12}F_2N_4O_4$: 471.0 $(M+H)^+$.

Step C – Synthesis of Compound 127

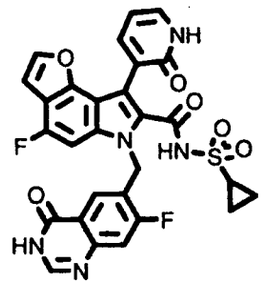


127C 127

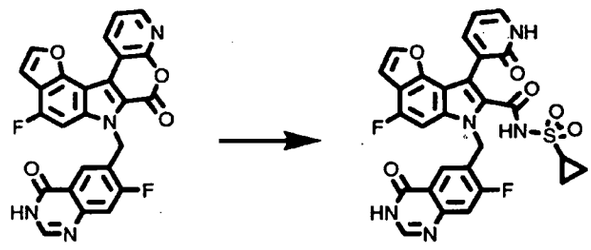
To a solution of the crude product **127C** (100 mg, < 0.213 mmol, from Step B above) in THF (10 mL) and water (10 mL) was added aqueous LiOH solution (3.0 mL, 3.0 mmol). The reaction was allowed to stir for 30 minutes, then the reaction mixture was acidified using 1 N aqueous HCl solution (3.5 mL), and the acidic solution was extracted with ethyl acetate (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide a residue which was purified using reverse-phase HPLC as described above in Step A to provide compound **127** (26 mg, 25 %). ^{1}H NMR (500 MHz, d_6-DMSO): δ 13.0 (bs, 1 H), 12.3 (bs, 1 H), 11.8 (bs, 1 H), 8.08 (s, 1 H), 7.96 (s, 1 H), 7.68-7.66 (m, 1 H), 7.53 (dd, J = 4.0, 11.0 Hz, 2 H), 7.42-7.41 (m, 2 H), 7.10 (s, 1 H), 6.34 (t, J = 6.8 Hz, 1 H), 6.01 (s, 2 H). MS found for $C_{25}H_{14}F_2N_4O_5$: 489.0 $(M+H)^+$.

Example 16

Preparation of Compound **212**



212

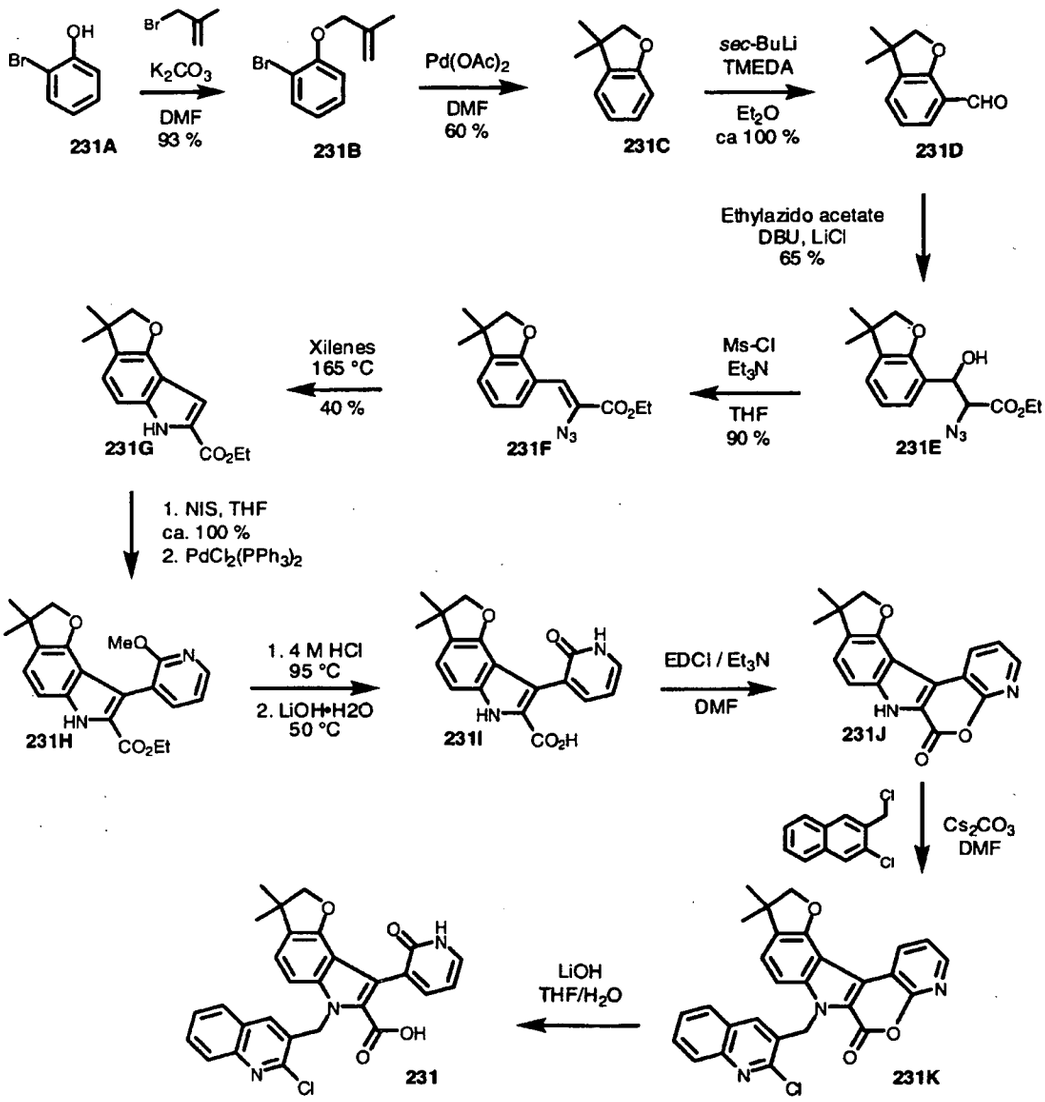


127C **212**

To a solution of compound **127C** (15.0 mg, 0.0318 mmol) in THF (10.0 mL) was added sulfonamide cyclopropylsulfonamide (8.0 mg, 0.064 mmol) and NaH (4.0 mg, 0.16 mmol). The resulting reaction was allowes to stir at room temperature for 3 hours, then was diluted with EtOAc (10 mL) and the resulting solution was washed with water (10 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated *in vacuo* and the resulting residue was purified using reverse-phase HPLC as described above in Example 14, Step A, to provide compound **212** as a white solid (3.5 mg, 19 %). MS found for $C_{28}H_{19}F_2N_5O_6S$: 592.3$(M+H)^+$.

Example 17

Preparation of Compound **231**



Step A – Synthesis of Compound 231B



An ice-cooled solution of 2-bromo-phenol (231.2 mmol, 40 g, 26.8 mL, d 1.492) in 460 mL of DMF was treated with 3-bromo-2-methylprop-1-ene (1.1 eq, 24.5 mL, d 1.339) followed by addition of potassium carbonate (2.0 eq, 63.9 g) and tetrabutylammonium iodide (1.0 g). The cooling bath was removed and the reaction mixture was stirred until all starting material had been consumed. After 6 h the mixture was concentrated to one third of its volume in rotavap (high vacuum pump). The mixture was diluted with ethyl acetate (2.0 L) and washed with water (2 x 200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to give the crude product as a slightly yellow oil. Compound **231B** was purified using bulb to bulb distillation in batches of 10 g each (130 °C / 1 mmHg) to give the product (49 g, 93 %) as a colorless oil. ^{1}H-NMR (400 MHz, in dmso-d6): δ 7.57 (1H, dd, J = 1.83, 7.93 Hz), 7.32 (1H, ddd, J = 1.83, 7.32, 7.93 Hz), 7.10 (1H, dd, J = 1.22, 7.93 Hz), 6.88 (1H, ddd, J = 1.22, 7.32, 7.93 Hz), 5.12 (1H, s), 4.97 (1H, s), 4.55 (2H, s), 1.79 (3H, s); ^{13}C-NMR (125 MHz, in dmso-d6): δ 159.2, 140.3, 132.8, 128.7, 121.9, 113.8, 112.2, 110.9, 71.4, 18.9 ppm.

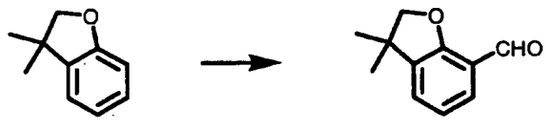
Step B – Synthesis of Compound 231C



A solution of 1-bromo-2-(2-methyl-allyloxy)-benzene (13.8 g, 60.76 mmol) in 140 mL of DMF (0.1 g / mL) was treated with sodium acetate (2.5 eq, 12.46 g), sodium formate (1.2 eq, 4.95 g) and tetraethylammonium chloride hydrate (1.2 eq, 72.91 mmol [183.72] 13.4 g) and 25 drops of water. The mixture was degassed (vacuum/argon flush) and palladium(II) acetate (5 mol%, 682 mg) was added. The mixture was heated at 90 °C and the flow of the reaction was followed by TLC (10 % ethyl acetate in hexanes). After 3 h the mixture was cooled to room temp and diluted with ether (500 mL). The solids were removed by filtration and the filtrate was washed with water (2 x 80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The slightly yellow residue was adsorbed on silica gel and purified on a Biotage 65-M silica gel column The column was eluted with hexanes (200 mL) and a gradient of 0 to 10 % ethyl acetate in hexanes. The product **231B** (5.3 g, 60 %) was obtained as a colorless oil. ^{1}H-NMR (400 MHz, in $CDCl_3$):δ 7.13 (1H, m), 7.11 (1H, d, J = 7.32 Hz), 6.89 (1H, ddd, J = 1.22, 7.32, 7.33 Hz), 6.80 (1H, d, J = 7.93 Hz),

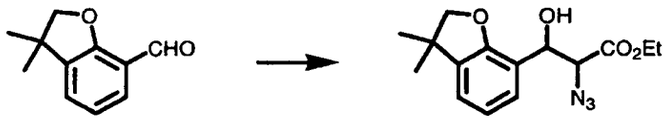
4.23 (2H, s), 1.35 (6H, s); ^{13}C-NMR (125 MHz, in $CDCl_3$):δ 159.1, 136.5, 127.9, 122.2, 120.5, 109.6, 84.4, 41.9, 27.5 ppm.

Step C – Synthesis of Compound 231D



sec-Butyllithium (1.2 eq, 36.43 mL of 1.4 M soln in cyclohexane) was added dropwise to a cooled (-78 °C) solution of TMEDA (1.3 eq, 7.63 mL, d 0.775) in 100 mL of dry ether. After 5 min, a solution of 3,3-dimethyl-2,3-dihydro-benzofuran (6.3 g, 42.51 mmol) in ether (100 mL) was added dropwise. The resulting yellow solution was stirred at -78 °C for 10 min and at 0 °C for 30 min. The slightly yellow solution was cooled again to -78 °C followed by addition of DMF (2.5 eq, 8.19 mL, d 0.948). The mixture was stirred for 10 min and then warmed to 0 °C and stirred for further 30 min. The reaction was quenched by addition of aqueous 1 M HCl (1 mL). The mixture was diluted with 1:1 ether / hexanes (400 mL) and washed with aqueous 1 M HCl (3 x 80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap to provide compound **231C** (ca. 100 %, 7.49 g) as a slightly yellow oil, which was used without further purification. ^{1}H-NMR (400 MHz, in $CDCl_3$): δ 10.20 (1H, s), 7.59 (1H, dd, J = 1.22, 7.32 Hz), 7.31 (1H, dd, J = 1.22, 7.32 Hz), 6.97 (1H, dd, J = 7.32, 7.32 Hz), 4.40 (2H, s), 1.37 (6H, s); ^{13}C-NMR (125 MHz, in $CDCl_3$): δ 188.9, 161.3, 139.0, 128.4, 127.6, 120.9, 120.0, 85.9, 41.2, 27.6 ppm. LR-MS (ESI): calcd. for $C_{11}H_{13}O_2$ $[M+H]^+$ 177.09, found 176.99.

Step D – Synthesis of Compound 231E



A solution of 3,3-dimethyl-2,3-dihydro-benzofuran-7-carbaldehyde (13.6 g; 77.45 mmol) in 380 mL of dry THF was cooled to 0 °C and treated with lithium chloride (2.0 eq, 6.56 g). The mixture was vigorously stirred for 3 min followed by addition of a solution of ethylazido acetate (2.0 eq, 80.0 mL of a 25 % soln in toluene). A solution of DBU (2.0 eq, 23.1 mL, d 1.018) in 38 mL of dry THF was added dropwise. After addition was completed the reaction mixture was stirred for further 4 h at which point TLC (20 % ethyl acetate in hexanes)

showed almost complete consumption of starting material. The reaction mixture was diluted with ethyl acetate (1.0 L) and washed with aqueous 0.5 M HCl (3 x 200 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was purified on a silica gel column (8 x 18 cm). The column was eluted with 4 L of a gradient of 5 to 20 % ethyl acetate in hexanes to provide compound **231E** (15.4 g; 65 %) as a pale yellow oil. ^{1}H-NMR (400 MHz, in $CDCl_3$, reported as diastereomeric mixture) δ 7.19 (0.7H, d, J = 7.93 Hz), 7.12 (0.3H, d, J = 7.32 Hz), 7.09 (1H, m), 6.93 (0.7H, t, J = 7.32 Hz), 6.91 (0.3H, t, J = 7.32 Hz), 5.31 (0.7H, dd, J = 4.27, 7.32 Hz), 5.07 (0.3H, dd, J = 7.32, 7.32 Hz), 4.34 – 4.20 (5H, m), 3.30 (0.3H, d, J = 7.32 Hz), 3.02 (0.7H, d, J = 7.32 Hz), 1.34 (6H, s), 1.26 (3H, t, J = 7.32 Hz); ^{13}C-NMR (125 MHz, in $CDCl_3$, major diastereomer):δ 168.7, 155.7, 136.9, 125.7, 122.3, 121.2, 121.1, 85.0, 71.8, 66.1, 62.0, 41.8, 27.4, 14.1 ppm; ^{13}C-NMR (125 MHz, in $CDCl_3$, minor diastereomer):δ 168.9, 156.2, 137.1, 126.4, 122.6, 121.1, 120.8, 85.0, 72.1, 65.3, 61.9, 41.7, 27.5, 14.0 ppm.

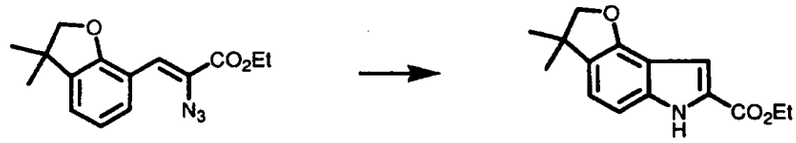
Step E – Synthesis of Compound 231F



A solution of 2-azido-3-(3,3-dimethyl-2,3-dihydro-benzofuran-7-yl)-3-hydroxy-propionic acid ethyl ester (18.2 g; 59.61 mmol) in 60 mL of dry dichloromethane was cooled to -30 °C and treated with methanesulfonyl chloride (2.0 eq, 9.22 mL, d 1.480). A solution of triethylamine (7.0 eq, 58.1 mL, d 0.726) in 30 mL of dry dichloromethane was added dropwise over 30 min (internal temp was maintained between -40 - 30 °C). The resulting slurry was stirred for 2 h at which point TLC (20 % ethyl acetate in hexanes) showed complete consumption of starting material. The mixture was diluted with ethyl acetate (1.5 L) and washed with aq 0.5 M HCl (2 x 200 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was adsorbed on silica gel and purified on a silica gel column (9 x 17 cm). The column was eluted with 5 L of 2 % THF in hexanes containing 200 mL of DCM to provide compound **231F** (15.25 g; 90 %) as a slightly yellow solid. ^{1}H-NMR (400 MHz, in $CDCl_3$):δ 8.04 (1H, d, J = 7.93 Hz), 7.18 (1H, s), 7.07 (1H, dd, J = 1.22, 7.32 Hz), 6.92 (1H, dd, J = 7.32, 7.93 Hz), 4.36 (2H, q, J = 7.32 Hz),

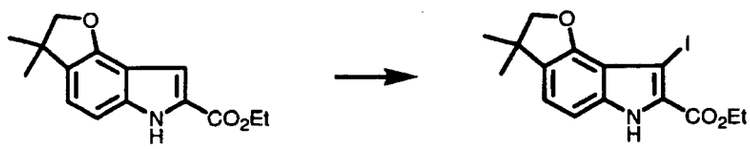
4.28 (2H, s), 1.39 (3H, t, J = 7.32 Hz), 1.34 (6H, s); ^{13}C-NMR (125 MHz, in $CDCl_3$): δ 163.6, 158.2, 136.5, 128.2, 125.3, 123.6, 120.7, 118.5, 116.4, 84.7, 62.1, 42.1, 27.5, 14.2 ppm.

Step F – Synthesis of Compound 231G



A solution of 2-azido-3-(3,3-dimethyl-2,3-dihydro-benzofuran-7-yl)acrylic acid ethyl ester (15.25 g; 53.07 mmol) in 70 mL of xylenes was added dropwise (over 30 min) to stirring xylenes (30 mL) pre-heated to 165 °C. After addition was completed the mixture was stirred for further 10 min and then cooled to room temp. The mixture was kept in freezer (-30 °C) overnight. No crystals were formed and the mixture was concentrated in rotavap. The residue was purified on a Biotage 65-M silica gel column. Elution of the column with 5 % THF in hexanes gave the product in fractions containing other impurities. Concentration of those fractions in rotavap provided compound **231G**, which precipitated as a white solid (4.0 g; 30 %). The mother liquour was concentrated again to give a second batch of product (1.0 g, 7 %). ^{1}H-NMR (400 MHz, in dmso-d6): δ 11.84 (1H, s), 7.08 (1H, d, J = 8.54 Hz), 6.96 (1H, d, J = 8.54 Hz), 6.95 (1H, s), 4.32 (2H, s), 4.31 (2H, q, J = 7.32 Hz), 1.32 (3H, t, J = 7.32 Hz), 1.29 (6H, s); ^{13}C-NMR (125 MHz, in dmso-d6): δ 161.0, 151.4, 138.9, 127.0, 124.5, 119.2, 113.0, 104.6, 103.4, 84.6, 60.3, 41.5, 27.7, 14.2 ppm. LR-MS (ESI): calcd. for $C_{15}H_{18}NO_3$ $[M+H]^+$ 260.13, found 260.02

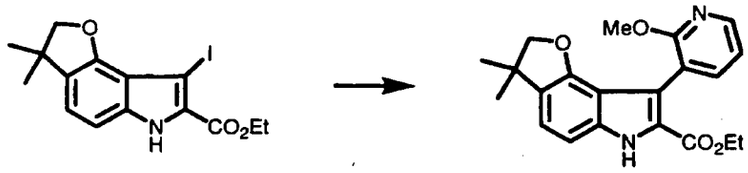
Step G – Synthesis of Compound 231H



A solution of 3,3-dimethyl-3,6-dihydro-2H-1-oxa-6-aza-indacene-7-carboxylic acid ethyl ester (5.0 g, 19.28 mmol) in THF (200 mL) was cooled to -78 °C and treated with a solution of N-iodosuccinimide (1.1 eq, 4.77 g) in 50 mL of THF. The mixture was stirred for 45 min and then quenched by addition of aqueous saturated sodium bicarbonate (100 mL). The product was taken into ethyl acetate (500 mL) and washed with aq saturated sodium bicarbonate (100 mL) and brine (80 mL). The organic layer was dried over magnesium

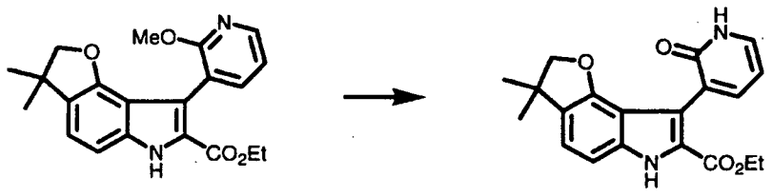
sulfate, filtered and concentrated in vacuo to provide compound **231H** (ca. 100 %, 7.42 g) as a dark brown solid which was used without further purification. LR-MS (ESI): calcd. for $C_{15}H_{17}INO_3$ $[M+H]^+$ 386.03, found 385.86

Step H – Synthesis of Compound 231I



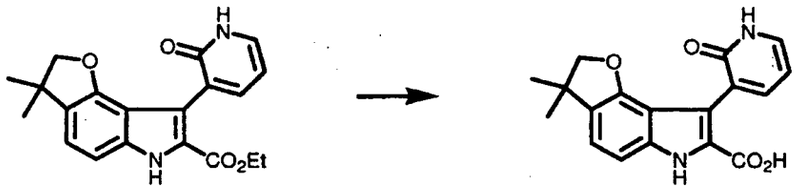
A solution of 8-iodo-3,3-dimethyl-3,6-dihydro-2H-1-oxa-6-aza-indacene-7-carboxylic acid ethyl ester (7.42 g; 19.28 mmol) in 200 mL of 1,2-dimethoxyethane was treated with 2-methoxypyridine-3-boronic acid (2.0 eq, 5.89 g) and bis(triphenylphosphine)palladium(II) chloride (0.1 eq, 1.34 g). The mixture was stirred for 10 min followed by addition of aqueous potassium carbonate (4.0 eq, 38.5 mL of 2 M soln). The mixture was stirred at 90 °C and the flow of the reaction was followed by TLC (30 % THF in hexanes). After 2 h the mixture was diluted with ethyl acetate (700 mL) and washed with aqueous saturated sodium bicarbonate (2 x 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated in rotavap. The residue was was adsorbed on silica gel and purified on a Biotage 65-M silica gel column. Elution of the column with a gradient of 5 to 20 % THF in hexanes/DCM (9:1) gave the product (7.0 g) which contained several impurities. A sample (1.0 g, 2.73 mmol) was dissolved in 10 mL of DMF and purified on a reverse phase prep column (Column: YMC, C18-reverse phase, 120A; 500 x 50 mm I.D); Flow rate = 100 mL/min; Gradient: 20 % solvent B for 10 min then increase to 90 % over 50 min and stay for 5 min (solvent A: water with 0.01 % v/v TFA; sovent B: THF). Three injections were carried out and three fractions were collected from each injection. Fraction A (340 mg) gave 11 % of pure product. Fraction B (850 mg) gave 29 % of compound **231I** with small amount of impurities; Fraction C (520 mg) gave 18 % of C7-methoxypyridyl (regioisomeric) product. ^{1}H-NMR (400 MHz, in dmso-d6):□11.86 (1H, s), 8.11 (1H, dd, J = 1.83, 4.88 Hz), 7.64 (1H, dd, J = 1.83, 7.32 Hz), 7.08 (1H, d, J = 7.93 Hz), 6.99 (1H, d, J = 7.93 Hz), 6.98 (1H, dd, J = 4.88, 7.32 Hz), 4.15 (2H, s), 4.11 (2H, q, J = 7.32 Hz), 3.74 (3H, s), 1.25 (6H, s), 1.05 (3H, t, J = 7.32 Hz); ^{13}C-NMR (125 MHz, in dmso-d6):□161.1, 161.0, 152.0, 145.0, 140.3, 137.7, 125.1, 123.7, 119.2, 118.0, 115.9, 114.4, 113.4, 104.4, 84.5, 59.9, 52.7, 41.0, 27.6, 13.7 ppm. LR-MS (ESI): calcd. for $C_{21}H_{23}N_2O_4$ $[M+H]^+$ 367.17, found 367.05

Step I – Synthesis of Compound 231J



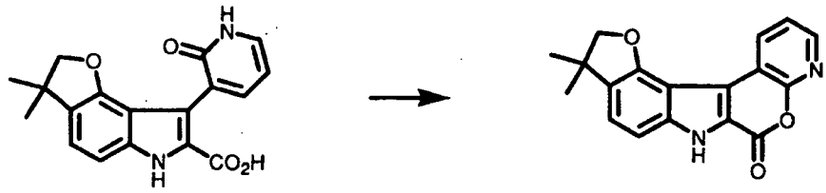
The 8-(2-methoxy-pyridin-3-yl)-3,3-dimethyl-3,6-dihydro-2H-1-oxa-6-aza-indacene-7-carboxylic acid ethyl ester (840 mg, 2.292 mmol) was dissolved in 4 M HCl solution in dioxane (20 mL) and methanol (5 mL). The homogeneous solution was heated in a sealed tube (95 °C) until all starting material had been consumed. After 3 h, the mixture was concentrated to dryness in rotavap to provide compound **231J** (ca 100 %, 807 mg) as a slightly yellow solid which was dried under high vacuum and used without further purification.

Step J – Synthesis of Compound 231K



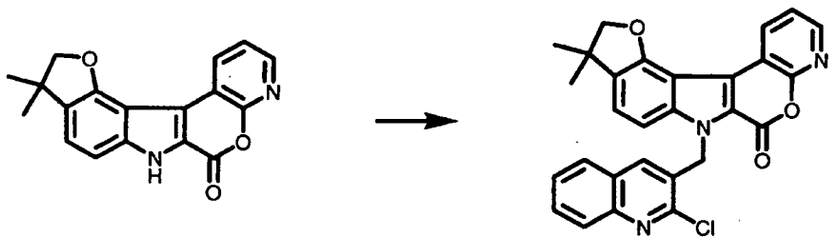
The 3,3-dimethyl-8-(2-oxo-1,2-dihydro-pyridin-3-yl)-3,6-dihydro-2H-1-oxa-6-aza-indacene-7-carboxylic acid ethyl ester (2.292 mmol) was dissolved in 20 mL of 2:1 THF/MeOH and water was added (2 mL). The resulting solution was treated with lithium hydroxide monohydrate (5.0 eq, 480 mg) and heated to 50 °C for 3 hours. TLC (50 % THF in dichloromethane) showed complete consumption of the starting material. The mixture was treated with 15 mL of aq 1 M HCl and the volatiles were removed in rotavap to give a tick slurry which was diluted with aq 1 M HCl (15 mL). The solids were recovered by filtration (whatman #1) to provide compound **231K** (480 mg, 67 %) as a pale green solid. The product contains impurities but no further purification was carried out.

Step K – Synthesis of Compound 231L



The 3,3-dimethyl-8-(2-oxo-1,2-dihydro-pyridin-3-yl)-3,6-dihydro-2H-1-oxa-6-aza-indacene-7-carboxylic acid (480 mg, 1.480 mmol) was suspended in 15 mL of dry DMF and treated with EDCI (2.0 eq, 567 mg) and triethylamine (10 eq, 2.08 mL, d 0.720). The mixture was stirred overnight at room temp. All the volatiles were removed in rotavap (high vacuum pump) and the residue was treated with 2:1 ethyl acetate / THF (60 mL) and washed with aqueous 1 M HCl (3 x 10 mL) and brine (10 mL). The organic layer was set aside overnight and a white precipitate was formed. It was recovered by filtration (50 mg; discard) and the filtrate was concentrated to one third of its volume and set aside for 2 hours. A precipitate was formed and was recovered by filtration (145 mg) to provide compound **231L** as a white solid. The filtrate was concentrated to almost dryness and set aside for 1 hour. A second crop of product was formed and was recovered by filtration (170 mg) to give a combined yield of 73 %. ^{1}H-NMR (400 MHz, in dmso-d6):δ 12.83 (1H, s), 9.21 (1H, dd, J = 1.83, 7.93 Hz), 8.39 (1H, dd, J = 1.83, 4.88 Hz), 7.55 (1H, dd, J = 4.88, 7.93 Hz), 7.40 (1H, d, J = 8.54 Hz), 7.16 (1H, d, J = 8.54 Hz), 4.56 (2H, s), 1.39 (6H, s); LR-MS (ESI): calcd. for $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307.11, found 306.95

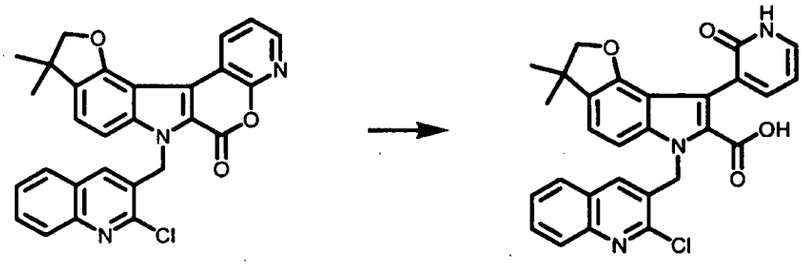
Step L – Synthesis of Compound 231M



The lactone (145 mg; 0.473 mmol) was suspended in 2.5 mL of DMF and treated with 2-chloro-3-chloromethyl-quinoline (1.20 eq, 120 mg) and cessium carbonate (2.0 eq, 308 g). The reaction mixture was stirred at room for 6 hours. TLC (40 % THF in hexanes) showed complete consumption of the starting material. The slurry was filtered using filter paper (whatman #1) and the solids were washed with dichloromethane (20 mL), water (2 x 20 mL)

and ether (2 x 20 mL) to provide compound **231M** (ca. 100 %, 227 mg) as a white solid which was used without further purification. ^{1}H-NMR (400 MHz, in dmso-d6):δ 9.35 (1H, dd, J = 1.83, 7.93 Hz), 8.44 (1H, dd, J = 1.83, 4.88 Hz), 7.96 (1H, m), 7.76 (2H, m), 7.60 (1H, dd, J = 4.88, 7.93 Hz), 7.53 (1H, d, J = 7.32 Hz), 7.44 (1H, d, J = 8.54 Hz), 7.25 (1H, d, J = 8.54 Hz), 6.08 (2H, s), 4.63 (2H, s), 1.40 (6H, s); LR-MS (ESI): calcd. for $C_{28}H_{21}ClN_3O_3$ $[M+H]^+$ 482.13, found 481.99

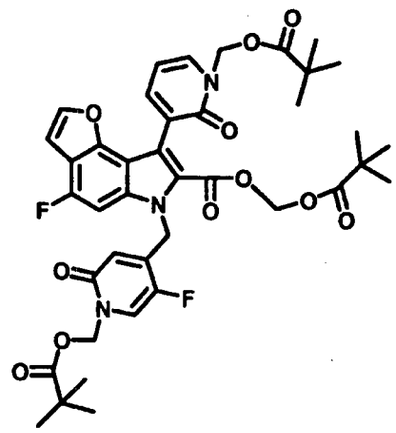
Step M – Synthesis of Compound 231



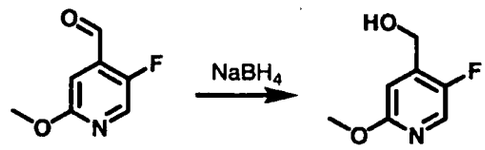
The lactone (40 mg; 0.100 mmol) was suspended in 5 mL of a 2:1 mixture of THF/water and treated with lithium hydroxide monohydrate (5.0 eq, 99 mg). The mixture was stirred at room temp. TLC (40 % THF in hexanes) showed complete consumption of the starting material after 1 hour. The reaction was quenched by addition of aqueous 1 M HCl (3 mL) and the THF was removed in rotavap. The product precipitated as a white solid and the mixture was dissolved in DMF (10 mL) and purified on prep-HPLC (reverse C-18) to give the product (60 mg, 25 %) as a white solid. NMR showed some impurities from chloroquinoline and the compound was treated with 10 mL of ether. The mixture was filtered to provide compound **231** (35 mg) as a white solid. ^{1}H-NMR (400 MHz, in dmso-d6):δ 12.90 (1H, broad s), 11.68 (1H, broad s), 7.98 (1H, d, J = 8.54 Hz), 7.82 (1H, d, J = 7.93 Hz), 7.78 (1H, dd, J = 7.32, 7.32 Hz), 7.58 (2H, m), 7.37 (1H, d, J = 4.88 Hz), 7.32 (1H, s), 7.13 (1H, d, J = 8.54 Hz), 7.03 (1H, d, J = 8.54 Hz), 6.31 (1H, dd, J = 6.71, 6.71 Hz), 5.90 (2H, s), 4.27 (2H, s), 1.29 (6H, s); LR-MS (ESI): calcd. for $C_{28}H_{23}ClN_3O_4$ $[M+H]^+$ 500.14, found 499.95.

Example 18

Preparation of Compounds **87** and **228**



Step A – Synthesis of Compound 228B



228A **228B**

To a solution of 5-Fluoro-2-methoxy-pyridine-4-carbaldehyde (0.3 g, 1.94 mmol) in ethanol (5 mL) was added sodium borohydride (0.037mg, 0.97 mmol) and the reaction was allowed to stir at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The reaction mixture was extracted with EtOAc (50 mL), washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide compound **228B** and used as it is in the next step.

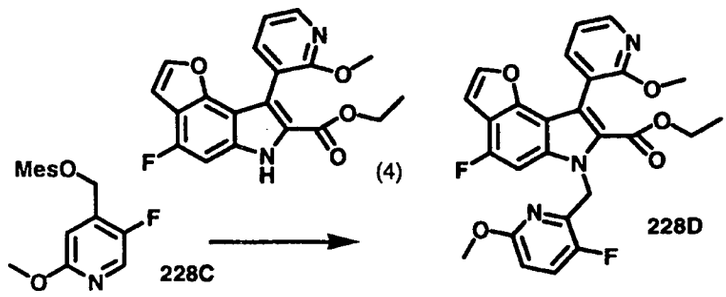
Step B – Synthesis of Compound 228C



228B **228C**

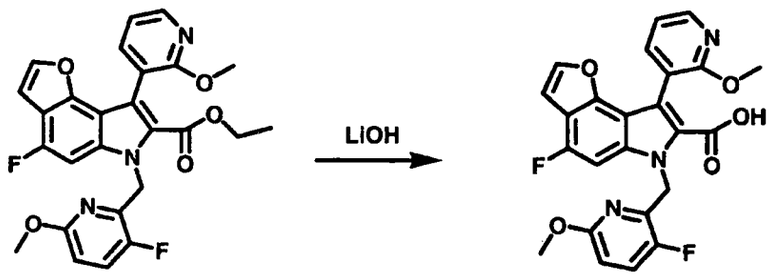
To a solution of (5-Fluoro-2-methoxy-pyridin-4-yl)-methanol in 5 ml of the THF and 1.0 ml TEA was dropped solution of the 0.45 ml methanesulfonyl chloride in 5 ml THF and the reaction was allowed to stir at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo*. The reaction mixture was extracted with EtOAc (50 mL), washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide compound **228C** and used as it is in the next step.

Step C – Synthesis of Compound 228D



To a solution of compound (4) (0.687g, 1.94 mmol) in DMF (10 mL) was added cesium carbonate (0.632g, 1.94 mmol) and compound (3) and the resulting reaction was allowed to stir at room temperature for 24 hour. The reaction mixture was diluted with EtOAc and washed with water, brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide compound **228D** 0.80g and used as it is in the next step.

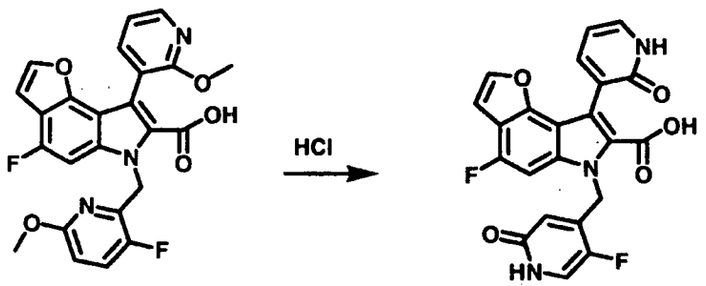
Step D – Synthesis of Compound 228E



228D **228E**

To a solution of compound **228D** water/THF (15 ml each) was added lithium hydroxide (0.288 g 12 mmol) and the resulting reaction was allowed to stir at 65 ^{0}C overnight. The reaction mixture was diluted with aqueous HCl and extracted into ethyl acetate. The combined organic layers were dried (Na_2SO_4), filtered, concentrated *in vacuo* to provide 0.755g of the product **228E.**

Step E – Synthesis of Compound 87

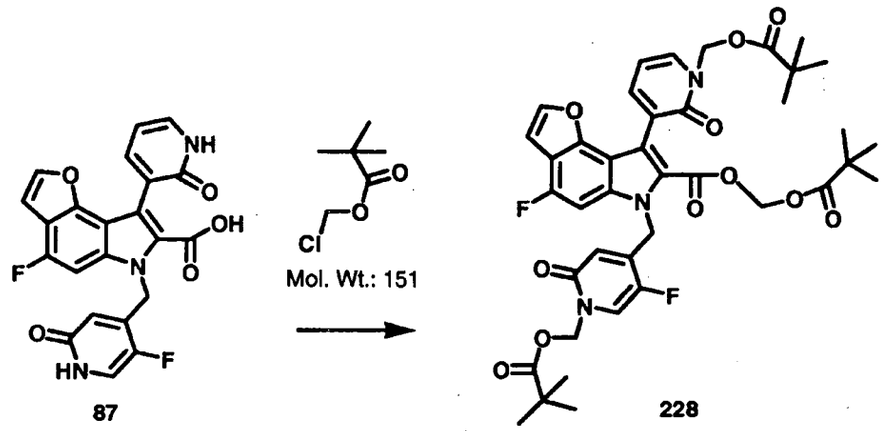


228E **87**

Compound **228E** (450 mg, 0.97 mmol) was dissolved in 5 ml Dioxane and 5 ml 4N HCl in a pressure tube and the resulting reaction mixture was heated to 90 °C and allowed to remain at this temperature for 4 hour. The reaction mixture was cooled to room temperature, then concentrated *in vacuo* to provide a crude product which was purified using preparative HPLC to provide compound **87** (150 mg, 37 %).

M.S. found: 438.2 $(M+H)^+$; ^{1}H NMR (500 MHz, DMSO): δ 7.97 (d, J = 2.2 Hz, 1H), 7.73 (m, 1H), 7.69 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7.54 (d, J = 11.0 Hz, 1H), 7.43 (m, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.34 (t, J = 6.6 Hz, 1H), 5.85 (s, 2H), 5.27 (s, 1H).

Step F – Synthesis of Compound 228

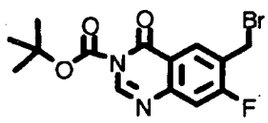


87 228

To a solution of compound **87** (0.06 g, 0.14 mmol) in DMF (5 mL) was added cesium carbonate (0.091g, 0.28 mmol) and 2,2-Dimethyl-propionic acid chloromethyl ester (0.042 g, 0.28 mmol) and the resulting reaction was allowed to stir at 40 ^{0}C for 24 hour. The reaction mixture was diluted with EtOAc and washed with water, then brine. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide compound **228** (0.003 g) . M.S. found: 780.4 $(M+H)^+$; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7.63 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7. 56 - 7.52 (m, 2H), 6.91 (d, J = 2.2 Hz, 1H), 6.83 (d, J = 9.8 Hz, 1H), 6.37 (t, J = 6.9 Hz, 1H), 6.01 (m, 2H), 5.81-5.77 (m, 4H), 5.75 (s, 2H), 5.70 (m, 1H), 1.26-1.22 (m, 18H), 1.16 (s, 9H).

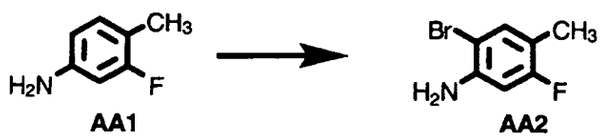
Example 19

Preparation of Intermediate Compound **AA7**



AA7

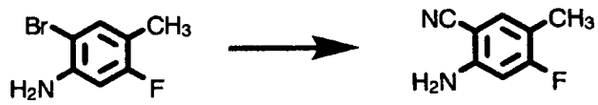
Step A – Synthesis of Compound AA2



AA1 **AA2**

A mixture of compound **AA1** (6.00 g, 47.9 mmol) and anhydrous potassium carbonate (6.70 g, 48.5 mmol) in anhydrous dichloromethane (130 mL) was cooled to -15 °C in a salt-ice bath and then added dropwise to a solution of bromine (7.70 g, 48.2 mmol) in anhydrous dichloromethane (80 mL). After addition was complete, the reaction was allowed to stir at -15 °C for 1 hour. Ice water (100 mL) was added to the reaction mixture and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **AA2** (11.0 g, quant.), which was used without further purification.

Step B – Synthesis of Compound AA3



AA2 **AA3**

Compound **AA2** was dissolved in DMF (150 mL) and to this solution was added copper (I) cyanide (11.0 g, 123 mmol). The mixture was heated to 160 °C and allowed to stir at this temperature for 20 hours. After being cooled to room temperature, with water (200 mL), iron (III) chloride (42.0 g, 155 mmol) and concentrated hydrochloric acid (20 mL) were added to the reaction mixture and the resulting reaction was stirred for 45 minutes. The reaction mixture was then basified to pH > 10 using commercial ammonium hydroxide solution. The basic solution was then extracted with ethyl acetate (4 x 400 mL). The combined organic extracts were washed with water, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue obtained was purified using flash chromatography to provide compound **AA3** (5.82 g, 81 %). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.34 (d, J = 8.4 Hz, 1H), 6.52 (d, J = 12.4 Hz, 1H), 6.10 (s, 2 H), 2.08 (s, 3 H).

Step C – Synthesis of Compound AA4

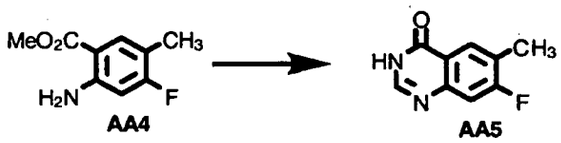


AA3 **AA4**

To the solution of **AA3** (2.0 g, 13.3 mmol) in anhydrous methanol (15 mL) at room temperature was added concentrated sulfuric acid (4.0 mL). The reaction mixture was heated to 70 °C and stirred for four days. After cooled to room temperature, it was poured into with ice

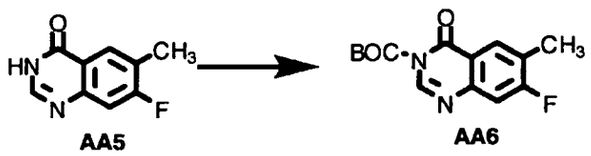
water. The mixture was then diluted with ethyl acetate (200 mL) and was made basic (pH > 10) with commercial ammonium hydroxide solution. The layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic solution was dried over $MgSO_4$ and concentrated in vacuo to provide the crude product which, was purified using flash chromatography to provide compound **AA4** (1.0 g, 41 %) and some recovered **AA3**. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.61 (d, J = 8.8 Hz, 1H), 6.69 (s, 2 H), 6.51 (d, J = 12.0 Hz, 1 H), 3.77 (s, 3 H), 2.06 (s, 3 H).

Step D – Synthesis of Compound AA5



The solution of compound **AA4** (500 mg, 2.73 mmol) in formamide (6.0 mL) was heated to 150 °C in an oil bath and stirred for 18 hours. After cooled to room temperature, ethyl acetate (100 mL) and water (100 mL) were added and the layers were separated. The organic solution was washed with water (2 x 60 mL), dried over $MgSO_4$ and concentrated in vacuo to provide the crude product **AA5** (0.50 g, quant.) which, was used without further purification. MS found for $C_9H_7FN_2O$: 179.0 $(M+H)^+$.

Step E – Synthesis of Compound AA6



To the solution of **AA5** (from Step 4) in anhydrous THF (20 mL) at room temperature was added di-*tert*-butyl dicarbonate (1.84 g, 8.43 mmol), 4-dimethylaminopyridine (350 mg, 2.86 mmol) and triethyl amine (0.40 mL, 2.87 mmol). The reaction mixture was stirred for 18 hours. Ethyl acetate (100 mL) and water (100 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic solution was dried over $MgSO_4$ and concentrated in vacuo to provide the crude product which, was purified using flash chromatography to provide compound **AA6** (285 mg, 36 %). MS found for $C_{14}H_{15}FN_2O_3$: 179.0 $(M+H-100)^+$.

Step F – Synthesis of Compound AA7

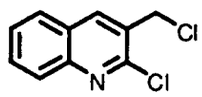


AA6 **AA7**

The mixture of **AA6** (282 mg, 1.01 mmol), NBS (253 mg, 1.42 mmol) and AIBN (58 mg, 0.353 mmol) in anhydrous carbon tetrachloride (60 mL) was heated to 90 °C in an oil bath and stirred for 4 hours. After cooled to room temperature and concentrated in vacuo, the residue was dissolved in ethyl acetate (100 mL) and water (100 mL). The layers were separated. The organic solution was washed with water (100 mL), dried over $MgSO_4$ and concentrated in vacuo to provide the crude product **AA7** (453 mg, quant.) which, was used without further purification.

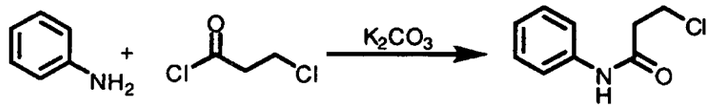
Example 20

Preparation of Intermediate Compound **BB2**



BB2

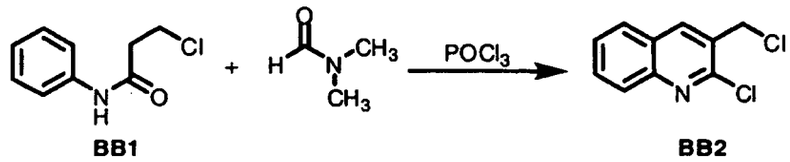
Step A – Synthesis of Compound BB1



BB1

A mixture of aniline (65.04 mL, 713.8 mmol), potassium carbonate (54.4 g, 394 mmol) and water (300 mL) were added to a 2000 mL flask. The resulting reaction was kept at room temperature using a room temperature water bath and stirred with a mechanic stirrer. 3-Chloro-propionyl chloride (75.18 mL, 787.6 mmol) was added dropwise via additional funnel and the resulting suspension was allowed to stir at room temperature for 3 hours. The reaction mixture was filtered and the collected solid was washed sequentially with water (300 mL), aq. HCl (1M, 2 x 300 mL), and water (300 mL), then dried to provide compound **BB1**, which was used without purification (114.5 g, 87%).

Step B – Synthesis of Compound BB2

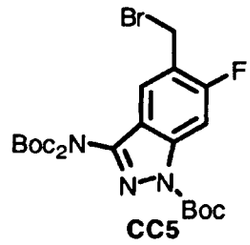


BB1 **BB2**

N,N-Dimethylformamide (53.7 mL, 694 mmol) was charged into a three necked flask and cooled to 0 °C and treated with phosphoryl chloride (177.7 mL, 1906 mmol) dropwise. The reaction was stirred at that temperature for 10 min and treated with 3-Chloro-N-phenylpropanamide **BB1** (50.00 g, 272.3 mmol) and stirred at room temperature. for 30 min. The reaction mixture was heated at 80 °C for 3 h and slowly poured into ice. The solid separating out was filtered and washed extensively with water (2x1000 mL), aq. saturated sodium bicarbonate (500 mL), and taken in EtOAc (1L), The solution was dried ($MgSO_4$) filtered concentrated *in vacuo* and the residue obtained was recrystallized from boiling hexanes to provide compound **BB2** (20 g).

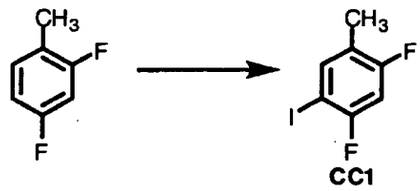
Example 21

Preparation of Intermediate Compound **CC5**



CC5

Step A – Synthesis of Compound CC1

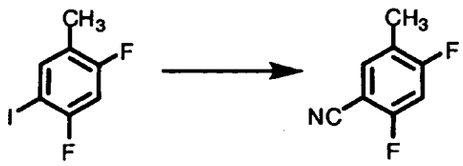


CC1

A solution of 2,4-difluorotoluene (4.72 g, 36.8 mmol) in trifluoroacetic acid (12.29 mL, 159.5 mmol) was cooled to 0 °C, then N-Iodosuccinimide (9.59 g, 42.6 mmol) was added and the resulting reaction was allowed to stir at room temperature for about 15 hours. The reaction

mixture was then concentrated *in vacuo* and the residue obtained was dissolved in hexanes (100 mL), washed with aquesous sodium thiosulfate (100 mL), brine (100 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified using bulb-to-bulb distillation to provide compound **CC1** (7.2 g, 77%) as a colorless oil.

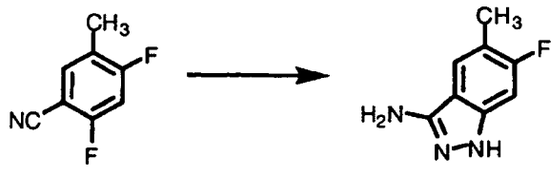
Step B – Synthesis of Compound CC2



CC1 **CC2**

A solution of compound **CC1** (7.11 g, 28.0 mmol), zinc cyanide (1.97 g, 16.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.23 g, 2.80 mmol) in DMF (30 mL) was heated to 90 °C and allowed to stir at this temperature for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue obtained was taken up in water (400 mL) and extracted with ether (400 mL). The organic extract was washed with aqueous ammonium hydroxide solution (1N). The organic layer was dried ($MgSO_4$) filtered, concentrated *in vacuo* to provide a residue that was purified using flash column chromatography (SiO_2, EtOAc/Hexanes) to provide a mixture that contained product and triphenylphosphine. This mixture was further purified using sublimation at 1 mm/Hg at 45 °C to provide compound **CC2** (1.8 g; Yield = 42%).

Step C – Synthesis of Compound CC3

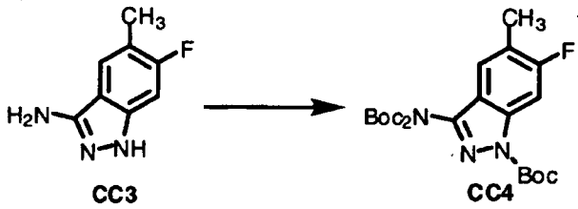


CC2 **CC3**

A solution of compound **CC2** (1.400 g, 9.154 mmol) and hydrazine (0.700 mL, 22.3 mmol) in isopropyl alcohol (50 mL, 653.1 mmol), was heated to reflux and allowed to stir at this temperature for 24 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was purified using flash column chromatography (SiO_2, Acetone/Hexanes 0→ 50%) to provide compound **CC3** (330 mg,

22%).

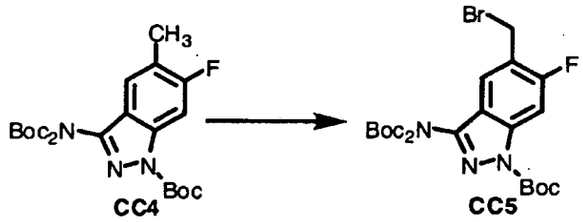
Step D – Synthesis of Compound CC4



CC3 CC4

A solution of compound **CC3** (330.00 mg, 1.998 mmol), di-tert-butyldicarbonate (2.6163 g, 11.98 mmol) and 4-dimethylaminopyridine (48.817 mg, 0.39959 mmol) in acetonitrile (15mL, 287.2 mmol) was heated to reflux and allowed to stir at this temperature for 2 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the resulting residue was purified using flash column chromatography (SiO_2, EtOAc/Hexanes 0- 20 %) to provide compound **CC4** (640.00 mg, 68%) as a colorless oil.

Step E - Synthesis of Compound CC5

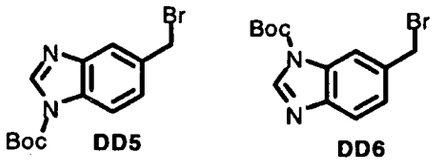


CC4 CC5

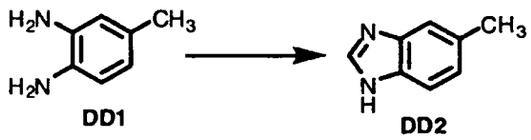
A solution of compound **CC4** (630.00 mg, 1.3533 mmol), N-bromosuccinimide (337.22 mg, 1.8947 mmol) and benzoyl peroxide (65.563 mg, 0.27067 mmol) in carbon tetrachloride (20 mL) was heated to reflux and allowed to stir at this temperature for 3 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was dissolved in EtOAc (300 mL). The resulting solution was washed with aqueous sodium thiosulfate (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (SiO_2, EtOAc/Hexanes) to provide compound **CC5** as a colorless oil.

Example 22

Preparation of Intermediate Compounds **DD5** and **DD6**

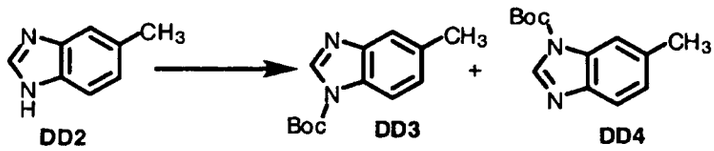


Step A – Synthesis of Compound DD2



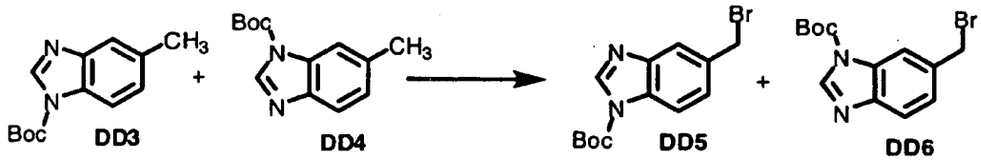
A solution of compound **DD1** (3 g, 24.5 mmol) in trimethyl orthoformate (15 mL) was treated with 2 drops conc. HCl and heated to 80 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo* to provide compound **DD2** (3.65 g), which was used without further purification. M.S. found for $C_8H_8N_2$: 133.2 $(M+H)^+$.

Step B – Synthesis of Compounds DD3 and DD4



To a solution of compound **DD2** (24.5 mmol) in CH_3CN (65 mL) was added di-tertbutyl dicarbonate (5.89 g, 27.0 mmol), triethylamine (3.76 mL, 27.0 mmol) and 4-dimethylamino pyridine (300 mg, 2.45 mmol) and the resulting reaction was heated to 80 °C and allowed to stir at this temperature for 1.5 hours. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, and the residue obtained was purified using flash column chromatography (silica gel, EtOAc/Hexanes 5-20%) to provide a mixture of isomeric compounds **DD3** and **DD4** (5.38 g, 94.3% yield over steps A and B).

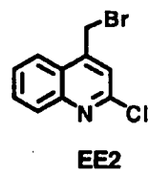
Step C – Synthesis of Compounds DD5 and DD6

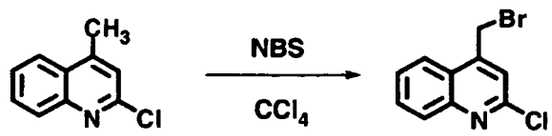


To a solution of compounds **DD3** and **DD4** (2 g, 8.61 mmol) in carbon tetrachloride (40 mL) was added N-bromosuccinimide (1.6 g, 9.04 mmol) and dibenzoyl peroxide (41.7 mg, 0.1722 mmol) and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for 12 hours. The reaction was cooled to room temperature, solids were filtered off and the filtrate was washed with water, dried over sodium sulfate and concentrated *in vacuo* to provide compounds **DD5** and **DD6** (2.58 g) which was used without further purification. M.S. found for $C_{13}H_{15}BrN_2O_2$: 334.7 $(M+Na)^+$.

Example 23

Preparation of Intermediate Compound **EE2**





EE1 **EE2**

A mixture of compound **EE1** (1.5 g, 8.44 mmol), NBS (1.8 g, 10.11 mmol) in carbon tetrachloride (50 mL) was heated to reflux, then benzoyl peroxide (0.21 g, 0.866 mmol) was added. The resulting suspension was allowed to stir at reflux for 19 hours, then cooled to room temperature and filtered. The filtrate was washed with saturated sodium carbonate, dried over sodium sulfate and concentrated *in vacuo* to provide a mixture (1.7 g) which contains about 50% of compound **EE2**, and was used without further purification.

Example 24

HCV NS5B Polymerase Inhibition Assay

An in vitro transcribed heteropolymeric RNA known as D-RNA or DCoH has been shown to be an efficient template for HCV NS5B polymerase (S.-E. Behrens et al., EMBO J. 15: 12-22 (1996); WO 96/37619). A chemically synthesized 75-mer version, designated DCoH75, whose sequence matches the 3'-end of D-RNA, and DCoH75ddC, where the 3'-terminal cytidine of DCoH75 is replaced by dideoxycytidine, were used for assaying the NS5B enzyme activity as described in Ferrari *et al.*, *12th International Symposium on HCV and Related Viruses*, P-306 (2005). The sequence of the template RNA was: 5'-UGU GCC GGU CUU UCU GAA CGG GAU AUA AAC CUG GCC AGC UUC AUC GAA CAA GUU GCC GUG UCU AUG ACA UAG AUC-3'. A soluble C-terminal 21-amino acid truncated NS5B enzyme form (NS5BΔCT21, from HCV-Con 1 isolate, genotype 1b, Genbank accession number AJ238799) was produced and purified from Escherichia coli as C-terminal polyhistidine-tagged fusion protein as described in Ferrari *et al.*, *J. Virol.* 73:1649-1654 (1999). A typical assay contained 20 mM Hepes pH 7.3, 10 mM $MgCl_2$, 60 mM NaCl, 100 μg/ml BSA, 20 units/ml RNasin, 7.5 mM DTT, 0.1 μM ATP/GTP/UTP, 0.026 μM CTP, 0.25 mM GAU, 0.03 μM RNA template, 20 μCi/ml [^{33}P]-CTP, 2% DMSO, and 30 or 150 nM NS5B enzyme. Reactions were incubated at 22 °C for 2 hours, then stopped by adding 150 mM EDTA, washed in DE81 filter plate in 0.5M di-basic sodium phosphate buffer, pH 7.0, and counted using Packard TopCount after the addition of scintillation cocktail. Polynucleotide synthesis was monitored by the incorporation of radiolabeled CTP. The effect of the Compounds of Formula (I) on the polymerase activity was evaluated by adding various concentrations of a Compound of Formula (I), typically in 10 serial 2-fold dilutions, to the assay mixture. The starting concentrations ranged from 200 μM to 1 μM. An IC_{50} value for the inhibitor, defined as the compound concentration that provides 50% inhibition of polymerase activity, was determined by fitting the cpm data to the Hill equation Y=100/(1+10^((LogIC50-X)*HillSlope)), where X is the logarithm of compound concentration, and Y is the % inhibition. Ferrari *et al.*, *12th International Symposium on HCV and Related Viruses*, P-306 (2005) described in detail this assay procedure. It should be noted that such an assay as described is exemplary and not intended to limit the scope of the invention. The skilled practitioner can appreciate that modifications including but not limited to RNA template, primer, nucleotides, NS5B polymerase form, buffer composition, can be

made to develop similar assays that yield the same result for the efficacy of the compounds and compositions described in the invention.

NS5B polymerase inhibition data for selected Compounds of Formula (I) is provided below in Table 2, wherein the compound numbers correspond to the compound numbering set forth in the above specification. The data is designated as follows: "A" for IC_{50} values less than 25 nanomolar (nM), "B" for IC_{50} values between 25 to and 100 nM and "C" for IC_{50} values greater than 100 nM.

Example 25

Cell-based HCV Replicon Assay

To measure cell-based anti-HCV activity of the a Compound of Formula (I), replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated Nunc plates in the presence of the Compound of Formula (I). Various concentrations of a Compound of Formula (I), typically in 10 serial 2-fold dilutions, were added to the assay mixture, with the starting concentration ranging from 250 μM to 1 μM. The final concentration of DMSO was 0.5%, fetal bovine serum was 5%, in the assay media. Cells were harvested on day 3 by the addition of 1x cell lysis buffer (Ambion cat #8721). The replicon RNA level was measured using real time PCR (Taqman assay). The amplicon was located in 5B. The PCR primers were: 5B.2F, ATGGACAGGCGCCCTGA; 5B.2R, TTGATGGGCAGCTTGGTTTC; the probe sequence was FAM-labeled CACGCCATGCGCTGCGG. GAPDH RNA was used as endogenous control and was amplified in the same reaction as NS5B (multiplex PCR) using primers and VIC-labeled probe recommended by the manufacturer (PE Applied Biosystem). The real-time RT-PCR reactions were run on ABI PRISM 7900HT Sequence Detection System using the following program: 48°C for 30 min, 95°C for 10 min, 40 cycles of 95°C for 15 sec, 60°C for 1 min. The ΔCT values (CT_{5B}-CT_{GAPDH}) were plotted against the concentration of test compound and fitted to the sigmoid dose-response model using XLfit4 (MDL). EC_{50} was defined as the concentration of inhibitor necessary to achieve ΔCT=1 over the projected baseline; EC_{90} the concentration necessary to achieve ΔCT=3.2 over the baseline. Alternatively, to quantitate the absolute amount of replicon RNA, a standard curve was established by including serially diluted T7 transcripts of replicon RNA in the Taqman assay. All Taqman reagents were from

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PE Applied Biosystems. Such an assay procedure was described in detail in e.g. Malcolm *et al., Antimicrobial Agents and Chemotherapy* 50: 1013-1020 (2006).

HCV Replicon assay data for selected Compounds of Formula (I) is provided below in Table 1, wherein the compound numbers correspond to the compound numbering set forth in the above specification. The data is designated as follows: "A" for EC_{50} values less than 0.5 micromolar (μM), "B" for EC_{50} values between 0.5 and 1.5 μM and "C" for EC_{50} values greater than 1.5 μM.

Table 1

#	IC50	EC50	LR-MS (M+H)	^{1}H NMR DATA
1	A	A	403.4	See Example 4 for Experimental Details and Data
2	A	B	421.4	1H NMR (400 MHz, D6-dmso), δ 11.75 (s, 1 H), 7.85 (d, 1H, J = 2.2 Hz), 7.66 (dd, 1 H, J = 2.2 & 6.6 Hz), 7.55 & 7.47 (AB, 2 H, J = 8.8 Hz), 7.40 (d, 1 H, J = 5.9 Hz), 7.28 (dt, 1 H, J = 2.2 & 10.9 Hz), 6.96 (d, 1 H, J = 2.2 Hz), 6.95 (dt, 1 H, J = 2.9 & 5.9 Hz), 6.68 (q, 1 H), 6.33 (t, 1 H), 5.91 (s, 2 H).
3	B	A	421.4	1H NMR (400 MHz, D6-dmso), δ 12.8 (s, 1 H), 11.74 (s, 1 H), 7.85 (d, 1H, J = 1.5 Hz), 7.68 (dd, 1 H, J = 2.2 & 6.6 Hz), 7.56 & 7.47 (AB, 2 H, J = 8.8 Hz), 7.40 (d, 1 H, J = 5.2 Hz), 7.30 (dt, 1 H, J = 4.4 & 5.0 Hz), 7.16-7.11 (m, 1 H), 6.97 (d, 1 H, J = 2.2 Hz), 6.36-6.31 (m, 2 H), 5.93 (s, 2 H).
4	A	A	480.5	See Example 5 for Experimental Details and Data
5	B	A	498.5	1H NMR (400 MHz, D6-dmso), δ 12.8 (s, 1 H), 12.9 (s, 1 H), 7.96 (d, 1H, J = 6.6 Hz), 7.84 (d, 1 H, J = 2.2 Hz), 7.66 (bt, 1 H), 7.59 & 7.51 (AB, 2 H, J = 8.8 Hz), 7.28 (dt, 1 H, J = 2.2 & 8.8 Hz), 6.98 (d, 1 H, J = 2.2 Hz), 6.98-6.87 (m, 2 H), 6.61 (t, 1 H, J = 6.6 Hz), 5.77 (s, 3 H), 3.25 (s, 3 H).
6	A	A	498.5	1H NMR (400 MHz, D6-dmso), δ 12.6 (s, 1 H), 12.7 (s, 1 H), 7.99 (d, 1H, J = 6.6 Hz), 7.85 (s, 1H), 7.69-7.65 (m, 1 H), 7.60 & 7.49 (AB, 2 H, J = 8.8 Hz), 7.33-7.24 (m, 1 H), 7.18-7.13 (m, 1 H), 6.99 (s, 1 H), 6.63–6.53 (m, 2 H), 5.78 (s, 2 H), 3.24 (s, 3 H)
7	A	C	413.5	^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59-7.10 (m, 11H), 5.98 (m, 2H), 2.07 (s, 3H), 1.90 (s, 3H).
8	C	C	441.5	1H NMR (500 MHz, CDCl3) δ 9.96 (s, 1H), 7.46-7.10 (m, 11H), 5.98 (ABq, JAB = 16.7 Hz, 2H), 4.03 (m, 2H), 2.30 (s, 3H), 1.46 (s, 3H), 0.84 (t, J = 7.3 Hz, 3H). C28H25FN2O2;
9	A	C	498.5	See Example 3 for Experimental Details and Data
10	B	C	590.6	1H NMR (400 MHz, D6-dmso), δ 12.9 (s, 1 H), 12.8 (s, 1

				H), 7.95 (s, 1 H), 7.79 (m, 2 H), 7.66 (d, 2 H), 7.61 & 7.52 (AB, 2 H, J = 8.8 Hz), 7.15 (t, 1 H, J = 9.5 Hz), 7.02 (d, 2 H, J = 8.8 Hz), 6.81 (t, 1 H, J = 8.8 Hz), 6.64-6.58 (m, 2 H), 6.41 (s, 1 H), 5.65 (s, 2 H), 3,81 (s, 3 H).
11	B	C	653.7	1H NMR (400 MHz, D6-dmso), δ 10.22 (s, 1 H), 7.82-7.77 (m, 4 H), 7.62 & 7.53 (AB, 2 H, J = 8.8 Hz), 7.49-7.40 (m, 4 H), 7.15 (dt, 1 H, J = 2.2 & 8.8 Hz), 6.82 (dt, 1 H, J = 3.0 Hz & 8.8 Hz), 6.66 (t, 2 H), 6.42 (d, 1 H, J = 1.5 Hz), 5.64 (s, 2 H), 3.00 (s, 3 H).
12	A	B	498.53	See Example 1 for Experimental Details and Data
13	C	C	418.4	1H NMR (400 MHz, D6-dmso), δ above 12 (s, 1 H), 11.89 (s, 1 H), 9.18 (s, 1 H), 8.04 (d, 1 H, J = 9.2 Hz), 7.95 (bs, 2 H), 7.90 (d, 1 H, J = 5.6 Hz), 7.74 (d, 1 H, J = 9.2 Hz), 7.57 (dd, 1 H, J = 2.0 & 5.2 Hz), 7.52-7.50 (m, 1 H), 6.66 (dd, 1 H, J = 1.6 & 5.2 Hz), 6.36 (t, 1 H, J = 6.4 Hz), 6.31 (s, 1 H), 5.99 (bd, 2 H).
14	A	B	418.4	1H NMR (500 MHz, d6-DMSO): δ 11.7 (s, 1 H), 9.33 (s, 1 H), 8.08 (d, J = 8.8 Hz, 1 H), 7.98-7.87 (m, 2 H), 7.71 (d, J = 8.8 Hz, 1 H), 7.60 (d, J = 6.3 Hz, 1 H), 7.39 (d, J = 5.7 Hz, 1 H), 6.65 (t, J = 6.3 Hz, 1 H), 6.31 (s, 2 H), 5.99 (s, 2 H), 4.46 (s, 1 H), 3.60 (s, 1 H)
16	C	C	438.4	See Example 2 for Experimental Details and Data
17	A	C	438.4	1H NMR (400 MHz, D6-DMSO) d, 9.15 (s, 1 H), 8.01 & 7.98 ((d, J = 9.52 Hz, 1H), 7.79 & 7.77 (d, J = 8.79 Hz, 1H), 7.59 & 7.57 (d, J = 6.59 Hz, 1H), 7.497 & 7.48 (d, J = 5.86 Hz, 1H), 7.29 (t, J = 9.52 Hz, 1H), 6.96 (t, J = 9.50 Hz, 1H), 6.70 (q, J = 8.79 & 15.38 Hz, 1H), 6.34 (t, J = 7.32 Hz, 1H), 5.98 (q, J = 16.11 & 46.87 Hz, 2H).
24	C	C	449.4	1H NMR (400 MHz, D6-dmso), δ 13.2 (s, 1 H), 11.92 (s, 1 H), 7.75 (d, 1 H, J = 6.6 Hz), 7.57 & 7.44 (AB, 2 H, J = 8.8 Hz), 7.50 (d, 1 H, J = 6.6 Hz), 7.47 (s, 1 H), 7.30 (dt, 1 H, J = 4.4 & 4.3 Hz), 7.15-7.09 (m, 1 H), 6.35 (t, 1 H, J = 6.6 Hz), 6.16-6.13 (m, 1 H), 6.00 (s, 2 H), 2.77 (q, 2 H, J = 7.3 Hz), 1.18 (t, 3 H, J = 7.3 Hz).
33	B	C	437.4	^{1}H NMR (400 MHz, D_6-dmso), δ 11.75 (s, 1 H), 7.79 & 7.60 (AB, 2 H, *J* = 8.8 Hz), 7.59 (t, 1 H, *J* = 3.7 Hz), 7.50 - 7.46 (m, 3 H), 7.31 (dt, 1 H, *J* = 4.4 Hz), 7.17-7.12 (m, 1H), 6.33 (t, 1 H, *J* = 6.6 Hz), 6.02 & 5.93 (AB, 2 H, *J* = 18.3 Hz).
34	B	B	419.5	^{1}H NMR (400 MHz, D_6-dmso), δ above 12 (s, 1 H), 11.76 (s, 1 H), 7.77 (d, 1 H, J = 8.8 Hz), 7.59-7.57 (m, 2 H), 7.48 & 7.45 (AB, 2 H, *J* = 5.2 Hz), 7.49 -7.44 (bs, 1 H), 7.30-7.20 (m, 2 H), 7.02 (dt, 1 H, *J* = 1.6 & 7.6 Hz), 6.58 (dt, 1 H, *J* = 1.6 & 7.6 Hz), 6.33 (t, 1 H, *J* = 6.8 Hz), 6.07 & 5.94 (AB, 2 H, *J* = 16.0 Hz)
37	A	C	461.3	1H NMR (400 MHz, d6-DMSO): δ, 11.8 (bs, 1 H), 7.62 (dd, J = 6.8, 2.0 Hz, 1 H), 7.47 (d, J = 9.2 Hz, 1 H), 7.43-

				7.41 (m, 2 H), 7.30 (td, J = 9.2, 4.4 Hz, 1 H), 7.19-7.14 (m, 1 H), 6.52-6.48 (m, 1 H), 6.32 (t, J = 6.6 Hz, 1 H), 5.88 (s, 2 H).
39	B	C	403.4	1H-NMR (400 MHz, in dmso-d6): δ 11.80 (1H, broad s), 7.94 (1H, s), 7.58 (2H, m), 7.48 (1H, d, J = 9.52 Hz), 7.45 (1H, m), 7.24 (2H, m), 7.01 (1H, t, J = 7.32 Hz), 6.57 (2H, s), 6.34 (1H, dd, J = 5.86, 6.59 Hz), 5.97 (2H, s)
40	B	C	421.4	1H-NMR (400 MHz, in dmso-d6): δ 11.81 (1H, broad s), 7.95 (1H, s), 7.60 (2H, d, J = 8.78 Hz), 7.5 (1H, d, J = 9.5 Hz), 7.46 (1H, d, J = 6.59 Hz), 7.30 (1H, ddd, J = 4.39, 8.78, 9.52 Hz), 7.13 (1H, m), 6.57 (1H, s), 6.32 (1H, m), 5.95 (2H, s)
41	A	A	399.4	^{1}H NMR (400 MHz, D_6-dmso), δ 12.8 (s, 1H), 11.72 (s, 1 H), 7.84 (s, 1 H), 7.70 (d, 1 H, *J* = 5.9 Hz), 7.49 &7.19 (AB, 2 H, *J* = 8.8 Hz), 7.40 (d, 1H, *J* = 4.4 Hz), 7.19 (d, 1H, *J* = 6.6 Hz), 7.07 (t, 1 H, *J* = 6.6 Hz), 6.96 (s, 1 H), 6.92 (t, 1 H, *J* = 6.0 Hz), 6.34 (t, 1 H, *J* = 5.9 Hz), 6.03 (d, 1 H, *J* = 7. 3 Hz), 5.86 (s, 2 H), 2.42 (s, 3 H).
43	C	C	431.4	1H NMR (400 MHz, D6-dmso), δ 13.04 (s, 1 H), 11.92 (s, 1 H), 7.75 (dd, 1 H, J = 2.1 & 4.7 Hz), 7.55 & 7.41 (AB, 2 H, J = 8.8 Hz), 7.50 (dd, 1 H, J = 1.7 & 4.7 Hz), 7.46 (s, 1 H), 7.29-7.19 (m, 2 H), 6.97 (dt, 1 H, J = 1.7 & 7.7 Hz), 6.36-6.33 (m, 2 H), 6.0 (s, 2 H), 2.76 (q, 2 H, J = 7.7 Hz), 1.18 (t, 3 H, J = 7.7 Hz).
45	A	A	437.8	1H NMR (400 MHz, D6-dmso), δ 13.04 (s, 1 H), 11.75 (s, 1 H), 8.16 (s, 1H), 7.67 (dd, 1H, J = 2.1 & 4.7 Hz), 7.60 & 7.47 (AB, 2 H, J = 9.0 Hz), 7.40 (d, 1 H, J = 6.4 Hz), 7.27 (q, 1 H, J = 7.7 Hz), 7.23 (q, 1 H, J = 10.3 Hz), 7.03 (t, 1 H, J = 7.2 Hz), 6.59 (t, 1 H, J = 7.7 Hz), 6.32 (t, 1 H, J = 6.8 Hz), 5.97 (s, 2 H).
46	A	A	455.8	1H NMR (400 MHz, D6-dmso), δ 13.11 (s, 1 H), 11.76 (s, 1 H), 8.18 (s, 1 H), 7.69 (dd, 1 H, J = 2.2 & 4.4 Hz), 7.63 & 7.49 (AB, 2 H, J = 8.8 Hz), 7.41 (d, 1 H, J = 5.5 Hz), 7.30 (dt, 1 H, J = 4.4 & 4.3 Hz), 7.17-7.11 (m, 1 H), 6.38-6.33 (m, 1 H), 6.32 (t, 1 H, J = 6.6 Hz), 5.95 (s, 2 H).
47	C	C	435.4	1H NMR (400 MHz, D6-dmso), δ above 12 (s, 1 H), 11.94 (s, 1 H), 7.77 (dd, 1 H, J = 2.0 & 8.5 Hz), 7.54 & 7.47 (AB, 2 H, J = 8.8 Hz), 7.54-7.44 (m, 2 H), 7.33-7.27 (m, 1 H), 7.17-7.08 (m, 1 H), 6.35 (t, 1 H, J = 6.8 Hz), 6.15-6.10 (m, 1H), 5.96 (s, 2 H), 2.28 (s, 3 H).
48	C	C	431.4	1H NMR (400 MHz, D6-dmso), δ above 12 (s, 1 H), 11.93 (s, 1 H), 7.77 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.51-7.39 (m, 4 H), 7.11 (t, 1 H, J = 8.0 Hz), 6.84 (t, 1 H, J = 7.6 Hz), 6.35 (t, 1 H, J = 6.8 Hz), 6.13 (t, 1 H, J = 7.2 Hz), 6.00 (s, 2 H), 2.27 (s, 3 H), 2.36 (d, 3 H, J = 1.2 Hz).
49	A	C	514.5	See Example 6 for Experimental Details and Data
50	A	A	497.5	1H NMR (400 MHz, d6-DMSO): δ, 9.31 (s, 1 H), 8.09 (d,

				J = 8.8 Hz, 1 H), 7.94 (dd, J = 6.8, 4.0 Hz, 1 H), 7.81 (d, J = 9.2 Hz, 1 H), 7.66 (d, J = 4.8 Hz, 1 H), 7.34-7.29 (m, 2 H), 7.26-7.21 (m, 1 H), 7.08 (t, J = 7.4 Hz, 1 H), 6.84 (t, J = 7.8 Hz, 1 H), 6.59 (t, J = 6.6 Hz, 1 H), 5.88 (s, 2 H), 3.57 (s, 3 H), 3.60 (s, 1 H).
51	A	A	493.6	See Example 7 for Experimental Details and Data
52	A	C	514.5	See Example 8 for Experimental Details and Data
53	A	C	480.5	1H-NMR (400 MHz, in dmso-d6): δ 12.77 (1H, broad s), 12.69 (1H, broad s), 7.97 (1H, s), 7.88 (1H, d, J = 6.84 Hz), 7.75 (1H, m), 7.64 (1H, d, J = 8.79 Hz), 7.54 (1H, d, J = 8.79 Hz), 7.29 (1H, m), 7.22 (1H, m), 7.05 (1H, dd, J = 7.32, 7.32 Hz), 6.82 (1H, dd, J = 7.32, 7.81 Hz), 6.65 (1H, dd, J = 6.35, 6.84 Hz), 6.47 (1H, s), 5.83 (2H, s), 3.23 (3H, s)
56	A	C	520.5	See Example 9 for Experimental Details and Data
57	A	A	512.5	1H NMR (400 MHz, D6-dmso), δ above 12 (s, 1 H), 8.00 (d, 1 H, J = 7.2 Hz), 7.84 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.69 (t, 1 H, J = 6.4 Hz), 7.61 & 7.53 (AB, 2 H, J = 9.2 Hz), 7.30 (dt, 1 H, J = 4.0 & 8.8 Hz), 7.18-7.13 (m, 1 H), 6.99 (dd, 1 H, J = 1.2 & 2.4 Hz), 6.64 (t, 1 H, J = 7.6 Hz), 6.57-6.53 (m, 1 H), 5.79 (s, 2 H), 3.35 (q, 2 H, J = 8.0 Hz), 1.04 (d, 3 H, J = 7.6 Hz)
58	A	C	498.5	1H-NMR (400 MHz, in dmso-d6): δ 12.92 (1H, broad s), 11.67 (1H, broad s), 7.98 (1H, d, J = 2.20 Hz), 7.91 (1H, dd, J = 2.20, 7.32), 7.75 (1H, m), 7.65 (1H, d, J = 9.52 Hz), 7.54 (1H, d, J = 9.52 Hz), 7.30 (1H, ddd, J = 4.39, 9.52, 9.52), 7.15 (1H, m), 6.65 (1H, t, J = 6.59 Hz), 6.57 (1H, ddd, J= 2.92, 5.86, 8.79 Hz), 6.38 (1H, d, J = 1.47 Hz), 5.80 (2H, s) 3.25 (3H, s)
59	A	A	500.5	See Example 10 for Experimental Details and Data
60	A	A	490.6	1H NMR (400 MHz, D6-dmso), δ 12.70 (s, 1 H), 12.59 (d, 1 H, J = 5.4 Hz), 7.99 (dd, 1 H, J = 1.9 & 4.9 Hz), 7.85 (t, 1 H, J = 1.5 Hz), 7.66 (t, 1 H, J = 4.9 Hz), 7.54 & 7.35 (AB, 2 H, J = 8.8 Hz), 7.00 (bs, 1 H), 6.98 (d, 1 H, J = 2.5 Hz), 6.76 (d, 1 H, J =7.8 Hz), 6.62 (t, 1 H, J = 6.4 Hz), 6.14 (d, 1 H, J = 7.8 Hz), 5.66 (s, 2 H), 3.10 (s, 3 H), 2.31 (s, 3 H), 2.18 (s, 3 H).
61	A	A	476.5	1H NMR (400 MHz, D6-dmso), δ 12.69 (s, 1 H), 12.60 (s, 1 H), 8.00 (dd, 1 H, J = 1.5 & 5.4 Hz), 7.85 (d, 1 H, J = 2.5 Hz), 7.66 (t, 1 H, J = 5.9 Hz), 7.55 & 7.36 (AB, 2 H, J = 8.8 Hz), 7.19 (d, 1 H, J = 7.3 Hz), 7.10 (t, 1 H, J = 7.3 Hz), 6.98 (d, 1 H, J = 2.0 Hz), 6.95 (t, 1 H, J =7.8 Hz), 6.62 (t, 1 H, J = 6.8 Hz), 6.22 (d, 1 H, J = 7.8 Hz). 5.71 (s, 2 H), 3.09 (s, 3 H), 2.37 (s, 3 H).
62	A	A	524.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.84 (d, 1 H, J = 2.0 Hz), 7.69 (t, 1 H, J = 5.2 Hz), 7.61 & 7.52 (AB, 2 H, J = 8.4 Hz),

				7.30 (dt, 1 H, J = 5.2 & 9.6 Hz), 7.19-7.13 (m, 1 H), 6.99 (d, 1 H, J = 2.0 Hz), 6.63 (t, 1 H, J = 6.4 Hz), 6.60-6.56 (m, 1 H), 5.80 (s, 2 H), 2.96-2.89 (m, 1 H), 0.96 (d, 4 H, J = 6.4 Hz).
63	A	A	526.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 8.00 (td, 1 H, J = 1.6 & 6.8 Hz), 7.84 (m, 1 H), 7.71 (t, 1 H, J = 6.8 Hz), 7.62 & 7.54 (AB, 2 H, J = 8.8 Hz), 7.30 (dt, 1 H, J = 4.4 & 8.8 Hz), 7.18-7.13 (m, 1 H), 6.99-6.98 (m, 1 H), 6.64 (t, 1 H, J = 7.2 Hz), 6.54-6.49 (m, 1 H), 5.80 (s, 2 H), 3.63-3.55 (m, 1 H), 1.14 (d, 6 H, J = 7.2 Hz)
64	A	A	508.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.83-7.26 (m, 1 H), 7.71 (t, 1 H, J = 5.6 Hz), 7.60 & 7.53 (AB, 2 H, J = 8.8 Hz), 7.29 (q, 1 H, J = 9.2 Hz), 7.21 (t, 1 H, J = 8.8 Hz), 7.05 (t, 1 H, J = 7.6 Hz), 6.99-6.98 (m, 1 H), 6.75 (t, 1 H, J = 8.0 Hz), 6.65 (t, 1 H, J = 6.8 Hz), 5.83 (s, 2 H), 3.62-3.55 (m, 1 H), 1.14 (d, 6 H, J = 6.8 Hz)
65	A	A	506.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.96 (td, 1 H, J = 1.2 & 9.0 Hz), 7.83-7.82 (m, 1 H), 7.69 (t, 1 H, J = 7.12 Hz), 7.59 & 7.52 (AB, 2 H, J = 8.8 Hz), 7.30 (q, 1 H, J = 6.0 Hz), 7.22 (t, 1 H, J = 8.8 Hz), 7.06 (t, 1 H, J = 7.6 Hz), 6.98-6.97 (m, 1 H), 6.83 (t, 1 H, J = 8.0 Hz), 6.63 (t, 1 H, J = 7.2 Hz), 5.83 (s, 2 H), 2.93-2.87 (m, 1 H), 0.95 (d, 4 H, J = 6.4 Hz)
66	A	A	494.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dd, 1 H, J = 1.6 & 6.8 Hz), 7.84-7.83 (m, 1 H), 7.66 (t, 1 H, J = 6.4 Hz), 7.58 & 7.48 (AB, 2 H, J = 8.8 Hz), 7.16 (t, 1 H, J = 8.5 Hz), 6.98-6.97 (m, 1 H), 6.92 (t, 1 H, J = 7.6 Hz), 6.61 (t, 1 H, J = 6.8 Hz), 6.57 (t, 1 H, J = 7.2 Hz), 5.79 (s, 2 H), 3.22 (s, 3 H), 2.23 (s, 3 H).
67	A	A	496.9	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 8.02 (dd, 1 H, J = 1.2 & 5.2 Hz), 7.86-7.85 (m, 1 H), 7.68 (t, 1 H, J = 6.4 Hz), 7.57 (d, 1 H, J = 8.8 Hz), 7.51 & 7.33 (AB, 2 H, J = 8.8 Hz), 7.30 (t, 1 H, J = 7.6 Hz), 7.15 (t, 1 H, J = 7.2 Hz), 7.00-6.99 (m, 1 H), 6.64 (t, 1 H, J = 6.8 Hz), 6.40 (d, 1 H, J = 8.0 Hz), 5.79 (s, 2 H), 3.17 (s, 3 H).
68	A	A	494.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.84-7.83 (m, 1 H), 7.70 (t, 1 H, J = 6.8 Hz), 7.60 & 7.53 (AB, 2 H, J = 8.8 Hz), 7.30 (q, 1 H, J = 7.6 Hz), 7.21 (t, 1 H, J = 8.4 Hz), 7.05 (t, 1 H, J = 7.6 Hz), 6.99-6.97 (m, 1 H), 6.78 (t, 1 H, J = 6.8 Hz), 6.64 (t, 1 H, J = 6.8 Hz), 5.82 (s, 2 H), 3.34 (q, 2 H, J = 8.0 Hz), 1.01 (t, 3 H, J = 7.2 Hz)
69	C	A	526.5	1H NMR (400 MHz, D6-dmso), δ 12.20 (s, 1 H), 11.95 (s, 1 H), 7.82 (s, 1 H), 7.73 (dd, 1 H, J = 2.2 & 4.7 Hz), 7.62 & 7.46 (AB, 2 H, J = 9.0 Hz), 7.52 (dd, 1 H, J = 1.7 & 4.3 Hz), 7.31 (dt, 1 H, J = 4.3 & 9.3 Hz), 7.16-7.10 (m, 1 H),

				6.36 (t, 1 H, J = 6.8 Hz), 6.27-6.22 (m, 1 H), 5.93 (s, 2 H), 3.32 (s, 3 H), 2.77 (q, 2 H, J = 7.7 Hz), 1.19 (t, 3 H, J = 7.7 Hz).
70	C	C	508.5	1H NMR (400 MHz, D6-dmso), δ 12.18 (s, 1 H), 11.94 (s, 1 H), 7.81 (s, 1 H), 7.72 (dd, 1 H, J = 1.7 & 5.1 Hz), 7.59 & 7.44 (AB, 2 H, J = 9.0 Hz), 7.52 (d, 1 H, J = 2.2 Hz), 7.27-7.19 (m, 2 H), 6.99 (t, 1 H, J = 7.7 Hz), 6.46 (t, 1 H, J = 7.7 Hz), 6.35 (t, 1 H, J = 6.8 Hz), 5.95 (s, 2 H), 3.32 (s, 3 H), 2.76 (q, 2 H, J = 7.2 Hz), 1.18 (t, 3 H, J = 7.7 Hz).
74	A	A	532.9	1H NMR (400 MHz, D6-dmso), δ 12.71 (s, 1 H), 12.59 (d, 1 H, J = 5.5 Hz), 8.18 (s, 1 H), 8.00 (dd, 1 H, J = 1.8 & 6.8 Hz), 7.67-7.63 (m, 1 H), 7. 65 & 7.53 (AB, 2 H, J = 8.5 Hz), 7.30 (dt, 1 H, J = 4.2 & 8.9 Hz), 7.18-7.13 (m, 1 H), 6.61-6.56 (m, 2 H), 5.80 (s, 2 H), 3.24 (s, 3 H).
76	B	C	417.4	1H NMR (400 MHz, D6-dmso), δ 12.95 (s, 1 H), 11.76 (s, 1 H), 7.69 (dd, 1 H, J = 1.8 & 6.9 Hz), 7.42 & 7.36 (AB, 2 H, J = 8.7 Hz), 7.43-7.40 (m, 1 H), 7.29- 7.18 (m, 2 H), 7.02 (t, 1 H, J = 7.3 Hz), 6.58 (t, 1 H, J = 6.9 Hz), 6.56 (s, 1 H), 6.34 (t, 1 H, J = 6.9 Hz), 5.92 (s, 2 H), 2.34 (s, 3 H).
77	A	A	419.4	1H NMR (400 MHz, D6-dmso), δ above 12 (1 H), 11.76 (s, 1 H), 7.95 (d, 1 H, J = 2.0 Hz), 7.89 (bs, 2 H), 7.87 (bs, 1 H), 7.64 (dd, 1 H, J = 2.4 & 6.8 Hz), 7.43 (d, 1 H, J = 10.8 Hz), 7.43-7.41 (m, 1 H), 7.09 (d, 1 H, J = 2.4 Hz), 6.62 (dd, 1 H, J = 1.6 Hz), 6.33 (t, 1 H, J = 6.8 Hz), 6.28 (s, 1 H), 5.88 (s, 2 H).
78	B	A	420.4	Compound 78 ; 1H NMR (500 MHz, DMSO): 7.95 (bs, 1H), 7.68 (m,1H), 7.44 (m, 2H), 7.31 (m, 1H), 7.09 (bs, 1H), 6.33 (t, 1H, J = 6.6 Hz), 5.95 (m, 1H), 5.72 (s, 2H), 5.64 (bs, 1H)
79	A	A	421.4	1H NMR (400 MHz, D6-dmso), δ above 12 (1 H), 11.74 (s, 1 H), 7.92 (d, 1 H, J = 2.0 Hz), 7.65 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.44 (d, 1 H, J = 10.8 Hz), 7.41-7.37 (m, 1 H), 7.28 (q, 1 H, J = 6.0 Hz), 7.21 (t, 1 H, J = 8.4 Hz), 7.07 (d, 1 H, J = 2.4 Hz), 7.04 (dt, 1 H, J = 7.6 & 1.2 Hz), 6.58 (t, 1 H, J = 8.8 Hz), 6.31 (t, 1 H, J = 6.4 Hz), 5.93 (s, 2 H)
80	A	A		See Example 11 for Experimental Details and Data
81	A	A	432.4	1H NMR (400 MHz, dmso) δ 3.965 (q, 2H, J = 5.5 Hz), 5.885 (s, 2H), 6.326 (t,1H, J = 6.7 Hz), 6.972 (d, 1H, J = 6.1 Hz), 7.0595 (d,1H, J = 2.4 Hz), 7.280 (s, 1H), 7.30-7.39 (m, 3H), 7.413 (d, 1H, J = 7.3 Hz), 7.644 (dd, 1 H, J = 6.7, 1.8 Hz), 7.922 (d, 1H, 2.4 Hz), 8.203 (br s, 3H)
82	A	A	432.4	1H NMR (400 MHz, dmso) δ 3.941 (q, 2H, J = 5.5 Hz). 5.883 (s, 2H), 6.316 (t,1H, J = 6.7 Hz), 7.056 (d, 1H, J = 1.8 Hz), 7.12 (d, 2H, J = 7.9 Hz), 7.369 (d, 2H, J = 7.9 Hz), 7.409 (dd, 1H, J = 6.1, 1.8 Hz), 7.443 (d, 1H, J = 11 Hz), 7.637 (dd, 1H, J = 6.7, 1.8 Hz), 7.915 (d, 1H, J = 1.8 Hz), 8.166 (br s, 3H)

83	A	A	434.4	1H NMR (500 MHz, CD3OD): δ 7.81(dd, 1H, J= 2.2Hz), 7.62 (d,1H, J= 2Hz), 7.42 (m, 1H, 7.24 (bs, 1H), 6.98 (d, 1H, J=10.7), 6.90 (d, 1H, J = 2.2 Hz), 6.48 (t, 1H, J= 6.3 Hz), 5.91 (s, 2H), 5.50 (bs, 1H), 2.29 (s, 3H)
84	A	A	435.4	1H NMR (400 MHz, D6-dmso), δ above 12 (1 H), 11.74 (s, 1 H), 7.92 (d, 1 H, J = 2.0 Hz), 7.65 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.42 (d, 1 H, J = 10.8 Hz), 7.39-7.38 (m, 1 H), 7.14 (t, 1 H, J = 7.6 Hz), 7.06 (d, 1 H, J = 2.0 Hz), 6.91 (t, 1 H, J = 7.6 Hz), 6.36 (t, 1 H, J = 7.6 Hz), 6.31 (t, 1 H, J = 6.4 Hz), 5.91 (s, 2 H), 2.23 (d, 3 H, J = 1.2 Hz)
85	A	C	435.4	1H NMR (400 MHz, D6-dmso), δ above 12.97 (s, H), 11.75 (s, 1 H), 7.70 (dd, 1 H, J = 1.8 & 6.8 Hz), 7.44 &7.38 (AB, 2 H, J = 8.7 Hz), 7.45-7.36 (m, 1 H), 7.29 (dt, 1 H, J = 4.6 & 9.1 Hz), 7.15-7.10 (m, 1 H), 6.57 (d, 1 H, J = 0.9 Hz), 6.34 (t, 1 H, J = 6.8 Hz), 6.35-6.30 (m, 1 H), 5.89 (s, 2 H), 2.34 (s, 3 H).
87	A	A	438.4	1H NMR (500 MHz, DMSO): δ 7.97 (d, J = 2.2 Hz, 1H), 7.73 (m, 1H), 7.69 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7.54 (d, J = 11.0 Hz, 1H), 7.43 (m, 1H), 7.11 (d, J = 2.2 Hz, 1H), 6.34 (t, J = 6.6 Hz, 1H), 5.85 (s, 2H), 5.27 (s, 1H).

#	IC50	EC50	LR-MS (M+H)	DATA
88	B	B	438.4	1H-NMR (400 MHz, in dmso-d6): δ 12.92 (1H, broad s), 9.74 (1H, s), 7.89 (1H, s), 7.49(1H, d, J = 10.90 Hz), 7.25 (2H, m), 7.04 (3H, m), 6.94 (2H, m), 6.56 (1H, dd, J = 7.266, 7.266 Hz), 5.97 (2H, s)
89	A	A	439.4	1H NMR (400 MHz, D6-dmso), δ above 12 (1 H), 11.75 (s, 1 H), 7.93 (d, 1 H, J = 2.0 Hz), 7.66 (dd, 1 H, J = 2.4 & 7.5 Hz), 7.48 (d, 1 H, J = 10.8 Hz), 7.41-7.39 (m, 1 H), 7.30 (dt, 1 H, J = 4.8 & 8.2 Hz), 7.17-7.12 (m, 1 H), 7.08 (d, 1 H, J = 2.0 Hz), 6.37-6.33 (m, 1 H), 6.31 (t, 1 H, J = 6.8 Hz), 5.90 (s, 2 H)
91	A	A	443.4	1H NMR (400 MHz, dmso) δ 6.058 (s, 2H), 6.328 (t,1H, J = 6.6 Hz), 7.063 (d, 1H, 2.2 Hz), 7.388 (dd, 1H, J = 8.7, 1.46 Hz), 7.41-7.45 (m, 1H), 7.479 (s, 1H), 7.502 (d, 1H, J = 10.3 Hz), 7.642 (dd, 1H, J = 7.3, 2.2 Hz), 7.796 (d, 1H, 8 Hz), 7.927 (d, 1H, J = 2.2 Hz), 9.456 (s, 1H)
92	A	A	446.4	1H NMR (400 MHz, dmso) δ 5.901 (s, 2H), 6.313 (t, 1H, J = 6.6 Hz), 7.05-7.07 (m, 1H), 7.09 (d, 1H, J = 8 Hz), 7.3-7.375 (m, 2H), 7.398 (d, 1H, J = 6.6 Hz), 7.45 (d, 1H, J = 10.3 Hz), 7.646 (d, 1H, J = 6.6 Hz), 7.712 (m, 2 H), 7.9-7.96 (m, 2H)
93	A	A	446.4	1H NMR (400 MHz, dmso) δ 5.911 (s, 2H), 6.313 (t, 1H, J = 6.6 Hz), 7.05-7.07 (m, 1H), 7.101 (d, 2H, J = 7.3 Hz), 7.306 (s, 1H), 7.402 (d,1H, J = 6.6 Hz), 7.437 (d, 1H, J = 11 Hz), 7.660 (dd,

				1H, J = 6.6, 1.5 Hz), 7.50 (d, 2H, J = 7.3 Hz), 7.879 (s, 1H), 7.9-7.94 (m, 1H)
94	A	A	446.4	1H NMR (400 MHz, D6-dmso), δ above 12 (1 H), 11.75 (s, 1 H), 7.86 (bs, 1 H), 7.84-7.83 (m, 1 H), 7.81-7.77 (m, 1 H), 7.66 (td, 1 H, J = 1.2 & 5.2 Hz), 7.55 (dd, 1 H, J = 1.2 & 8.4 Hz), 7.46 (d, 1 H, J = 8.8 Hz), 7.41 (d, 1 H, J = 5.6 Hz), 7.32-7.28 (m, 3 H), 6.97-6.96 (m, 1H), 6.34 (t, 1 H, J = 6.8 Hz), 5.95 (s, 2 H).
95	A	A	450.4	1H NMR (400 MHz, D6-dmso), δ 11.79 (s, 2 H), 8.38 (b, 3 H), 7.93 (d, 1 H, J = 2.0 Hz), 7.65 (dd, 1 H, J = 2.0 & 4.8 Hz), 7.46-7.39 (m, 3 H), 7.15 (d, 1 H, J = 8.0 Hz), 7.07 (d, 1 H, J = 2.0 Hz), 6.62 (t, 1 H, J = 7.6 Hz), 6.32 (t, 1 H, J = 6.8 Hz), 5.93 (s, 2 H), 3.98-3.94 (m, 2 H).
96	A	A	452.4	1H NMR (500 MHz, DMSO): 7.99 (m, 1H), 7.98 (m, 1H), 7.69 (m, 1H), 7.53 (m, 1H), 7.44 (s, 1H), 7.11 (m, 1H), 6.34 (m, 1H), 5.84 (s, 2H), 5.21(m, 1H), 3.33 (s, 3H)
97	A	A	452.4	1H-NMR (400 MHz, in dmso-d6): δ 12.94 (1H, broad s), 11.73 (1H, broad s), 7.94(1H, Broad s), 7.90 (1H, dd, J = 0.55, 2.20 Hz), 7.62 (1H, dd, J = 2.2, 6.6 Hz), 7.54 (1H, s), 7.52 (1H, dd, J = 1.1, 1.65 Hz), 7.40 (1H, m), 7.37 (1H, d, 1.1 Hz), 7.31 (1H, Broad s), 7.06 (1H, d, J = 2.2 Hz), 6.31 (1H, dd, J = 6.6, 7.14), 5.0 (1H, s)
98	B	B	453.4	1H-NMR (400 MHz, in dmso-d6): δ 13.09 (1H, broad s), 11.73 (1H, broad s), 8.06 (2H, m), 7.90 (1H, s), 7.74 (2H, m), 7.60 (1H, d, J = 6.04 Hz), 7.40 (1H, d, J = 4.94 Hz), 7.06 (1H, s), 6.30 (1H, dd, J = 6.04, 6.59 Hz), 6.09 (2H, s)
99	A	B	454.5	1H-NMR (400 MHz, in dmso-d6): δ 12.87 (1H, broad s), 11.64 (1H, broad s), 7.94 (1H, s), 7.50 (1H, d, J = 1.65 Hz), 7.43 (1H, dd, J = 1.65, 6.59 Hz), 7.33 (1H, d, J = 2.2.0 Hz), 7.31 (2H, s), 7.00 (1H, d, J = 9.89 Hz), 6.24 (1H, t, J = 6.59 Hz), 5.65 (2H, s), 4.60 (2H, t, J = 8.79 Hz), 3.18 (2H, t, J = 8.79 Hz)
100	A	A	458.4	1H NMR (400 MHz, D6-dmso), δ 12.96 (s, 1 H), 11.74 (s, 2 H), 7.90 (d, 1 H, J = 2.0 Hz), 7.64 (dd, 1 H, J = 1.2 & 5.6 Hz), 7.51 (s, 1 H), 7.45 (d, 1 H, J = 10.8 Hz), 7.40 (d, 1 H, J = 6.8 Hz), 7.17 (d, 1 H, J = 8.4 Hz), 7.05-7.03 (m, 2 H), 6.32 (t, 1 H, J = 6.4 Hz), 5.88 (s, 2 H), 3.35 (s, 2 H).
101	A	A	458.4	1H NMR (400 MHz, D6-dmso), δ 13.02 (s, 1 H), 12.45 (s, 1 H), 12.36 (s, 1 H), 11.75 (s, 1 H), 8.42 (s, 2 H), 7.92 (d, 1 H, J = 2.0 Hz), 7.63 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.48 (d, 1 H, J = 10.8 Hz), 7.41 (d, 1 H, J = 6.0 Hz), 7.27 (d, 1 H, J = 8.4 Hz), 7.08-7.05 (m, 3 H), 6.32 (t, 1 H, J = 6.4 Hz), 5.93 (s, 2 H).
102	A	A	459.4	1H NMR (400 MHz, D6-dmso), δ 12.89 (s, 1 H), 11.74 (s, 1 H), 7.91 (dd, 1 H, J = 2.0 & 0.4 Hz), 7.65 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.55 (bs, 1 H), 7.46 (d, 1 H, J = 10.8 Hz), 7.40 (d, 1 H, J = 6.8 Hz), 7.37 (d, 1 H, J = 8.8 Hz), 7.24

				(dd, 1 H, J = 1.2 & 8.8 Hz), 7.06 (d, 1 H, J = 2.4 Hz), 6.33 (s, 2 H), 6.32 (t, 1 H, J = 6.8 Hz), 5.93 (s, 2 H).
103	A	A	459.4	1H NMR (400 MHz, d6-DMSO): δ 11.76 (br s, 1H), 10.54 (s, 1H), 10.48 (S, 1H), 7.90 (d, J = 2.0 Hz, 1H), 7.62 (dd, J = 2.0, 6.8 Hz, 1H), 7.48 (d, J = 6.8 Hz, 1H), 7.40 (dd, J = 1.6, 6.4 Hz, 1H), 7.05 (d, J = 2.0 Hz, 1H), 6.83-6.77 (m, 2 H), 6.69 (s, 1 H), 6.31 (t, J = 6.8 Hz, 1H), 5.82 (s, 2 H); LCMS found for C24H15FN4O5: 459.3 (M+H)+.
104	A	C	460.4	1H NMR (400 MHz, D6-dmso), δ 13.01 (s, 1 H), 11.76 (s, 1 H), 8.17 (dd, 1 H, J = 2.8 & 9.2 Hz), 7.85 (d, 1 H, J = 2.0 Hz), 7.68 (dd, 1 H, J = 2.4 & 6.8 Hz), 7.53 & 7.38 (AB, 2 H, J = 8.8 Hz), 7.43-7.41 (m, 1 H), 7.35 (d, 1 H, J = 2.8 Hz), 7.28 (d, 1 H, J = 9.2 Hz), 6.96 (d, 1 H, J = 2.0 Hz), 6.35 (t, 1 H, J = 6.8 Hz), 5.86 (s, 2 H), 4.01 (s, 3 H)
105	A	A	461.4	1H NMR (400 MHz, dmso) δ 6.058 (s, 2H), 6.335 (t, 1H, J = 6.6 Hz), 6.946 (d, 1H, J = 5.9 Hz), 7.079 (d, 1H, J = 2.2 Hz), 7.425 (dd, 1H, J = 6.6, 2.2 Hz), 7.507 (d, 1H, J = 11 Hz), 7.652 (dd, 1H, J = 6.6, 2.2 Hz), 7.791 (d, 1H, J = 9.5 Hz), 7.944 (d, 1H, J = 2.2 Hz), 9.370 (s, 1H)
106	A	A	499.3	1H NMR (500 MHz, CDCl3): 8.06(d, 1H, J= 6.9 Hz), 7.54 (m,1H), 7.49 (d, 1H, J= 2.2 Hz), 7.29 (m, 1H), 7.14 (d, 1H, J=10.08 Hz), 7.06 (dd, 1H, J = 3.7 Hz), 6.91 (d, 1H, J= 2.2 Hz), 6.73 (t, 1H, J = 6.6 Hz), 5.96 (bs, 2H), 1.90 (m, 1H), 0.85(m, 4H)
107	A	A	464.4	1H NMR (400 MHz, D6-dmso), δ above 12.91 (s, H), 11.74 (s, 1 H), 7.92 (d, 1 H, J = 2.4 Hz), 7.87 (s, 1 H), 7.82-7.78 (m, 1 H), 7.64 (dd, 1 H, J = 2.1 & 6.8 Hz), 7.47 (d, 1 H, J = 10.8 Hz), 7.40 (d, 1 H, J = 7.6 Hz), 7.31-7.27 (m, 3 H), 7.07 (d, 1 H, J = 2.4 Hz), 6.32 (t, 1 H, J = 6.8 Hz), 5.92 (s, 2 H).
108	A	B	465.4	1H NMR (400 MHz, D6-dmso), δ above 12.94 (s, H), 11.74 (s, 1 H), 7.93 (d, 1 H, J = 2.0 Hz), 7.89-7.85 (m, 1 H), 7.63 (dd, 1 H, J = 2.4 & 4.4 Hz), 7.49 (d, 1 H, J = 10.8 Hz), 7.42-7.32 (m, 3 H), 7.08 (d, 1 H, J = 2.0 Hz), 6.32 (t, 1 H, J = 6.4 Hz), 5.93 (s, 2 H).
109	A	A	465.4	1H-NMR (400 MHz, in dmso-d6): δ 12.96 (1H, broad s), 11.76 (1H, broad s), 8.60 (1H, d, J = 1.1 Hz), 8.12 (1H, s), 7.94 (1H, d, J = 2.2 Hz), 7.64 (1H, dd, J = 2.20, 6.59 Hz), 7.59 (1H, s), 7.57 (1H, s), 7.41 (1H, d, J = 5.5 Hz), 7.09 (1H, d, J = 2.2 Hz), 6.32 (1H, dd, J = 6.59, 6.59 Hz), 5.88 (2H, s)
111	A	A	466.4	1H NMR (400 MHz, D6-dmso), δ 13.00 (s, 1 H), 11.74 (s, 1 H), 8.23-8.19 (m, 1 H), 7.94 (d, 1 H, J = 2.0 Hz), 7.64 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.58-7.57 (m, 1 H), 7.56, 7.53 (AB, 2 H, J = 3.6 Hz), 7.41 (d, 1 H, J = 7.2 Hz), 7.08 (d, 1 H, J = 2.0 Hz), 6.31 (t, 1 H, J = 6.8 Hz), 5.95 (s, 2 H).
113	A	A	467.4	1H-NMR (400 MHz, in dmso-d6): δ 12.90 (1H, broad s),

				11.66 (1H, broad s), 8.59 (1H, d, J = 1.65 Hz), 8.12 (1H, s), 7.59 (1H, s), 7.55 (1H, dd, J = 1.65, 9.34 Hz), 7.45 (1H, dd, J = 2.2, 6.59 Hz), 7.02 (1H, d, J = 0.89, Hz), 6.25 (1H, dd, J = 6.59, 6.59 Hz), 5.74 (2H, s), 4.63 (2H, t, J = 8.79 Hz), 3.20 (2H, t, J = 8.79 Hz)
114	A	A		See Example 12 for Experimental Details and Data
115	A	A	470.4	1H NMR (400 MHz, dmso) δ 5.686 (s, 2H), 6.338 (t, 1H, J = 6.7 Hz), 6.854 (d, 2H, J = 1.8 Hz), 7.025-7.09 (m, 2H), 7.296 (d, 1H, J = 7.9 Hz), 7.38-7.46 (m, 4H), 7.694 (dd, 1H, J = 6.7, 1.8 Hz), 7.926 (d, 1H, J = 2.4 Hz)
116	A	A	470.9	1H NMR (400 MHz, D6-dmso), δ above 12.93 (s, H), 11.77 (s, 1 H), 7.96 (d, 1 H, J = 8.8 Hz), 7.88 (d, 1 H, J = 2.0 Hz), 7.77-7.74 (m, 3 H), 7.55, 7.48 (AB, 2 H, J = 8.4 Hz), 7.56-7.49 (m, 1 H), 7.43 (dd, 1 H, J = 2.0 & 4.8 Hz), 7.18 (s, 1 H), 6.99 (d, 1 H, J = 2.0 Hz), 6.36 (t, 1 H, J = 6.4 Hz), 6.05 (s, 2 H).
117	A	A		See Example 13 for Experimental Details and Data
119	A	A	473.8	1H NMR (400 MHz, D6-dmso), δ 13.06 (s, 1 H), 11.76 (s, 1 H), 8.20 (s, 1 H), 7.66 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.61 (d, 1 H, J = 11.6 Hz), 7.40 (d, 1 H, J = 6.4 Hz), 7.29 (dt, 1 H, J = 4.4 & 9.2 Hz), 7.17-7.10 (m, 1 H), 6.40-6.35 (m, 1 H), 6.30 (t, 1 H, J = 6.8 Hz), 5.91 (s, 2 H).
120	A	A	477.9	1H NMR (400 MHz, dmso) δ 6.044 (s, 2H), 6.349 (t, 1H, J = 6.6 Hz), 6.535 (s, 1H), 7.091 (d, 1H, J = 2.2 Hz), 7.406 (d, 1H, J = 11 Hz), 7.435 (dd, 1H, J = 6.6, 1.5 Hz), 7.665-7.695 (m, 1H), 7.966 (d, 1H, J =2.2 Hz), 8.049 (s, 1H), 9.305 (s, 1H)
121	A	A	478.4	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 11.41 (s, 1 H), 8.26 (b, 1 H), 7.80 (s, 1 H), 7.70-7.65 (m, 1 H), 7.54-7.46 (m, 1 H), 7.27 (t, 1 H, J = 8.0 Hz), 7.21-7.14 (m, 1H), 7.12-7.05 (m, 1 H), 6.96 (s, 1 H), 6.19 (b, 1H), 6.04 (b, 2 H), 2.64 (d, 3 H, J = 4.4 Hz).
126	A	A	488.9	1H NMR (400 MHz, D6-dmso), δ above 12.90 (s, H), 11.77 (s, 1 H), 7.96-7.94 (m, 2 H), 7.79-7.71 (m, 3 H), 7.56-7.51 (m, 2 H), 7.42 (d, 1 H, J = 6.0 Hz), 7.17 (s, 1 H), 7.09 (d, 1 H, J = 2.8 Hz), 6.34 (t, 1 H, J = 6.4 Hz), 6.01 (s, 2 H).
127	A	A	489.4	See Example 14 for Experimental Details and Data
128	C	A	489.9	1H NMR (400 MHz, D6-dmso), δ 12.94 (s, 1 H), 7.96 (d, 1 H, J = 8.8 Hz), 7.93- 7.92 (m, 1 H), 7.81 (d, 1 H, J = 7.2 Hz), 7.76 (tt, 1 H, J = 6.8 & 1.2 Hz), 7.65 (tt, 1 H, J = 7.6 & 1.2 Hz), 7.61 (d, 1 H, J = 11.2 Hz), 7.55-7.51 (m, 1 H), 7.45 (q, 1 H, J = 7.2 Hz), 7.31-7.26 (m, 2 H), 7.21 (s, 1 H), 7.10-7.09 (m, 1 H), 6.06 (s, 2 H).
130	B	A	492.5	1H NMR (400 MHz, D6-dmso), δ 11.74 (s, 1 H), 7.95 (dd, 1 H, J = 0.4 & 2.5 Hz), 7.89 (b, 1 H), 7.82-7.78 (m, 1 H), 7.68 (dd, 1 H, J = 1.6 & 6.8 Hz), 7.52 (d, 1 H, J = 10.8

				Hz), 7.40 (d, 1 H, J = 6.4 Hz), 7.33-7.27 (m, 3 H), 7.09 (dd, 1 H, J = 0.4 & 1.6 Hz), 6.30 (t, 1 H, J = 6.4 Hz), 5.89 (s, 2 H), 4.02 (q, 2 H, J = 6.8 Hz), 0.98 (t, 2 H, J = 6.8 Hz).
131	A	A	493.9	1H NMR (400 MHz, d6-DMSO): ? 11.75 (br s, 1H), 10.71 (s, 1H), 10.40 (S, 1H), 7.94 (s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.42 (s, 1H), 7.28 (d, J = 11.2 Hz, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 6.34 (s, 1 H), 5.87 (s, 3 H); LCMS found for C24H14ClFN4O5: 493.3 (M+H)+.
132	B	B	494.5	1H NMR (400 MHz, D6-dmso), δ above 12.80 (s, H), 12.62 (d, 1 H), 7.97 (dd, 1 H, J = 2.0 & 4.8 Hz), 7.69 (dt, 1 H, J = 16 & 6.0 Hz), 7.46, 7.40 (AB, 2 H, J = 8.4 Hz), 7.31-7.26 (m, 1 H), 7.20 (t, 1 H, J = 9.2 Hz), 7.04 (t, 1 H, J = 8.0 Hz), 6.80 (t, 1 H, J = 8.0 Hz), 6.62 (t, 1 H, J = 6.8 Hz), 6.59 (d, 1 H, J = 0.8 Hz), 5.78 (s, 2 H), 3.22 (s, 3 H), 2.33 (s, 3 H).
133	A	A	496.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dd, 1 H, J = 2.4 & 4.8 Hz), 7.88 (d, 1 H, J = 6.8 Hz), 7.79 (b, 1 H), 7.72 (b, 1H), 7.44 (d, 1 H, J = 10.4 Hz), 7.12 (d, 1 H, J = 2.4 Hz), 6.66 (t, 1 H, J = 6.8 Hz), 6.61 (dd, 1 H, J = 6.4 & 1.6 Hz), 6.37 (s, 1 H), 5.72 (s, 2 H), 3.27 (s, 3 H).
134	A	A	498.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (m, 1 H), 7.92 (d, 1 H, J = 2.0 Hz), 7.66 (b, 1 H), 7.51 (d, 1 H, J = 10.4 Hz), 7.30 (dd, 1 H, J = 7.2 & 14.4 Hz), 7.21 (t, 1 H, J = 8.0 Hz), 7.09 (d, 1 H, J = 2.4 Hz), 7.07 (dt, 1 H, J = 1.2 & 7.2 Hz), 6.83 (t, 1 H, J = 8.4 Hz), 6.60 (b, 1 H), 5.79 (s, 2 H), 3.19 (s, 3 H).
135	A	A	499.3	1H NMR (500 MHz, DMSO): δ 7.93(bs, 1H), 7.80 (m,1H), 7.66 (m, 1H), 7.41 (m, 2H), 7.08 (m, 1H), 6.34 (m, 1H), 5.76 (bs, 2H), 5.03 (m, 1H). M.S. found: 498.3 (M)+.
136	A	A	502.9	1H NMR (500 MHz, DMSO): 7.93(d, 1H, J = 2.2 Hz), 7.60-7.80(m,3H), 7.52(d, 1H, J =10 Hz), 7.42 (m, 1H), 7.09 (d, 1H, J = 2.2 Hz), 6.34 (t, 1H, J = 6.9 Hz, 6.3 Hz), 5.99 (bs, 2H)
138	A	A	502.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.99 (b, 1 H), 7.83 (d, 1 H, J = 2.0 Hz), 7.69 (b, 1 H), 7.55 (d, 1 H, J = 8.0 Hz), 7.37 (d, 1 H, J = 8.8 Hz), 7.20 (d, 1 H, J = 8.4 Hz), 7.11 (t, 1 H, J = 7.6 Hz), 6.98-6.94 (m, 2 H), 6.64 (b, 1 H), 6.22 (d, 1 H, J = 7.6 Hz), 5.74 (s, 2 H), 2.85-2.70 (m, 1 H), 2.38 (s, 3 H), 0.90-0.83 (m, 4 H).
139	A	A	502.9	1H NMR (500 MHz, DMSO): δ 7.98 (d, 1H, J= 2.2 Hz), 7.76 (bs,1H), 7.75(dd, 1H, J= 1.89 Hz, 2.2 Hz), 7.68 (d, 1H, J = 8.5 Hz), 7.57 (d, 1H, J=10.7 Hz), 7.45 (m, 1H), 7.40 (dd, 1H, J= 1.57 Hz), 7.12 (m, 2H), 6.36 (t, 1H, J = 6.3 Hz), 6.01 (bs, 2H), 2.50 (s, 3H, hidden in DMSO). M.S. found: 502.3 (M+H)+.

140	A	A	502.9	1H NMR (500 MHz, CD3OD): 7.95 - 7.80 (m, 2H), 7.66 (m, 1H), 7.57 (m, 1H), 7.51 (s, 1H), 7.45 (m, 1H), 7.40 (s, 1H), 6.96 (d, J = 10.4 Hz, 1H), 6.91 (m, 1H), 6.53 (m, 1H), 6.15(s, 2H), 2.43 (s, 3H).
141	A	C	504.5	1H NMR (400 MHz, D6-dmso), δ above 12.92 (s, H), 11.47 (s, 1 H), 8.36 (d, 1 H, J = 4.0 Hz), 7.93 (d, 1 H, J = 2.4 Hz), 7.75- 7.71 (m, 1 H), 7.40 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.47 (d, 1 H, J = 10.8 Hz), 7.41 (d, 1 H, J = 5.2 Hz), 7.31-7.23 (m, 2 H), 7.08 (d, 1 H, J = 2.4 Hz), 6.32 (t, 1 H, J = 6.4 Hz), 5.93 (s, 2 H), 2.72-2.66 (m, 1 H), 0.63-0.58 (m, 2 H), 0.49-0.45 (m, 2 H).
143	A	A	506.9	1H NMR (500 MHz, CD3OD): δ 7.88 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.45 - 7.41 (m, 2H), 6.94-6.90 (m, 2H), 6.50 (t, J = 6.6 Hz, 1H), 6.05(s, 2H), 3.97 (s, 3H), 2.34 (s, 3H).
145	A	B	511.4	1H NMR (400 MHz, dmso) δ 6.011 (s, 2H), 6.322 (t, 1H, J = 6.7 Hz), 7.055 (d, 1H, J = 1.8 Hz), 7.212 (dd, 1H, J = 8.5, 1.2 Hz), 7.351 (s, 1H), 7.407 (dd, 1H, J = 6.1, 1.8 Hz), 7.508 (d, 1H, J = 11 Hz), 7.642 (d, 1H, J = 1.8 Hz), 7.659 (d, 1H, J = 1.8 Hz), 7.91 (d, 1H, J = 1.8 Hz)
146	A	A	512.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.95 (dd, 1 H, J = 6.4 & 1.2 Hz), 7.91 (d, 1 H, J = 2.0 Hz), 7.66 (t, 1 H, J = 5.2 Hz), 7.49 (d, 1 H, J = 10.8 Hz), 7.17 (t, 1 H, J = 8.0 Hz), 7.08 (d, 1 H, J = 2.0 Hz), 6.94 (t, 1 H, J = 7.6 Hz), 6.64-6.55 (m, 2 H), 5.76 (s, 2 H), 3.19 (s, 3 H), 2.22 (m, 3 H).
147	A	C	512.5	1H NMR (400 MHz, D6-dmso), δ above 12.79 (s, 1 H), 12.61 (s, 1 H), 8.00 (td, 1 H, J = 2.0 & 7.2 Hz), 7.67 (t, 1 H, J = 6.0 Hz), 7.50 7.39 (m, 2 H), 7.32-7.26 (m, 1 H), 7.17-7.12 (m, 1 H), 6.62 (t, 1 H, J = 6.8 Hz), 6.59-6.53 (m, 2 H), 5.75 (s, 2 H), 3.24 (d, 3 H, J = 1.2 Hz), 2.34 (s, 3 H).
148	A	A	514.5	1H-NMR (400 MHz, in dmso-d6): δ 12.96 (1H, broad s), 11.76 (1H, broad s), 7.76 (1H, d, J = 5.86 Hz), 7.59 (1H, m), 7.28 (1H, ddd, J = 3.66, 8.79, 8.79 Hz), 7.20 (1H, d, J = 8.79), 7.16 (1H, m), 7.03 (1H, d, J = 8.79), 6.59 (1H, m), 6.54 (1H, dd, J = 6.59, 6.59 Hz), 5.64 (2H, s), 4.66 (1H, dd, J = 8.79, 9.52 Hz), 4.04 (1H, dd, J = 7.32, 8.79 Hz), 3.51 (1H, m), 3.23 (3H, s), 1.23 (3H, d, J = 5.86 Hz)
149	A	A	514.9	1H NMR (400 MHz, D6-dmso), δ 12.73 (s, 1 H), 12.59 (s, 1 H), 8.17 (s, 1 H), 7.97 (d, 1 H, J = 8.0 Hz), 7.66 & 7.51 (AB, 2 H, J = 9.0 Hz), 7.67-7.36 (bm, 1 H), 7.30 (q, 1 H, J = 7.3 Hz), 7.21 (t, 1 H, J = 8.5 Hz), 7.05 (t, 1 H, J = 7.3 Hz), 6.82 (t, 1 H, J = 7.7 Hz), 6.59 (t, 1 H, J = 6.8 Hz), 5.83 (s, 2 H), 3.22 (s, 3 H).
150	A	A	516.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (d, 1 H, J = 6.4 Hz), 7.93 (d, 1 H, J = 2.4 Hz), 7.66 (t, 1 H, J = 5.2 Hz), 7.52 (d, 1 H, J = 10.8 Hz), 7.30 (dt, 1 H, J =

				4.0 & 8.8 Hz), 7.19-7.13 (m, 1 H), 7.10 (d, 1 H, J = 2.4 Hz), 6.62-6.57 (m, 2 H), 5.76 (s, 2 H), 3.22 (m, 2 H).
151	A	B	516.5	1H NMR (400 MHz, D6-dmso), δ 12.71 (s, 1 H), 12.54 (s, 1 H), 7.99 (dd, 1 H, J = 6.8 & 2.1 Hz), 7.89 (d, 1 H, J = 2.1 Hz), 7.66 (s, 1 H), 7.42 (d, 1 H, J = 12.8 Hz), 7.30 (dt, 1 H, J = 4.7 & 9.4 Hz), 7.18-7.12 (m, 1 H), 6.96 (d, 1 H, J = 1.7 Hz), 6.60 (t, 1 H, J = 6.8 Hz), 6.55-6.51 (m, 1 H), 5.79 (s, 2 H), 3.27 (s, 3 H).

#	IC50	EC50	LR-MS (M+H)	DATA
152	A	A	516.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (d, 1 H, J = 6.4 Hz), 7.83 (s, 1 H), 7.69 (b, 1 H), 7.54 (t, 1 H, J = 10.0 Hz), 7.36 (d, 1 H, J = 9.6 Hz), 7.00 (bs, 1 H), 6.97 (bs, 1 H), 6.77 (d, 1 H, J = 9.2 Hz), 6.64 (t, 1 H, J = 11.2 Hz), 6.14 (d, 1 H, J = 8.8 H.z), 5.69 (s, 2 H), 2.83-2.76 (m,1 H), 2.33 (s, 3 H), 2.18 (s, 3 H), 0.89 (bm, 4 H).
153	A	A	518.9	1H NMR (500 MHz, DMSO): δ 7.98 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 1.9 Hz, J = 6.8 Hz, 1H), 7.71 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 10.8 Hz, 1H), 7.45 (m, 1H), 7.39 (d, J = 2.4 Hz, 1H), 7.19 (dd, J = 2.4 Hz, J = 9.0 Hz, 1H), 7.13 (s, 1H), 7.11 (d, J = 2.0 Hz, 1H), 6.37 (t, J = 6.5 Hz, 1H), 6.0 (s, 2H), 3.91 (s, 3H).
154	A	A	518.9	1H NMR (500 MHz, DMSO): δ 7.99 (d, J = 2.2 Hz, 1H), 7.87 (d, J = 9.2 Hz, 1H), 7.74 (dd, J = 2.1 Hz, J = 6.8 Hz, 1H), 7.55 (d, J = 10.9 Hz, 1H), 7.45 (m, 1H), 7.38 (dd, J = 2.8 Hz, J = 9.2Hz, 1H), 7.21 (m, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.11 (m, 1H), 6.37 (t, J = 6.6 Hz, 1H), 6.02 (s, 2H), 3.77 (s, 3H).
155	A	A	520.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.95 (d, 1 H, J = 5.6 Hz), 7.82 (bd, 1 H, J = 2.0 Hz), 7.69 (b, 1 H), 7.58, 7.50 (AB, 2 H, J = 8.8 Hz), 7.16 (t, 1 H, J = 7.6 Hz), 6.97 (d, 1 H, J = 2.4 Hz), 6.94 (t, 1 H, J = 6.4 Hz), 6.68-6.57 (m, 2 H), 5.81 (s, 2 H), 2.95-2.88 (m,1 H), 2.22 (s, 3 H), 0.97 (s, 2 H), 0.93 (s,2 H).
156	A	B	520.9	1H NMR (500 MHz, DMSO): 7.98 (d, J = 2.2 Hz, 1H), 7.72 (dd, J = 2.1 Hz, J = 6.8 Hz, 1H), 7.49 (d, J = 10.9 Hz, 1H), 7.45 (m, 1H), 7.11 (d, J = 2.2 Hz, 1H), 7.03 (m, 1H), 6.36 (t, J = 6.7 Hz, 1H), 5.97 (s, 2H), 5.12 (m, 1H), 1.49 (s, 3H), 1.47 (s, 3H).
158	A	B	522.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dt, 1 H, J = 2.0 & 6.8 Hz), 7.83 (bd, 1 H), 7.73-7.69 (m, 1 H), 7.59, 7.52 (AB, 2 H, J = 8.8 Hz), 7.16 (t, 1H, J = 8.0 Hz), 6.98 (t, 1 H, J = 2.4 Hz), 6.92 (t, 1 H, J = 8.0 Hz), 6.64 (t, 1 H, J = 6.8 Hz), 6.53 (t, 1 H, J = 8.0 Hz), 5.81 (s, 2 H), 3.60 - 2.54 (m,1 H), 2.22 (s, 3 H), 1.12 (d, 6 H, J = 6.8 Hz).

159	A	A	523.3	1H NMR (400 MHz, D6-dmso), δ 12.98 (s, 1 H), 11.77 (s, 1 H), 8.24 (d, 1 H, J = 2.4 Hz), 7.95 (d, 1 H, J = 8.5 Hz), 7.77 (t, 1 H, J = 7.3 Hz), 7.73-7.66 (m, 3 H), 7.53 (t, 1 H, J = 7.9 Hz), 7.42 (d, 1 H, J = 6.1 Hz), 7.17 (s, 1 H), 6.33 (t, 1 H, J = 6.7 Hz), 6.02 (s, 2 H).
161	A	A	523.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (dt, 1 H, J = 2.4 & 7.2 Hz), 7.86 (s, 1 H), 7.82-7.80 (m, 2 H), 7.68 (t, 1H, J = 6.0 Hz), 7.59, 7.52 (AB, 2 H, J = 3.2 Hz), 7.53-7.51 (m, 1 H), 7.33 (s, 1 H), 7.30 (t, 1H, J = 9.2 Hz), 6.98-6.96 (m, 1 H), 6.63 (t, 1 H, J = 7.2 Hz), 5.81 (s, 2 H), 3.25 (s, 3 H).
162	A	A	524.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.95 (d, 1 H, J = 6.4 Hz), 7.92 (d, 1 H, J = 2.0 Hz) 7.69 (s, 1 H), 7.53 (d, 1 H, J = 10.8 Hz), 7.31 (dd, 1 H, J = 1.5 & 1.4 Hz), 7.21 (t, 1H, J = 8.0 Hz), 7.10-7.06 (m, 2 H), 6.84 (t, 1 H, J = 8.4 Hz), 6.62 (s, 1 H), 5.81 (s, 2 H), 2.91-2.85 (m, 1 H), 0.95 (s, 2 H), 0.93 (s, 2 H).
163	A	A	526.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dd, 1 H, J = 1.6 & 6.8 Hz), 7.91 (d, 1 H, J = 2.4 Hz) 7.71 (t, 1H, J = 6.4 Hz), 7.55 (d, 1 H, J = 10.8 Hz), 7.30 (dd, 1 H, J = 6.0 & 8.4 Hz), 7.21 (t, 1H, J = 8.4 Hz), 7.08 (d, 1H, J = 2.0 Hz), 7.06 (t, 1H, J = 7.6 Hz), 6.77 (t, 1 H, J = 7.2 Hz), 6.63 (t, 1H, J = 6.8 Hz), 5.81 (s, 2 H), 3.56 (h, 1 H, J = 6.8 Hz), 1.10 (d, 6 H, J = 6.8 Hz).
164	A	A	526.5	1H-NMR (400 MHz, in dmso-d6): δ 12.61 (1H, broad s), 12.53 (1H, broad s), 7.74 (1H, dd, J = 2.20, 6.59 Hz), 7.62 (1H, ddd, J = 2.2, 6.59, 6.59 Hz), 7.29 (1H, ddd, J = 4.39, 8.79, 8.79 Hz), 7.21 (1H, d, J = 8.79 Hz), 7.15 (1H, m), 7.03 (1H, d, J = 8.79 Hz), 6.55 (2H, m), 5.66 (2H, s), 4.52 (2H, t, J = 8.79 Hz), 3.15 (2H, t, 8.79 Hz), 2.90 (1H, dt, J = 5.86, 12.45 Hz), 0.94 (4H, d, J = 5.86 Hz)
164	A	A	526.5	1H-NMR (400 MHz, in dmso-d6): δ 12.61 (1H, broad s), 12.53 (1H, broad s), 7.74 (1H, dd, J = 2.20, 6.59 Hz), 7.62 (1H, ddd, J = 2.2, 6.59, 6.59 Hz), 7.29 (1H, ddd, J = 4.39, 8.79, 8.79 Hz), 7.21 (1H, d, J = 8.79 Hz), 7.15 (1H, m), 7.03 (1H, d, J = 8.79 Hz), 6.55 (2H, m), 5.66 (2H, s), 4.52 (2H, t, J = 8.79 Hz), 3.15 (2H, t, 8.79 Hz), 2.90 (1H, dt, J = 5.86, 12.45 Hz), 0.94 (4H, d, J = 5.86 Hz)
165	A	A	529.5	1H-NMR (400 MHz, in dmso-d6): δ 12.67 (2H, m), (7.93 (1H, dd, J = 2.2., 7.14 Hz), 7.91 (1H, d, J = 2.20 Hz), 7.87 (1H, s), 7.65 (1H, ddd, J = 1.10, 5.49 Hz), 7.59 (1H, d, J = 10.99 Hz), 7.50 (1H, s), 7.49 (1H, d, J = 11.54 Hz), 7.34 (1H, s), 7.09 (1H, d, J = 2.20 Hz), 6.60 (1H, t, J = 6.59 Hz), 5.66 (2H, s), 3.23 (3H, s)
167	A	A	531.6	1H-NMR (400 MHz, in dmso-d6): δ 12.61 (1H, broad s), 12.53 (1H, broad s), 7.87 (1H, s), 7.68 (1H, dd, J = 2.20, 7.14 Hz), 7.58 (1H, d, J = 6.04 Hz), 7.49 (1H, d, J= 1.65

				Hz), 7.42 (1H, s), 7.33 (1H, s), 7.05 (1H, d, J = 10.44 Hz), 6.51 (1H, dd, J = 6.59, 7.14 Hz), 5.52 (2H, s), 4.61 (2H, t, J = 8.79 Hz), 3.26 (3H, s), 3.19 (2H, t, J = 8.79 Hz)
168	A	A	535.0	1H NMR (500 MHz, DMSO): 7.84 (t, 1H, J= 2.2 Hz), 7.68 (bs,1H), 7.61(d, 1H, J= 8.2 Hz), 7.57 (m, 1H), 7.38 (d, 1H, J= 8.8 Hz), 7.29 (m, 1H), 7.17 (m, 1H), 7.11 (bs, 1H), 6.99 (m, 1H), 6.20 (m, 1H), 6.10 (bs, 2H), 2.60 (s, 3H)
169	A	A	535.5	1H NMR (400 MHz, D6-dmso), δ 12.73 (s, 1 H), 12.62 (s, 1H), 12.42 (s, 2 H), 8.42 (s, 1 H), 7.95 (s, 1 H), 7.92 (d, 1 H, J = 7.9 Hz), 7.69-7.66 (m, 1 H), 7.54 (d, 1 H, J = 11.0 Hz), 7.27 (d, 1 H, J = 7.9 Hz), 7.14 (s, 1 H), 7.09-7.07 (m, 2 H), 6.59 (t, 1 H, J = 6.7 Hz), 5.77 (s, 2 H), 3.26 (s, 3 H).
170	A	A	536.5	1H NMR (400 MHz, D6-dmso), δ 12.63 (s, 2 H), 7.95 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.91 (d, 1 H, J = 2.4 Hz), 7.65 (t, 1 H, J = 4.4 Hz), 7.58 (bs, 1 H), 7.54 (d, 1 H, J = 10.8 Hz), 7.38 (d, 1 H, J = 8.4 Hz), 7.30 (dd, 1 H, J = 2.0 & 8.4 Hz), 7.09 (d, 1 H, J = 2.0 Hz), 6.60 (t, 1 H, J = 7.6 Hz), 6.31 (s, 2 H), 5.79 (s, 2 H), 3.22 (s, 3 H).
171	A	A	538.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.94 (dd, 1 H, J = 1.2 & 6.4 Hz), 7.91 (d, 1 H, J = 2.0 Hz) 7.69 (t, 1H, J = 6.0 Hz), 7.52 (d, 1 H, J = 10.8 Hz), 7.17 (t, 1 H, J = 8.8 Hz), 7.08 (d, 1H, J = 2.4 Hz), 6.96 (t, 1H, J = 7.6 Hz), 6.62 (q, 2H, J = 6.8 Hz), 5.79 (s, 2 H), 2.89 (h, 1 H, J = 1.3 Hz), 2.21 (s, 3 H), 0.95 (s, 2 H), 0.94 (s, 2 H).
173	A	A	540.6	
174	A	A	541.5	1H NMR (500 MHz, DMSO): 7.96 (d, J = 2.2 Hz, 1H), 7.73 (m, 2H), 7.59 (d, J = 10.9 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 6.66 (m, 1H), 5.72 (s, 2H), 5.53 (s, 1H), 2.94 (m, 1H), 1.02 - 0.96 (m, 4H).
175	A	A	541.5	1H NMR (400 MHz, D6-dmso), δ 12.72 (s, 1 H), 12.68 (s, 1H), 7.96 (dd, 1 H, J = 2.2 & 7.1 Hz), 7.92 (d, 1 H, J = 2.2 Hz), 7.88 (d, 1 H, J = 2.2 Hz), 7.84-7.80 (m, 1 H), 7.69-7.64 (m, 1 H), 7.58-7.50 (m, 3 H), 7.36-7.27 (m, 2 H), 7.09 (d, 1 H, J = 2.2 Hz), 6.62 (t, 1 H, J = 7.1 Hz), 5.79 (s, 2 H), 3.21 (s, 3 H).
176	A	A	542.5	1H-NMR (400 MHz, in dmso-d6): δ 12.74 (1H, broad s), 12.73 (1H, broad s), 8.61 (1H, d, J = 1.65 Hz), 8.11 (1H, s), 8.00 (1H, dd, J = 2.2, 7.14 Hz), 7.94 (1H, d, J = 2.2 Hz), 7.77 (1H, dd, J = 2.2, 9.3 Hz), 7.70 (1H, ddd, J = 2.2, 6.59, 6.04 Hz), 7.60 (1H, s), 7.57 (1H, s), 7.11 (1H, d, J = 2.2 Hz), 6.64 (1H, dd, J = 6.59, 7.14 Hz), 5.76 (2H, s), 3.23 (3H, s)
177	A	A	542.5	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.92 (d, 1 H, J = 2.4 Hz) 7.69 (t, 1H, J = 6.8 Hz), 7.54 (d, 1 H, J = 10.8 Hz), 7.29 (dt, 1 H, J = 4.8 & 9.2 Hz), 7.18 -7.14 (m, 1 H), 7.09 (d, 1H, J =

				2.0 Hz), 6.63-6.59 (m, 2 H), 5.78 (s, 2 H), 2.93-2.86 (m, 1 H), 0.95 (d, 4 H, J = 6.4 Hz)
178	A	A	542.5	1H NMR (400 MHz, D6-dmso), d, 12.71 (s, 1 H), 12.60 (s, 1 H), 7.97 (dd, 1 H, J = 1.7 & 6.8 Hz), 7.89 (d, 1 H, J = 2.1 Hz), 7.68 (bs, 1 H), 7.43 (d, 1 H, J = 12.8 Hz), 7.31 (dt, 1 H, J = 9.3 & 4.3 Hz), 7.19-7.13 (d, 1 H, J = 2.2 Hz), 6.97 (d, 1 H, J = 2.2 Hz), 6.61 (t, 1 H, J = 6.4 Hz), 6.56-6.51 (m, 1 H), 5.81 (s, 2 H), 2.97-2.91 (m, 1 H), 0.99 (d, 2 H, J = 3.0 Hz), 0.97 (s, 2 H).
179	A	A	543.5	1H NMR (400 MHz, D6-dmso), d, 12.67 (s, 2 H), 8.25-8.21 (m, 1 H), 7.98-7.97 (m, 1H), 7.94 (d, 1 H, J = 2.4 Hz), 7.74 (dd, 1 H, J = 3.0 & 6.1 Hz), 7.68-7.66 (m, 1 H), 7.61 (d, 1 H, J = 10.3 Hz), 7.55 (t, 1 H, J = 9.2 Hz), 7.11 (d, 1 H, J = 2.4 Hz), 6.62-6.59 (m, 1 H), 5.86 (s, 2 H), 3.22 (s, 3 H).
180	A	A	548.0	
181	A	A	552.5	
182	A	A	555.0	1H NMR (400 MHz, dmso) δ 3.17 (s, 3H), 5.885 (s, 2H), 6.653 (t, 1H, J = 6.6), 6.747 (s, 1H), 7.111 (d, 1H, J = 2.2 Hz), 7.411 (d, 1H, J = 10.3 Hz), 7.68-7.74 (br s, 1H), 7.959 (d, 1H, J = 2.2 Hz), 7.985 (s, 1H), 7.995-8.03 (m, 1H), 9.09 (br s, 1H)
183	A	A	555.6	1H-NMR (400 MHz, in dmso-d6): δ 12.65 (1H, broad s), 11.60 (1H, broad s), 7.91 (2H, m), 7.86 (1H, broad s), 7.67 (1H, ddd, J = 2.2, 6.04, 6.6 Hz), 7.62 (1H, d, J= 10.99 Hz), 7.50 (1H, s), 7.46 (1H, s), 7.34 (1H, broad s), 7.09 (1H, d, J = 2.2 Hz), 6.60 (1H, dd, J = 6.59, 6.59 Hz), 5.68 (2H, s), 3.02 (1H, m), 1.1 (4H, d, J = 7.7 Hz)
184	A	A	557.6	1H NMR (400 MHz, D6-dmso), δ above 12 (s, 1 H), 12.36 (bd, 1 H, J = 6.4 Hz), 7.96 (d, 1 H, J = 2.1 Hz), 7.91 (dd, 1 H, J = 2.2 Hz), 7.80 (dd, 1 H, J = 1.5 & 8.1 Hz), 7.67 (t, 1 H, J = 7.7 Hz), 7.59 (d, 1 H, J = 10.4 Hz), 7.60-7.55 (m, 1 H), 7.46 (t, 1 H, J = 8.1 Hz), 7.28-7.23 (m, 1 H), 7.19 (d, 1H, J = 8.1 Hz), 7.17 – 7.11 (m, 1 H), 7.12 (d, 1 H, J = 2.2 Hz), 7.03 (t, 1 H, J = 7.3 Hz), 6.97 (t, 1 H, J = 7.3 Hz), 6.50 (t, 1 H, J = 6.6 Hz), 5.98 (s, 2 H).
185	A	A	557.6	1H-NMR (400 MHz, in dmso-d6): δ 12.60 (2H, broad m), 7.87 (1H, s), 7.68 (1H, dd, J = 1.65, 6.59 Hz), 7.60 (1H, m), 7.48 (1H, s), 7.40 (1H, s), 7.35 (1H, s), 7.09 (1H, d, J = 9.89 Hz), 6.53 (1H, t, J = 6.59 Hz), 5.54 (2H, s), 4.61 (2H, t, J = 8.79 Hz), 3.19 (2H, t, J = 8.79 Hz), 2.99 (1H, m), 0.98 (4H, m)
186	A	A	557.6	1H-NMR (400 MHz, in dmso-d6): δ 12.74 (1H, d, J = 5.49 Hz), 12.54 (1H, s), 7.93 (1H, dd, J = 1.65, 7.14 Hz), 7.91 (1H, d, J = 2.20 Hz), 7.87 (1H, s), 7.69 (1H, ddd, J = 1.65, 6.04, 6.59 Hz), 7.64 (1H, d, J = 10.44 Hz), 7.49 (1H, d, J = 1.10 Hz), 7.41 (1H, d, J = 1.10 Hz), 7.35 (1H, s), 7.09 (1H, d, J = 2.20 Hz), 6.62 (1H, t, J = 6.59 Hz), 5.67 (2H, s),

				3.67 (2H, s), 1.15 (6H, d, J = 6.59 Hz)
187	A	A	558.5	
188	A	A	559.6	1H-NMR (400 MHz, in dmso-d6): δ 12.67 (1H, broad s), 12.54 (1H, broad s), 7.88 (1H, s), 7.70 (1H, dd, J = 2.20, 7.14 Hz), 7.62 (1H, m), 7.48 (1H, d, J = 1.10 Hz), 7.35 (1H, s), 7.11 (1H, d, J = 9.89 Hz), 6.54 (1H, dd, J = 6.59, 7.14 Hz), 5.53 (2H, s), 4.61 (2H, t, J = 8.79 Hz), 3.64 (1H, h, J = 7.12 Hz), 3.19 (2H, t, j = 8.79 Hz), 1.13 (6H, d, J = 7.12 Hz)
190	A	A	562.6	1H NMR (400 MHz, D6-dmso), δ 12.67 (d, 1 H, J = 5.5 Hz), 12.59 (s, 1 H), 8.00 (dd, 1 H, J = 1.9 & 7.3 Hz), 7.91 (d, 1 H, J = 2.4 Hz), 7.70-7.65 (m, 1 H), 7.61-7.58 (m, 2 H), 7.38 (d, 1 H, J = 8.5 Hz), 7.29 (dd, 1 H, J = 1.2 & 8.5 Hz), 7.09 (d, 1 H, J = 2.4 Hz), 6.61 (t, 1 H, J = 6.7 Hz), 6.32 (s, 2 H), 5.81 (s, 2 H), 2.99-2.95 (m, 1 H), 0.93-0.89 (m, 4 H).
192	A	A	564.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.97 (d, 1 H, J = 8.0 Hz), 7.93-7.89 (m, 1 H), 7.84 (d, 1H, J = 2.0 Hz), 7.72 (t, 1 H, J = 6.0 Hz), 7.61, 7.54 (AB, 2 H, J = 8.8 Hz), 7.58 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.39 (dd, 1 H, J = 8.8 & 9.6 Hz), 6.99 (d, 1H, J = 2.0 Hz), 6.65 (t, 1 H, J = 4.4 Hz), 5.86 (s, 2 H), 3.73 (s, 3 H), 2.93-2.86 (m, 1 H), 0.96-0.92 (m, 4 H).
193	A	B	566.0	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 8.32 (d, 1 H, J = 8.4 Hz), 8.10 (d, 1 H, J = 8.0 Hz), 8.03 (dd, 1 H, J = 0.8 & 8.4 Hz), 7.96 (d, 1 H, J = 2.0 Hz), 7.91 (ddd, 1 H, J = 1.6, 7.2 & 6.8 Hz), 7.79 (ddd, 1 H, J = 1.6, 7.2 & 6.8 Hz), 7.71 (t, 1 H, J = 8.0 Hz), 7.47 (d, 1 H, J = 10.8 Hz), 7.12 (d, 1 H, J = 2.0 Hz), 6.66 (t, 1 H, J = 5.2 Hz), 6.34 (s, 1 H), 6.28 (s, 2 H), 3.11 (s, 3 H).
194	A	A	566.0	1H NMR (400 MHz, D6-dmso), δ 12.69 (s, 2 H), 8.06 (dd, 1 H, J = 1.8 & 6.7 Hz), 7.97-7.95 (m, 2 H), 7.81-7.74 (m, 2 H), 7.71 (t, 1 H, J = 4.9 Hz), 7.56 (dt, 1 H, J = 4.2 & 1.2 Hz), 7.54 (s, 1 H), 7.38 (s, 1 H,), 7.11 (d, 1 H, J = 1.8 Hz), 6.67 (t, 1 H, J = 6.7 Hz), 5.87 (s, 2 H), 3.12 (s, 3 H).
195	A	A	567.5	1H NMR (400 MHz, D6-dmso), δ 12.75 (d, 1 H, J = 5.5 Hz), 12.71 (s, 1 H), 7.95 (dd, 1 H, J = 1.8 & 6.7 Hz), 7.92 (d, 1 H, J = 1.8 Hz), 7.88 (s, 1 H) 7.70 (t, 1 H, J = 4.9 Hz) 7.57 (d, 1 H, J =11.0 Hz), 7.53 (t, 1H, J = 6.1 Hz), 7.40 (s, 1 H), 7.29 (t, 1H, J = 8.5 Hz) 7.09 d, 1 H, J = 1.8 Hz), 6.63 (t, 1 H, J = 6.7 Hz), 5.82 (s, 2 H), 2.92-2.83 (m, 1 H), 0.95 (s, 2 H), 0.93 (s, 2 H).
196	A	A	568.0	1H-NMR (400 MHz, in dmso-d6): δ 12.92 (1H, broad s), 11.67 (1H, broad s), 7.96 (1H, d, J = 8.06 Hz), 7.83 (1H, d, J = 7.32 Hz), 7.82 (1H, d, J = 7.32), 7.77 (1H, m), 7.63 (1H, ddd, J = 2.2, 6.6, 6.6 Hz), 7.57 (1H, dd, J = 7.32, 7.32 Hz), 7.38 (1H, s), 7.01 (1H, d, J = 9.52 Hz), 6.59 (1H, dd, J

				= 6.59, 6.59 Hz), 5.73 (2H, s), 4.66 (2H, t, J = 8.79 Hz), 3.21 (2H, t, J = 8.79 Hz), 3.09 (3H, s)
197	A	A	568.5	1H-NMR (400 MHz, in dmso-d6): δ 12.75 (2H, broad s); 8.62 (1H, d, J = 1.95 Hz), 8.11 (1H, s), 7.98 (1H, dd, J = 1.95, 6.84 Hz), 7.93 (1H, d, J = 1.95 Hz), 7.80 (1H, dd, J = 1.95, 9.77 Hz), 7.72 (1H, d, J = 5.37 Hz), 7.62 (1H, s), 7.60 (1H, s), 7.19 (1H, d, J = 2.44 Hz), 6.64 (1H, t, J = 6.35, 6.84 Hz), 5.79 (2H, s), 2.88 (1H, q, J = 6.35 Hz), 0.95 (4H, d, J = 6.35 Hz); LR-MS (ESI)
197	A	A	568.5	1H-NMR (400 MHz, in dmso-d6): δ 12.75 (2H, broad s); 8.62 (1H, d, J = 1.95 Hz), 8.11 (1H, s), 7.98 (1H, dd, J = 1.95, 6.84 Hz), 7.93 (1H, d, J = 1.95 Hz), 7.80 (1H, dd, J = 1.95, 9.77 Hz), 7.72 (1H, d, J = 5.37 Hz), 7.62 (1H, s), 7.60 (1H, s), 7.19 (1H, d, J = 2.44 Hz), 6.64 (1H, t, J = 6.35, 6.84 Hz), 5.79 (2H, s), 2.88 (1H, q, J = 6.35 Hz), 0.95 (4H, d, J = 6.35 Hz); LR-MS (ESI): calcd. for C26H20F2NO6S+ [M+H]+ 568.11, found 567.97
198	A	A	569.5	1H NMR (400 MHz, D6-dmso), δ 12.71 (s, 2 H), 8.25-8.21 (m, 1 H), 7.97 (dd, 1 H, J = 1.8 & 7.3 Hz), 7.93 (d, 1 H, J = 2.4 Hz), 7.75-7.69 (m, 2 H), 7.62 (d, 1 H, J = 10.4 Hz), 7.55 (t, 1 H, J = 9.8 Hz), 7.10 (d, 1 H, J = 2.4 Hz), 6.63 (t, 1 H, J = 6.7 Hz), 5.88 (s, 2 H), 2.91-2.84 (m, 1H), 0.94 (d, 4 H, J = 6.7 Hz).
199	A	A	569.6	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.98 (d, 1 H, J = 7.2 Hz), 7.93-7.92 (m, 1 H), 7.89 (b, 1 H), 7.84-7.81 (m, 1H), 7.72 (t, 1 H, J = 5.2 Hz), 7.60 (d, 1 H, J =11.0 Hz), 7.50 (d, 1 H, J = 6.8 Hz), 7.38 (b, 1 H), 7.29 (t, 1 H, J = 9.6 Hz), 7.10 – 7.09 (m, 1H), 6.64 (t, 1 H, J = 6.8 Hz), 5.82 (s, 2 H), 3.53 (h, 1 H, J = 7.2 Hz), 1.07 (d, 6 H, J = 6.8 Hz).
200	A	A	570.5	1H-NMR (400 MHz, in dmso-d6): δ 12.67 (1H, broad s), 8.60 (1H, s), (8.12 (1H, s), 7.76 (2H, m), 7.63 (1H, m), 7.60 (1H, s), 7.06 (1H, d, J = 9.77 Hz), 6.56 (1H, dd, J = 6.35, 6.84 Hz), 5.64 (2H, s), 4.62 (2H, t, J = 8.79 Hz), 3.20 (2H, t, J = 8.79 Hz), 2.87 (1H, m), 0.92 (4H, d, J = 5.86 Hz)
201	A	A	574.0	1H NMR (400 MHz, D6-dmso), d, 12.74 (s, 1 H), 12.70 (d, 1 H, J = 5.5 Hz) 8.05 (dd, 1 H, J = 1.8 & 6.7 Hz), 7.96 (d, 1 H, J = 8.0 Hz), 7.87 (d, 1 H, J = 2.5 Hz), 7.79-7.75 (m, 2 H), , 7.71 (dt, 1 H, J = 1.8 & 6.1 Hz), 7.58 (t, 2 H, J = 9.2 Hz), 7.53 (t, 1 H, J = 9.2 Hz), 7.38 (s, 1 H), 7.00 (d, 1 H, J = 2.4 Hz), 6.68 (t, 1 H, J = 6.7 Hz), 5.92 (s, 2 H), 2.79-2.74 (m, 1 H), 0.83 -0.79 (m, 2 H), 0.76-0.71 (m, 2 H).
202	A	A	575.6	1H NMR (400 MHz, dmso) δ 5.656 (s, 2H), 6.546 (t, 1H, J = 7.3 Hz), 6.60-6.69 (m, 2H), 6.729 (d, 1H, J = 7.3 Hz),6.979 (t, 1H, J = 7.3 Hz), 7.066 (d, 1H, J = 2.2 Hz), 6.95-7.00 (m, 1H), 7.22-7.3 (m, 2H), 7.445 (d, 1H, J = 11

				Hz), 7.480 (dd, 1H, J = 8, 1.5 Hz), 7.70-7.756 (m, 1H), 7.87-7.91 (m, 2H).
204	A	A	577.0	1H NMR (400 MHz, D6-dmso), δ 12.70 (d, 1 H, J = 4.9 Hz), 12.45 (d, 1 H) 8.04 (dd, 1 H, J = 1.8 & 6.7 Hz), 7.96 (d, 1 H, J = 9.2 Hz), 7.87 (d, 1 H, J = 2.4 Hz), 7.79-7.75 (m, 2 H), 7.70 (t, 1 H, J = 6.7 Hz), 7.59-7.52 (m, 3 H), 7.34 (s, 1 H), 7.00 (d, 1 H, J = 2.4 Hz), 6.66 (t, 1 H, J = 6.7 Hz), 5.92 (s, 2 H), 2.52 (s, 6 H).
205	A	A	581.0	1H NMR (400 MHz, dmso) δ 0.82-0.92 (m, 4H), 2.78-2.86 (m, 1H), 5.907 (s, 2H), 6.664 (t, 1H, J = 6.6 Hz), 6.714 (s, 1H), 7.109 (d, 1H, J = 2.2 Hz), 7.445 (d, 1H, J = 11 Hz), 7.731 (br s, 1H), 7.953 (d, 1H, J = 2.2 Hz), 7.97-8.03 (m, 2H), 9.087 (br s, 1H).

#	IC50	EC50	LR-MS (M+H)	DATA
206	A	B	581.6	1H NMR (400 MHz, D6-dmso), d, 12.75 (s, 1H), 12.70 (d, 1 H, J = 4.9 Hz), 8.38 (d, 1 H, J = 4.3 Hz), 7.96 (dd, 1 H, J = 2.4 & 7.3 Hz), 7.93 (d, 1 H, J = 2.4 Hz), 7.78-7.43 (m, 1 H), 7.69 (dt, 1 H, J = 1.8 & 6.1 Hz), 7.55 (d, 1 H, J = 10.4 Hz), 7.51 (d, 1 H, J = 7.3 Hz), 7.29 (t, 1 H, J = 9.1 Hz), 7.10 (d, 1 H, J = 1.8 Hz), 6.63 (t, 1 H, J = 6.1 Hz), 5.80 (s, 2 H), 3.23 (s, 3 H), 2.75-2.69 (m, 1 H), 0.65-0.60 (m, 2 H), 0.51-0.46 (m, 2 H).
207	A	A	584.6	1H NMR (400 MHz, d6-DMSO): ? 12.71 (s, 1H), 12.67 (s, 1H), 7.94 (dd, J = 2.0, 6.8 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.70 (m, 1H), 7.54 (d, J = 10.8 Hz, 1H), 7.26 (m, 1H), 7.13 (dd, J = 8.4, 10.0 Hz, 1H), 7.09 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 2.0, 7.2 Hz, 1H), 6.62 (t, J = 6.8 Hz, 1H), 5.80 (s, 2 H), 4.37 (t, J = 6.0 Hz, 1H), 3.26 (d, J = 6.4 Hz, 2H), 2.86 (m, 1H), 0.95-0.92 (M, 4H)
208	A	A	588.5	1H NMR (400 MHz, dmso) δ 3.253 (s, 3H), 5.857 (s, 2H), 6.597 (t, 1H, J = 6.6 Hz), 7.076 (d, 1H, J = 2.2 Hz), 7.242 (dd, 1H, J = 8.8, 1.5 Hz), 7.456 (s,1H), 7.558 (d, 1H, J = 11 Hz), 7.653 (d, 2H, J = 8 Hz), 7.912 (d, 1H, J = 2.2 Hz), 7.959 (dd, 1H, J = 7.3, 2.2 Hz)
209	A	A	591.1	1H NMR (400 MHz, d6-DMSO): d, 9.34 (s, 1 H), 8.09 (d, J = 9.2 Hz, 1 H), 8.02-8.01 (m, 1 H), 7.98 (d, J = 8.8 Hz, 1 H), 7.85-7.77 (m, 3 H), 7.72-7.70 (m, 1 H), 7.57 (t, J = 7.0 Hz, 1 H), 7.40 (s, 1 H), 6.64 (t, J = 6.0 Hz, 1 H), 6.00 (s, 2 H), 2.79-2.76 (m, 1 H), 0.81-0.74 (m, 4 H).
210	A	B	592.0	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 8.34 (d, 1 H, J = 8.8 Hz), 8.08 (d, 1 H, J = 8.0 Hz), 8.02 (d, 1 H, J = 8.4 Hz), 7.96 (d, 1 H, J = 2.4 Hz), 7.91 (t, 1 H, J = 7.2 Hz), 7.79 (t, 1 H, J =8.0 Hz), 7.72 (t, 1 H, J = 4.0 Hz), 7.52 (d, 1 H, J = 10.4 Hz), 7.11 (d, 1 H, J = 2.0 Hz), 6.66 (t, 1 H, J = 6.4 Hz), 6.32 (s, 1 H), 6.30 (s, 2 H), 2.74-2.69 (m, 1

				H), 0.85 (b, 2 H), 0.75 (b, 2 H).
211	A	A	592.0	
212	A	A		See Example 15 for Experimental Details and Data
213	A	A	594.0	1H NMR (500 MHz, DMSO): δ 8.07 (dd, 1H, J= 1.89 Hz), 7.98 (m,2H), 7.80 (m, 2H), 7.74(m, 1H), 7.65 (d, 1H, J= 10.7Hz), 7.58 (t, 1H, J = 8.19 Hz), 7.14 (d, 1H, J = 2.2 Hz), 6.69 (t, 1H, J = 6.3 Hz), 5.93 (s, 2H), 3.16 (t, 2H, J= 7.5 Hz), 1.23 (p, 2H), 0.60 (t, 3H). M.S. found: 593.3 (M)+.
215	A	A	595.0	1H NMR (400 MHz, D6-dmso), δ, 12.70 (d, 1 H, J = 5.5 Hz), 12.38 (d, 1 H) 8.03 (dd, 1 H, J = 1.8 & 7.3 Hz), 7.97-7.95 (m, 2 H), 7.79-7.74 (m, 2 H), 7.70 (dt, 1 H, J = 1.2 & 6.1 Hz), 7.61 (d, 1 H, J.= 11.0 Hz) 7.56 (dt, 1 H, J = 7.3 & 1.2 H), 7.33 (s, 1 H), 7.11 (d, 1 H, J = 1.8 Hz), 6.65 (t, 1 H, J = 6.7 Hz), 5.89 (s, 2 H), 2.48 (s, 6 H).
216	A	A	596.1	1H-NMR (400 MHz, in dmso-d6): δ 12.96 (1H, broad s), 11.76 (1H, broad s), 7.95 (1H, d, J = 8.79 Hz), 7.74 (2H, m), 7.58 H1H, dd, J = 4.39, 7.32 Hz), 7.50 (1H, dd, J = 7.32, 8.06 Hz), 7.35 (1H, s), 7.26 (1H, d, J = 10.25 Hz), 6.63 (2H, s), 6.02 (2H, s), 5.01 (2H, t, J = 8.79 Hz), 3.40 (2H, t, J = 8.79 Hz), 1.21 (6H, d, J = 6.6 Hz)
218	A	C	599.4	1H NMR (400 MHz, D6-dmso), δ above 12 (2 H), 7.95 (d, 1 H, J = 6.0 Hz), 7.92 (dd, 1 H, J = 1.2 & 2.4 Hz), 7.79 (d, 1 H, J = 10.4 Hz), 7.70-7.66 (b, 1 H), 7.57 (d, 1 H, J = 7.6 Hz), 7.49 (d, 1 H, J = 8.0 Hz), 7.14 (dt, 1 H, J = 0.8 & 7.6 Hz), 7.10 (dd, 1 H, J = 0.8 & 2.0 Hz), 6.84 (s, 1 H), 6.60 (t, 1 H, J = 7.6 Hz), 5.99 (s, 2 H), 3.15 (s, 3 H).
219	C	A	603.0	1H NMR (400 MHz, cdcl3) δ 1.232 (s, 9H), 5.940 (s, 2H), 6.094 (s, 2H), 6.705-6.752 (m, 1H), 6.819 (d, 1H, J = 9.5 Hz), 6.911 (d, 1H, J = 2.2 Hz), 7.382 (s, 1H), 7.418-7.437 (m, 1H), 7.494 (d, 1H, J = 2.2 Hz), 7.565 (d, 1H, J = 7.3 Hz), 7.65-7.71 (m, 1H), 7.871 (dd, 1H, J = 6.6, 1.5 Hz), 8.02 (d, 1H, J = 8 Hz), 8.06-8.11 (m, 1H)
221	A	C	607.6	1H NMR (400 MHz, D6-dmso), δ 12.76 (d, 1 H, J = 5.6 Hz) 12.74 (s, 1H), 8.39 (d, 1 H, J = 4.0 Hz), 7.95 (dd, 1 H, J = 2.0 & 6.8 Hz), 7.92 (d, 1 H, J = 2.4 Hz), 7.78-7.43 (m, 1 H), 7.71 (dt, 1 H, J = 1.6 & 6.0 Hz), 7.57 (d, 1 H, J = 10.8 Hz), 7.53 (dd, 1 H, J = 2.0 & 7.2 Hz), 7.28 (dd, 1 H, J = 1.2 & 8.8 Hz), 7.09 (d, 1 H, J = 2.4 Hz), 6.64 (t, 1 H, J = 6.4 Hz), 5.80 (s, 2 H), 2.92-2.86 (m, 1 H), 2.72 (m, 1H), 0.95 (s, 2 H), 0.94 (m, 2 H), 0.65-0.61 (m, 2 H), 0.50-0.47 (m, 2 H).
222	A	A	614.6	1H NMR (400 MHz, dmso) δ 0.93-0.97 (m, 4H), 2.47-2.495 (m, 1H), 5.88 (s, 2H), 6.615 (t, 1H, J = 6.6 Hz), 7.077 (d, 1H, J = 2.2 Hz), 7.248 (dd, 1H, J = 8.8, 1.5 Hz), 7.471 (s, 1H), 7.607 (d, 1H, J = 11 H), 7.635-7.715 (m, 2H), 7.904 (d, 1H, J = 2.2 Hz), 7.948 (dd, 1H, J = 7.3, 2.2 Hz)

223	A	A	643.1	1H NMR (400 MHz, dmso) δ 4.09-4.14 (m, 2H), 5.703 (s, 2H), 6.28-6.35 (m, 1H), 6.538 (d, 1H, J = 8.8Hz), 6.66-6.74 (m, 1H), 7.06-7.13 (m, 2H), 7.26-7.34 (m, 2H), 7.48 (d, 1H, J = 11 Hz), 7.52-7.58 (m, 1H), 7.64-7.72 (m, 2H), 7.72-7.8 (m, 2H), 7.91-8.04 (m, 2H)
225	A	B	671.7	1H NMR (400 MHz, D6-dmso), δ, 12.76 (s, 2 H) 12.13 (s, 1H), 7.96-7.92 (m, 3 H), 7.71 (bs, 1 H), 7.66 (d, 1 H, J = 6.8 Hz), 7.60 (d, 1 H, J = 10.8 Hz), 7.38 (t, 1 H, J = 8.0 Hz), 7.10 (s, 1 H), 6.38 (t, 1 H, J = 7.6 Hz), 5.84 (s, 2 H), 3.09-3.01 (m, 1 H), 2.90-2.83 (m, 1H), 1.16-1.05 (m, 4 H), 1.00-0.90 (m, 4 H)
226	C	A	680.7	1H NMR (500 MHz, CDCl3): δ 8.02 (s, 1H), 7.72 (dd, J = 7.25 Hz, J = 2.21 Hz, 1H), 7.63 (dd, J = 7.25 Hz, J = 2.21 Hz, 1H), 7.52 (d, J = 2.20 Hz, 1H), 6.905 (d, J = 2.20 Hz, 1H), 6.85 (d, J = 9.8 Hz 1H), 6.37 (t, J = 6.9 Hz 1H), 6.01 (s, 2H), 5.99 (s, 1H), 5.84 (s, 2H), 5.79 (s, 2H), 3.79 (s, 3H), 1.244(s, 9H), 1.135 (s, 9H).
227	C	A	740.8	1H NMR (500 MHz, CDCl3) δ 8.50 (s, 1H), 7.96 (m, 2H), 7.73 (m, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.11 (s, 1H), 6.67 (m, 1H), 6.53 (s, 1H), 5.91 (s, 1H), 5.77 (s, 2H), 1.16 (m, 18H), 0.98 (m, 4H)
228	C	A	780.8	M.S. found: 780.4 (M+H)+; 1H NMR (500 MHz, CDCl3): δ 7.69 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7.63 (dd, J = 2.2 Hz, J = 6.9 Hz, 1H), 7. 56 - m, 2H), d, J = 2.2 Hz, 1H), 6.83 (d, J = 9.8 Hz, 1H), 6.37 (t, J = 6.9 Hz, 1H), 6.01 (m, 2H), 5.81-5.77 (m, 4H), 5.75 (s, 2H), 5.70 (m, 1H), 1.26-1.22 (m, 18H), 1.16 (s, 9H).
231	A	A		See Example 16 for Experimental Details and Data

Uses of the Compounds of Formula (I)

The Compounds of Formula (I) are useful in human and veterinary medicine for treating or preventing a viral infection or a virus-related disorder in a patient. In accordance with the invention, the Compounds of Formula (I) can be administered to a patient in need of treatment or prevention of a viral infection or a virus-related disorder.

Accordingly, in one embodiment, the invention provides methods for treating a viral infection in a patient comprising administering to the patient an effective amount of at least one Compound of Formula (I) or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof. In another embodiment, the invention provides methods for treating a virus-related disorder in a patient comprising administering to the patient an effective amount of at least one

Compound of Formula (I) or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Viral Infection

The Compounds of Formula (I) can be used to treat or prevent a viral infection. In one embodiment, the Compounds of Formula (I) can be inhibitors of viral replication. In a specific embodiment, the Compounds of Formula (I) can be inhibitors of HCV replication. Accordingly, the Compounds of Formula (I) are useful for treating viral diseases and disorders related to the activity of a virus, such as HCV polymerase.

Examples of viral infections that can be treated or prevented using the present methods, include but are not limited to, hepatitis A infection, hepatitis B infection and hepatitis C infection.

In one embodiment, the viral infection is hepatitis C infection.

In one embodiment, the hepatitis C infection is acute hepatitis C. In another embodiment, the hepatitis C infection is chronic hepatitis C.

The compositions and combinations of the present invention can be useful for treating a patient suffering from infection related to any HCV genotype. HCV types and subtypes may differ in their antigenicity, level of viremia, severity of disease produced, and response to interferon therapy as described in Holland *et al.*, *Pathology*, 30(2):192-195 (1998). The nomenclature set forth in Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) is widely used and classifies isolates into six major genotypes, 1 through 6, with two or more related subtypes, e.g., 1a, 1b. Additional genotypes 7-10 and 11 have been proposed, however the phylogenetic basis on which this classification is based has been questioned, and thus types 7, 8, 9 and 11 isolates have been reassigned as type 6, and type 10 isolates as type 3 (see Lamballerie *et al, J Gen Virol*, 78(Pt1):45-51 (1997)). The major genotypes have been defined as having sequence similarities of between 55 and 72% (mean 64.5%), and subtypes within types as having 75%-86% similarity (mean 80%) when sequenced in the NS-5 region (see Simmonds *et al.*, *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Treatment or Prevention of a Virus-Related Disorder

The Compounds of Formula (I) can be used to treat or prevent a virus-related disorder. Accordingly, the Compounds of Formula (I) are useful for treating disorders related to the

activity of a virus, such as liver inflammation or cirrhosis. Virus-related disorders include, but are not limited to, RNA-dependent polymerase-related disorders and disorders related to HCV infection.

Treatment or Prevention of a RNA-Dependent Polymerase-Related Disorder

The Compounds of Formula (I) are useful for treating or preventing a RNA dependent polymerase (RdRp) related disorder in a patient. Such disorders include viral infections wherein the infective virus contain a RdRp enzyme.

Accordingly, in one embodiment, the present invention provides a method for treating a RNA dependent polymerase-related disorder in a patient, comprising administering to the patient an effective amount of at least one Compound of Formula (I) or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Disorder Related to HCV Infection

The Compounds of Formula (I) can also be useful for treating or preventing a disorder related to an HCV infection. Examples of such disorders include, but are not limited to, cirrhosis, portal hypertension, ascites, bone pain, varices, jaundice, hepatic encephalopathy, thyroiditis, porphyria cutanea tarda, cryoglobulinemia, glomerulonephritis, sicca syndrome, thrombocytopenia, lichen planus and diabetes mellitus.

Accordingly, in one embodiment, the invention provides methods for treating an HCV-related disorder in a patient, wherein the method comprises administering to the patient a therapeutically effective amount of at least one Compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Combination Therapy

In another embodiment, the present methods for treating or preventing a viral infection can further comprise the administration of one or more additional therapeutic agents which are not Compounds of Formula (I).

In one embodiment, the additional therapeutic agent is an antiviral agent.

In another embodiment, the additional therapeutic agent is an immunomodulatory agent, such as an immunosuppressive agent.

Accordingly, in one embodiment, the present invention provides methods for treating a viral infection in a patient, the method comprising administering to the patient: (i) at least one Compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) at least one other antiviral agent that is other than a Compound of Formula (I), wherein the amounts administered are together effective to treat or prevent a viral infection.

When administering a combination therapy of the invention to a patient, the therapeutic agents in the combination, or a pharmaceutical composition or compositions comprising the therapeutic agents, may be administered in any order such as, for example, sequentially, concurrently, together, simultaneously and the like. The amounts of the various actives in such combination therapy may be different amounts (different dosage amounts) or same amounts (same dosage amounts). Thus, for non-limiting illustration purposes, a Compound of Formula (I) and an additional therapeutic agent may be present in fixed amounts (dosage amounts) in a single dosage unit (e.g., a capsule, a tablet and the like). A commercial example of such single dosage unit containing fixed amounts of two different active compounds is VYTORIN® (available from Merck Schering-Plough Pharmaceuticals, Kenilworth, New Jersey).

In one embodiment, the at least one Compound of Formula (I) is administered during at time when the additional antiviral agent(s) exert their prophylactic or therapeutic effect, or *vice versa*.

In another embodiment, the at least one Compound of Formula (I) and the additional antiviral agent(s) are administered in doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In another embodiment, the at least one Compound of Formula (I) and the additional antiviral agent(s) are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In still another embodiment, the at least one Compound of Formula (I) and the additional antiviral agent(s) act synergistically and are administered in doses lower than the doses commonly employed when such agents are used as monotherapy for treating a viral infection.

In one embodiment, the at least one Compound of Formula (I) and the additional antiviral agent(s) are present in the same composition. In one embodiment, this composition is suitable for oral administration. In another embodiment, this composition is suitable for intravenous administration.

Viral infections and virus-related disorders that can be treated or prevented using the combination therapy methods of the present invention include, but are not limited to, those listed above.

In one embodiment, the viral infection is HCV infection.

The at least one Compound of Formula (I) and the additional antiviral agent(s) can act additively or synergistically. A synergistic combination may allow the use of lower dosages of one or more agents and/or less frequent administration of one or more agents of a combination therapy. A lower dosage or less frequent administration of one or more agents may lower toxicity of the therapy without reducing the efficacy of the therapy.

In one embodiment, the administration of at least one Compound of Formula (I) and the additional antiviral agent(s) may inhibit the resistance of a viral infection to these agents.

Non-limiting examples of other therapeutic agents useful in the present compositions and methods include an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, an antisense agent, a therapeutic vaccine, a viral protease inhibitor, a virion production inhibitor, an antibody therapy (monoclonal or polyclonal), and any agent useful for treating an RNA-dependent polymerase-related disorder.

In one embodiment, the other antiviral agent is a viral protease inhibitor.

In another embodiment, the other antiviral agent is an HCV protease inhibitor.

In another embodiment, the other antiviral agent is an interferon.

In still another embodiment, the other antiviral agent is a viral replication inhibitor.

In another embodiment, the other antiviral agent is an antisense agent.

In another embodiment, the other antiviral agent is a therapeutic vaccine.

In a further embodiment, the other antiviral agent is an virion production inhibitor.

In another embodiment, the other antiviral agent is antibody therapy.

In another embodiment, the other antiviral agents comprise a protease inhibitor and a polymerase inhibitor.

In still another embodiment, the other antiviral agents comprise a protease inhibitor and an immunosuppressive agent.

In yet another embodiment, the other antiviral agents comprise a polymerase inhibitor and an immunosuppressive agent.

In a further embodiment, the other antiviral agents comprise a protease inhibitor, a polymerase inhibitor and an immunosuppressive agent.

In another embodiment the other agent is ribavirin.

HCV polymerase inhibitors useful in the present methods and compositions include, but are not limited to VP-19744 (Wyeth/ViroPharma), HCV-796 (Wyeth/ViroPharma), NM-283 (Idenix/Novartis), R-1626 (Roche), MK-0608 (Merck), A848837 (Abbott), GSK-71185 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), and those disclosed in Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); and Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Interferons useful in the present methods and compositions include, but are not limited to, interferon alfa-2a, interferon alfa-2b, interferon alfacon-1 and PEG-interferon alpha conjugates. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, Hoffman La-Roche, Nutley, New Jersey) in the form of pegylated interferon alpha-2a (*e.g.*, as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (*e.g.*, as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, Boehringer Ingelheim, Ingelheim, Germany), interferon alpha fusion polypeptides, or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, Amgen, Thousand Oaks, California).

Antibody therapy agents useful in the present methods and compositions include, but are not limited to, antibodies specific to IL-10 (such as those disclosed in US Patent Publication No. US2005/0101770, humanized 12G8, a humanized monoclonal antibody against human IL-10, plasmids containing the nucleic acids encoding the humanized 12G8 light and heavy chains were deposited with the American Type Culture Collection (ATCC) as deposit numbers PTA-5923 and PTA-5922, respectively), and the like). Viral protease inhibitors useful in the present methods and compositions include, but are not limited to, NS3 serine protease inhibitors (including, but are not limited to, those disclosed in U.S. Patent Nos. 7,012,066, 6,914,122, 6,911,428, 6,846,802, 6,838,475, 6,800,434, 5,017,380, 4,933,443, 4,812,561 and 4,634,697; and U.S. Patent Publication Nos. US20020160962, US20050176648 and US20050249702), HCV protease inhibitors (*e.g.*, SCH503034 (Schering-Plough), VX-950 (Vertex), GS-9132 (Gilead/Achillion), ITMN-191 (InterMune/Roche)), amprenavir,

atazanavir, fosemprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir and TMC114.

Viral replication inhibitors useful in the present methods and compositions include, but are not limited to, NS3 helicase inhibitors, NS5A inhibitors, ribavirin, viramidine, A-831 (Arrow Therapeutics); an antisense agent or a therapeutic vaccine.

In one embodiment, viral replication inhibitors useful in the present methods and compositions include, but are not limited to, NS3 helicase inhibitors or NS5A inhibitors.

Examples of protease inhbitors useful in the present methods include, but are not limited to, an HCV protease inhibitor and a NS-3 serine protease inhbitor.

Examples of HCV protease inhbitors useful in the present methods include, but are not limited to, those disclosed in Landro *et al.*, *Biochemistry*, 36(31):9340-9348 (1997); Ingallinella *et al.*, *Biochemistry*, 37(25):8906-8914 (1998); Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, 8(13):1713-1718 (1998); Martin *et al.*, *Biochemistry*, 37(33):11459-11468 (1998); Dimasi *et al.*, *J Virol*, 71(10):7461-7469 (1997); Martin *et al.*, *Protein Eng*, 10(5):607-614 (1997); Elzouki *et al.*, *J Hepat*, 27(1):42-48 (1997); *BioWorld Today*, 9(217):4 (November 10, 1998); and

International Publication Nos. WO 98/14181; WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734.

Further examples of protease inhibitors useful in the present methods include, but are not limited to,

Additional examples of other therapeutic agents useful in the present methods include, but are not limited to, Levovirin™ (ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (Ribozyme Pharmaceuticals, Boulder, Colorado), VX-950™ (Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), NKB-122 (JenKen Bioscience Inc., North Carolina), mycophenolate mofetil (Hoffman-LaRoche, Nutley, New Jersey).

The doses and dosage regimen of the other agents used in the combination therapies of the present invention for the treatment or prevention of a viral infection can be determined by the attending clinician, taking into consideration the the approved doses and dosage regimen in the package insert; the age, sex and general health of the patient; and the type and severity of

the viral infection or related disease or disorder. When administered in combination, the Compound of Formula (I)(s) and the other agent(s) for treating diseases or conditions listed above can be administered simultaneously (*i.e.*, in the same composition or in separate compositions one right after the other) or sequentially. This is particularly useful when the components of the combination are given on different dosing schedules, *e.g.*, one component is administered once daily and another every six hours, or when the preferred pharmaceutical compositions are different, *e.g.* one is a tablet and one is a capsule. A kit comprising the separate dosage forms is therefore advantageous.

Generally, a total daily dosage of the at least one Compound of Formula (I) and the additional antiviral agent(s), when administered as combination therapy, can range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the dosage is from about 10 to about 500 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 1 to about 100 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 1 to about 50 mg/day, administered in a single dose or in 2-4 divided doses. In a further embodiment, the dosage is from about 1 to about 20 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 500 to about 1500 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 1000 mg/day, administered in a single dose or in 2-4 divided doses. In yet another embodiment, the dosage is from about 100 to about 500 mg/day, administered in a single dose or in 2-4 divided doses.

In one embodiment, when the other therapeutic agent is INTRON-A interferon alpha 2b (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 3MIU(12 mcg)/0.5mL/TIW is for 24 weeks or 48 weeks for first time treatment.

In another embodiment, when the other therapeutic agent is PEG-INTRON interferon alpha 2b pegylated (commercially available from Schering-Plough Corp.), this agent is administered by subcutaneous injection at 1.5 mcg/kg/week, within a range of 40 to 150 mcg/week, for at least 24 weeks.

In another embodiment, when the other therapeutic agent is ROFERON A inteferon alpha 2a (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous or intramuscular injection at 3MIU(11.1 mcg/mL)/TIW for at least 48 to 52 weeks, or alternatively 6MIU/TIW for 12 weeks followed by 3MIU/TIW for 36 weeks.

In still another embodiment, when the other therapeutic agent is PEGASUS interferon alpha 2a pegylated (commercially available from Hoffmann-La Roche), this agent is administered by subcutaneous injection at 180mcg/1mL or 180mcg/0.5mL, once a week for at least 24 weeks.

In yet another embodiment, when the other therapeutic agent is INFERGEN interferon alphacon-1 (commercially available from Amgen), this agent is administered by subcutaneous injection at 9mcg/TIW is 24 weeks for first time treatment and up to 15 mcg/TIW for 24 weeks for non-responsive or relapse treatment.

In a further embodiment, when the other therapeutic agent is Ribavirin (commercially available as REBETOL ribavirin from Schering-Plough or COPEGUS ribavirin from Hoffmann-La Roche), this agent is administered at a daily dosage of from about 600 to about 1400 mg/day for at least 24 weeks.

Compositions and Administration

Due to their activity, the Compounds of Formula (I) are useful in veterinary and human medicine. As described above, the Compounds of Formula (I) are useful for treating or preventing a viral infection or a virus-related disorder in a patient in need thereof.

When administered to a patient, the IDs can be administered as a component of a composition that comprises a pharmaceutically acceptable carrier or vehicle. The present invention provides pharmaceutical compositions comprising an effective amount of at least one Compound of Formula (I) and a pharmaceutically acceptable carrier. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as

lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate.

Liquid form preparations include solutions, suspensions and emulsions and may include water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The Compounds of Formula (I) of the present invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, *i.e.* anti-inflammatory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

In one embodiment, the one or more Compounds of Formula (I) are administered orally.

In another embodiment, the one or more Compounds of Formula (I) are administered intravenously.

In another embodiment, the one or more Compounds of Formula (I) are administered topically.

In still another embodiment, the one or more Compounds of Formula (I) are administered sublingually.

In one embodiment, a pharmaceutical preparation comprising at least one Compound of Formula (I) is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present compositions can contain, in one embodiment, from about 0.1% to about 99% of the Compound of Formula (I)(s) by weight or volume. In various embodiments, the the present compositions can contain, in one embodiment, from about 1% to about 70% or from about 5% to about 60% of the Compound of Formula (I)(s) by weight or volume.

The quantity of Compound of Formula (I) in a unit dose of preparation may be varied or adjusted from about 0.1 mg to about 2000 mg. In various embodiment, the quantity is from about 1 mg to about 2000 mg, 100 mg to about 200 mg, 500 mg to about 2000 mg, 100 mg to about 1000 mg, and 1 mg to about 500 mg.

For convenience, the total daily dosage may be divided and administered in portions during the day if desired. In one embodiment, the daily dosage is administered in one portion. In another embodiment, the total daily dosage is administered in two divided doses over a 24

hour period. In another embodiment, the total daily dosage is administered in three divided doses over a 24 hour period. In still another embodiment, the total daily dosage is administered in four divided doses over a 24 hour period.

The amount and frequency of administration of the Compounds of Formula (I) will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. Generally, a total daily dosage of the Compounds of Formula (I) range from about 0.1 to about 2000 mg per day, although variations will necessarily occur depending on the target of the therapy, the patient and the route of administration. In one embodiment, the dosage is from about 1 to about 200 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 10 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In another embodiment, the dosage is from about 100 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses. In still another embodiment, the dosage is from about 500 to about 2000 mg/day, administered in a single dose or in 2-4 divided doses.

The compositions of the invention can further comprise one or more additional therapeutic agents, selected from those listed above herein. Accordingly, in one embodiment, the present invention provides compositions comprising: (i) at least one Compound of Formula (I) or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; (ii) one or more additional therapeutic agents that are not a Compound of Formula (I); and (iii) a pharmaceutically acceptable carrier, wherein the amounts in the composition are together effective to treat a viral infection or a virus-related disorder.

Kits

In one aspect, the present invention provides a kit comprising a therapeutically effective amount of at least one Compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

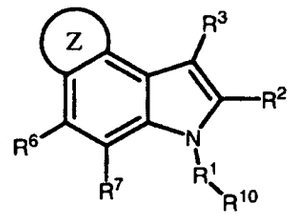
In another aspect the present invention provides a kit comprising an amount of at least one Compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts of the two or more ingredients result in a desired therapeutic effect.

The present invention is not to be limited by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparant to those skilled in the art and are intended to fall within the scope of the appended claims.

A number of references have been cited herein, the entire disclosures of which are incorporated herein by reference.

WHAT IS CLAIMED IS:

1. A compound having the formula:



(I)

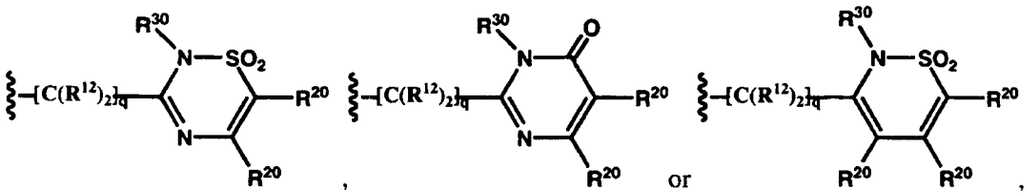
and pharmaceutically acceptable salts and solvates thereof,

wherein

ring Z, of formula (I), is a cyclopentyl, cyclopentenyl, 5-membered heterocycloalkyl, 5-membered heterocycloalkenyl or 5-membered heteroaryl ring, wherein ring Z may be: (i) optionally substituted on one or more ring carbon atoms with substituents, which are the same or different, and which are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$; and/or (ii) optionally substituted on a ring nitrogen atom with substituents, which are the same or different, and which are selected from alkyl, aryl, haloalkyl, heteroaryl, hydroxyalkyl, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_r-OR^9$, $-[C(R^{12})_2]_r-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$;

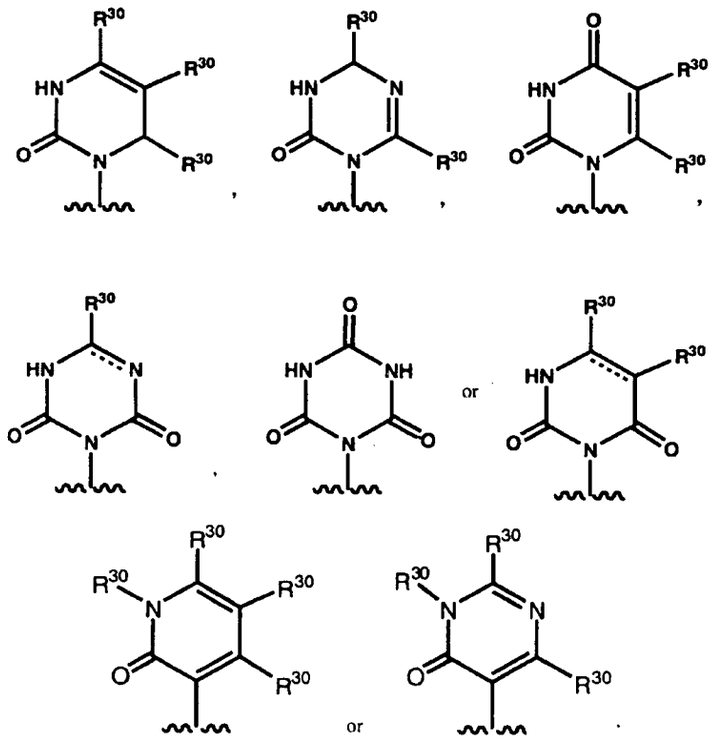
R^1 is a bond, $-[C(R^{12})_2]_r-$, $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$, or $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$;

R^2 is $-C(O)R^9$, $-C(O)OR^9$, $-C(O)OCH_2OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)N(R^9)C=N(R^9)_2$, $-[C(R^{12})_2]_q-$aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heteroaryl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$, alkyl,



wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl, group can be optionally substituted with up to 4 substituents, which are each independently selected from alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ and -$SO_2N(R^9)C(O)N(R^9)_2$;

R^3 is –H, -$[C(R^{12})_2]_q$-alkyl, -$[C(R^{12})_2]_q$-aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heteroaryl or -$[C(R^{12})_2]_q$-heterocycloalkenyl,



wherein an aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl or heteroaryl group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$;

R^6 and R^7 are each, independently, H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, $-[C(R^{12})_2]_q-$haloalkyl, $-[C(R^{12})_2]_q-$hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ or $-SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^8 is independently H, alkyl, alkenyl, alkynyl, $-[C(R^{12})_2]_q-$aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, haloalkyl or hydroxyalkyl;

each occurrence of R^9 is independently H, alkyl, alkenyl, alkynyl, $-[C(R^{12})_2]_q-$aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, haloalkyl or hydroxyalkyl, or two R^9 groups that are attached to a common nitrogen atom, together with the nitrogen atom to which they are attached, combine to form a heterocycloalkyl, heterocycloalkenyl or heteroaryl group;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q-$cycloalkyl, $-[C(R^{12})_2]_q-$cycloalkenyl, $-[C(R^{12})_2]_q-$heterocycloalkyl, $-[C(R^{12})_2]_q-$heterocycloalkenyl, $-[C(R^{12})_2]_q-$heteroaryl, $-[C(R^{12})_2]_q-$haloalkyl, $-[C(R^{12})_2]_q-$hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ and $-SO_2N(R^9)C(O)N(R^9)_2$, such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, aryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, heteroaryl, haloalkyl, hydroxy or hydroxyalkyl, wherein

a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from –H, alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2$alkyl, -$[C(R^{12})_2]_q$-$NHSO_2$cycloalkyl, -$[C(R^{12})_2]_q$-$NHSO_2$aryl, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ and -$SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^{12} is independently H, halo, -$N(R^9)_2$, -OR^9, alkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl group can be optionally substituted with up to 4 substituents, which are each independently selected from alkyl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)NHalkyl, -$C(O)N(alkyl)_2$, -O-alkyl, -NH_2, -NH(alkyl), -$N(alkyl)_2$, -NHC(O)alkyl, -$NHSO_2$alkyl, -SO_2alkyl or -SO_2NH-alkyl, or two R^{12} groups, together with the carbon atoms to which they are attached, join to form a cycloalkyl, heterocycloalkyl or C=O group;

each occurrence of R^{20} is independently H, alkyl, aryl, cycloalkyl, heterocycloalkyl or heteroaryl, or both R^{20} groups and the carbon atoms to which they are attached, join to form a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group wherein a cycloalkyl, cycloheteroalkyl, aryl or heteroaryl group can be substituted with up to 4 groups, which are each independently selected from alkyl, alkenyl, alkynyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ and -$SO_2N(R^9)C(O)N(R^9)_2$;

each occurrence of R^{30} is independently H, alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ or -$SO_2N(R^9)C(O)N(R^9)_2$,

or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form a -3- to 7-membered ring selected from aryl, cycloalkyl, heteroaryl and heterocycloalkyl;

each occurrence of p is independently 0, 1 or 2;

each occurrence of q is independently an integer ranging from 0 to 4; and

each occurrence of r is independently an integer ranging from 1 to 4.

2. The compound of claim 1, wherein R^1 is a bond or $-[C(R^{12})_2]_r-$.

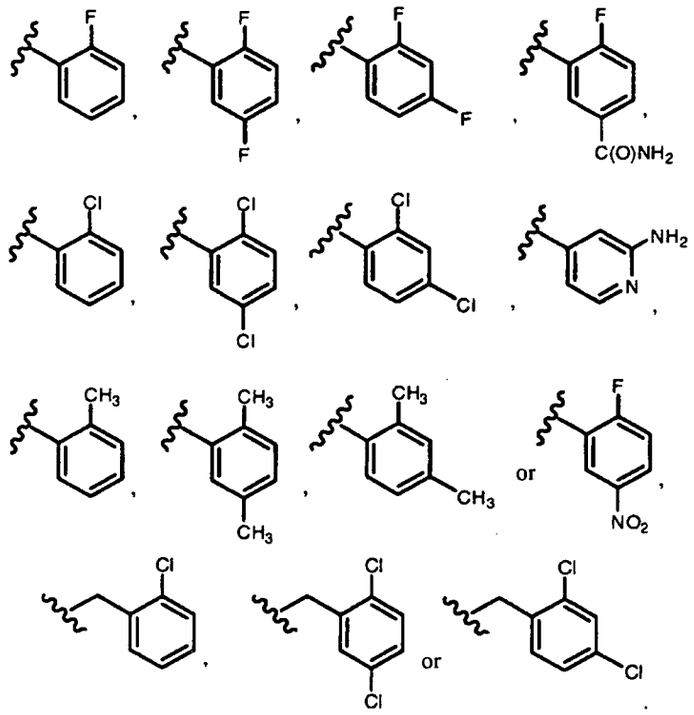
3. The compound of claim 2, wherein R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

4. The compound of claim 2, wherein R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

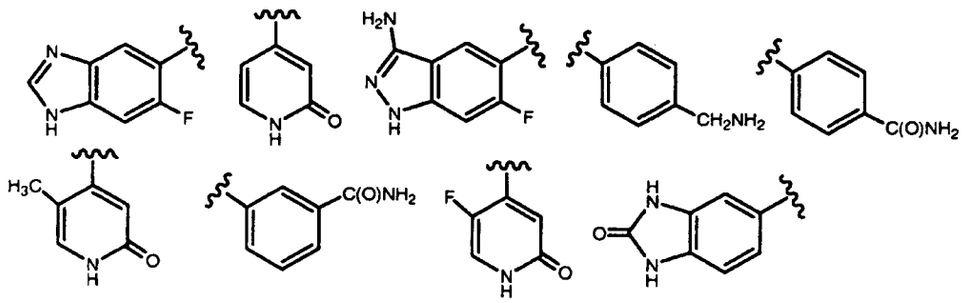
5. The compound of claim 2, wherein R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

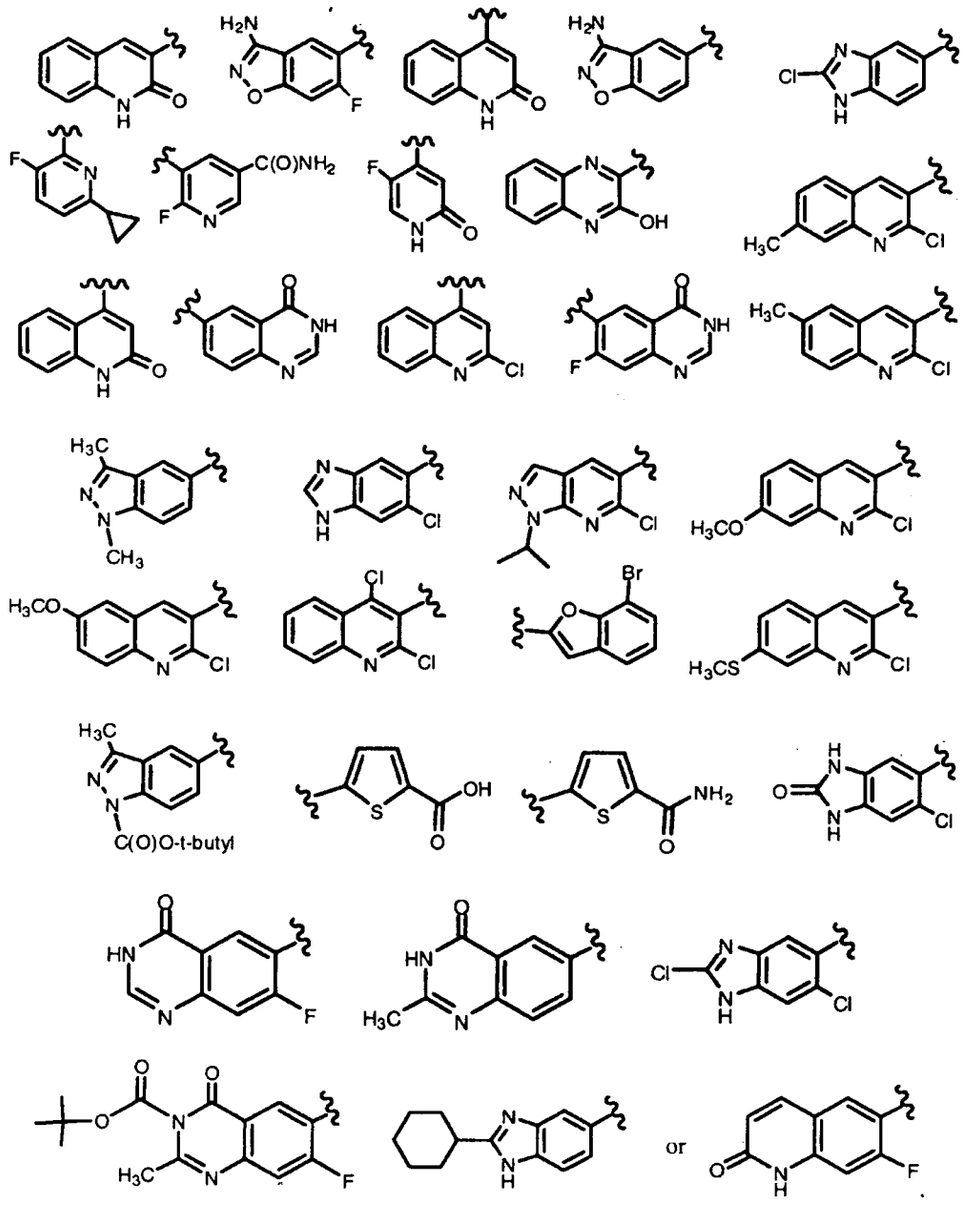
6. The compound of claim 5, wherein the R^{10} group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from methyl, cyclopropyl, halo, -OH, $-NH_2$, $-NHCH_3$ and $-N(CH_3)_2$.

7. The compound of claim 2, wherein R^{10} is:

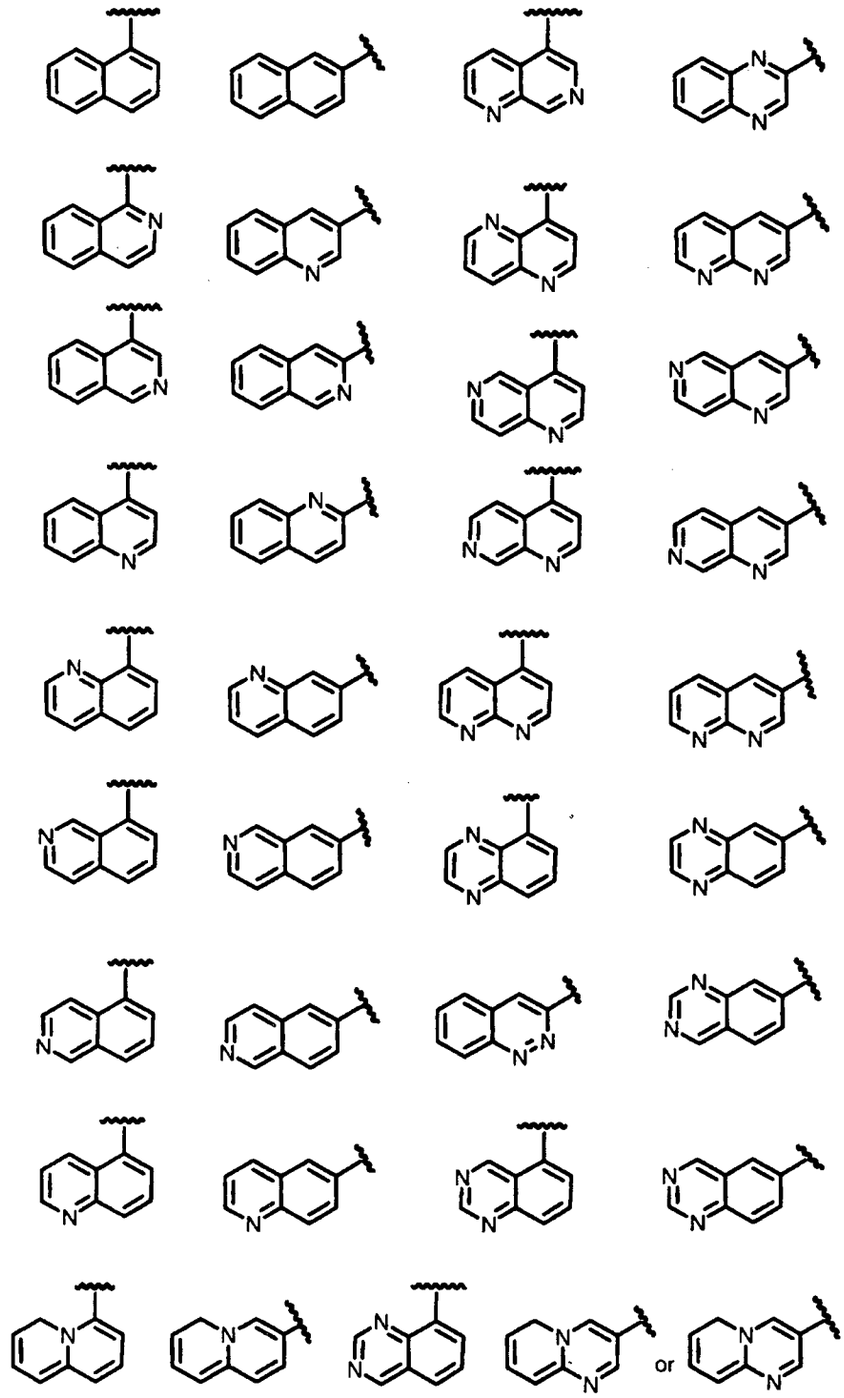


8. The compound of claim 2, wherein R^{10} is:



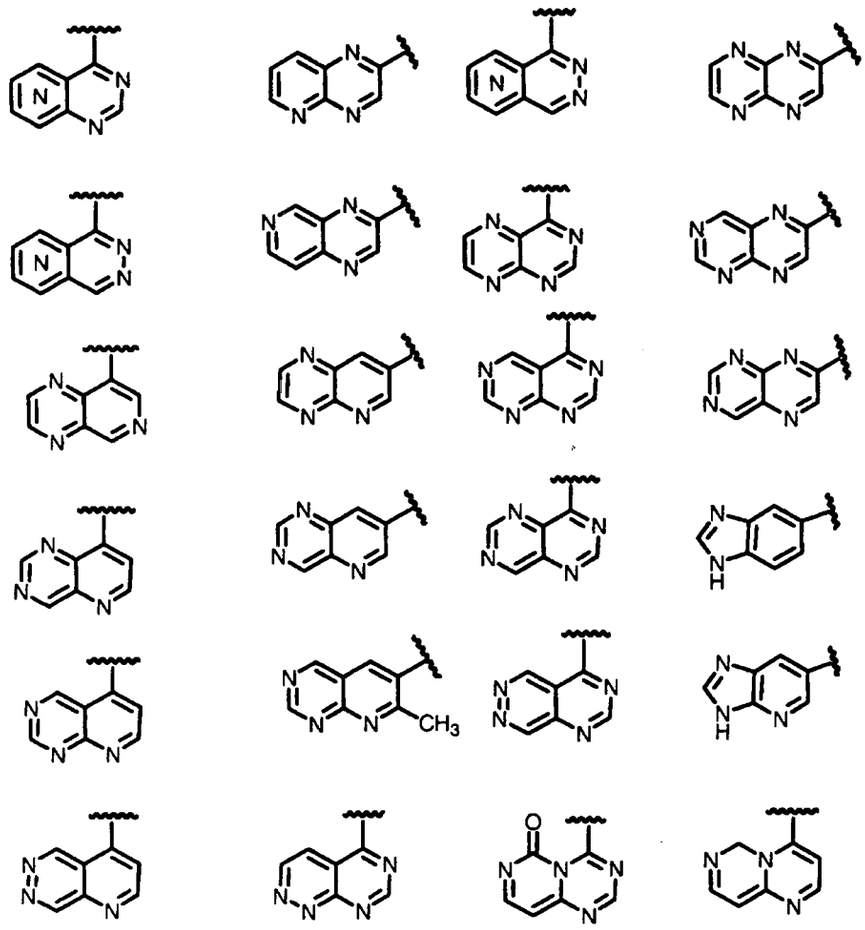


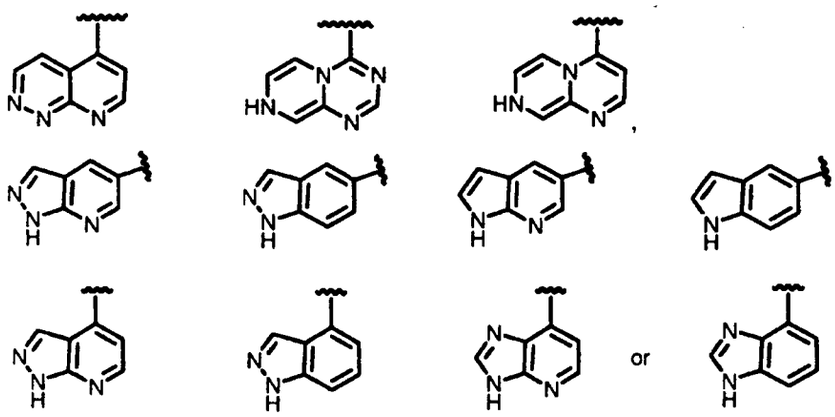
9. The compound of claim 2, wherein R^{10} is:


or

each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

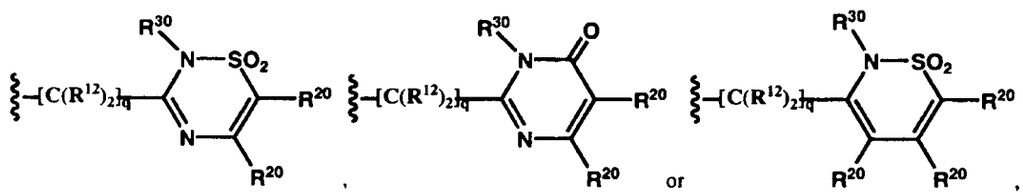
10. The compound of claim 2, wherein R^{10} is:





, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, -NH_2, -NH-alkyl, -N(alkyl)$_2$ or –$NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

11. The compound of claim 1, wherein R^2 is -C(O)OH, -C(O)Oalkyl, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)NH-cycloalkyl, -$C(O)NHSO_2R^{11}$, heteroaryl ,



wherein the arylthiazin-yl- or arylthiadiazol-yl- group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -$C(O)R^8$, -$C(O)OR^9$, -$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ or -$SO_2N(R^9)_2$; such that if Z is thiophene-yl, R^2 is other than –C(O)O-alkyl.

12. The compound of claim 4, wherein R^2 is -$C(O)NHSO_2$-alkyl, -$C(O)NHSO_2$-aryl, -$C(O)NHSO_2$-cycloalkyl or -$C(O)NHSO_2$-alkylene-cycloalkyl.

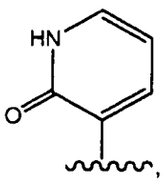
13. The compound of claim 4, wherein R^2 is -C(O)NHSO$_2$-methyl, -C(O)NHSO$_2$-ethyl, -C(O)NHSO$_2$-isopropyl, -C(O)NHSO$_2$-t-butyl, -C(O)NHSO$_2$-phenyl or -C(O)NHSO$_2$-cyclopropyl.

14. The compound of claim 4, wherein R^2 is –C(O)OH.

15. The compound of claim 1, wherein R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -C(O)N(R^9)$_2$, -N(R^9)$_2$, -O-haloalkyl, -NHC(O)NH$_2$, -NHC(O)NH-alkyl, -NHSO$_2$R^{11}, -S(O)$_2$R^{11} or -SO$_2$NHR^{11}.

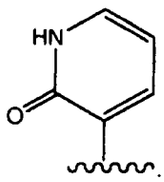
16. The compound of claim 6, wherein R^3 is pyridyl, or phenyl which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)R^8, -C(O)N(R^9)$_2$, -[C(R^{12})$_2$]$_q$-OR^9, -[C(R^{12})$_2$]$_q$-N(R^9)$_2$, or -NHC(O)R^8.

17. The compound of claim 1, wherein R^3 is phenyl, pyridyl or



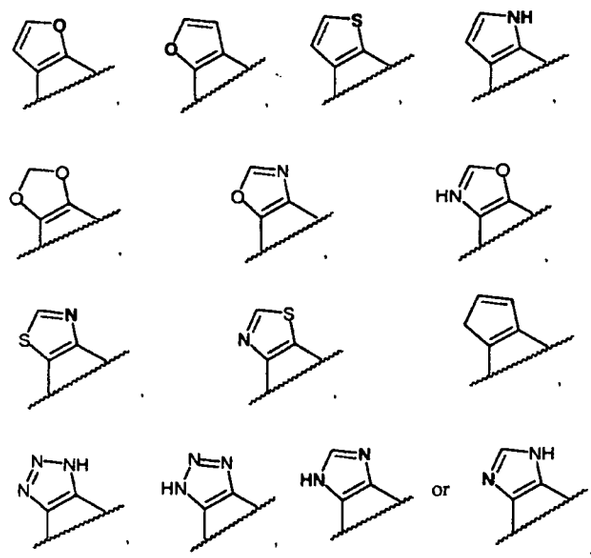
, each of which can be optionally substituted with one to 3 substituents, which are the same or different, and are selected from alkyl, -CF$_3$, -CN, -C(O)alkyl, -C(O)NH$_2$, -C(O)NHalkyl, F, Cl, -OH, -OCF$_3$, -NH$_2$, -NHalkyl, -NHC(O)NH$_2$, -NHC(O)NH-alkyl, -NHSO$_2$alkyl, -S(O)$_2$-alkyl or -SO$_2$NHalkyl.

18. The compound of claim 1, wherein R^3 is:



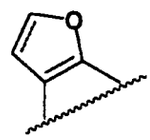
19. The compound of claim 1, wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl.

20. The compound of claim 8 wherein ring Z is:



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1.

21. The compound of claim 8 wherein ring Z is:



22. The compound of claim 1, wherein R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ or $-NHSO_2$-alkyl.

23. The compound of claim 2, wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^2 is -C(O)OH, heteroaryl, or -C(O)NHSO$_2$R^{11};

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -C(O)N(R^9)$_2$, -N(R^9)$_2$, -O-haloalkyl, -NHC(O)NH$_2$, -NHC(O)NH-alkyl, -NHSO$_2$R^{11}, -S(O)$_2$R^{11} or -SO$_2$NHR^{11};

R^6 and R^7 are each independently selected from H, alkyl, F, Cl, -CF$_3$, -OH, -O-alkyl, -OCF$_3$, -NH$_2$ or -NHSO$_2$-alkyl; and

R^{10} is phenyl, pyridyl or pyrimidinyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -OH, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO$_2$R^{11}, -S(O)$_p$R^{11} or -SO$_2$N(R^9)$_2$.

24. The compound of claim 2, wherein ring Z is a 5-membered heterocycloalkenyl or 5-membered heteroaryl;

R^2 is -C(O)OH, heteroaryl or -C(O)NHSO$_2$R^{11};

R^3 is aryl, heteroaryl or heterocycloalkenyl, each of which is unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, -C(O)alkyl, -C(O)N(R^9)$_2$, -N(R^9)$_2$, -O-haloalkyl, -NHC(O)NH$_2$, -NHC(O)NH-alkyl, -NHSO$_2$R^{11}, -S(O)$_2$R^{11} or -SO$_2$NHR^{11};

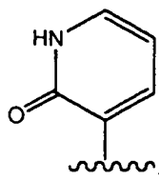
R^6 and R^7 are each independently selected from H, alkyl, F, Cl, -CF$_3$, -OH, -O-alkyl, -OCF$_3$, -NH$_2$ or -NHSO$_2$-alkyl; and

R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, -C(O)N(R^9)$_2$, -alkylene-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO$_2$R^{11}, -S(O)$_p$R^{11} or -SO$_2$N(R^9)$_2$.

25. The compound of claim 11, wherein R^2 is -C(O)OH.

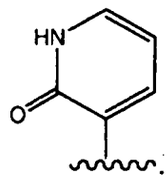
26. The compound of claim 11, wherein R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is alkyl, aryl or cycloalkyl.

27. The compound of claim 11, wherein R^3 is phenyl, pyridyl or

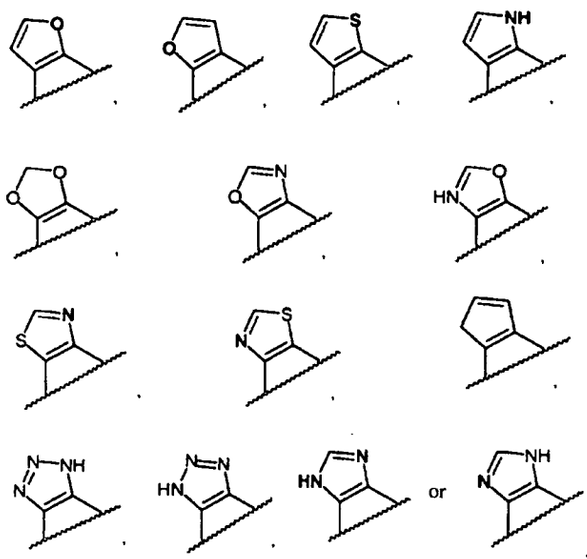


, each of which can be optionally substituted with one to 3 substituents, which are the same or different, and are selected from alkyl, $-CF_3$, -CN, -C(O)alkyl, $-C(O)NH_2$, -C(O)NHalkyl, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalkyl, $-NHC(O)NH_2$, -NHC(O)NH-alkyl, $-NHSO_2$alkyl, $-S(O)_2$-alkyl or $-SO_2$NHalkyl.

28. The compound of claim 11, wherein R^3 is:



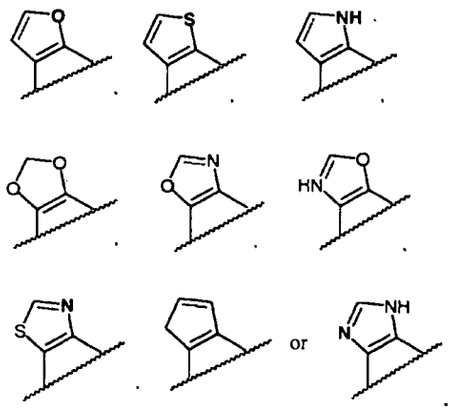
29. The compound of claim 11, wherein ring Z is:



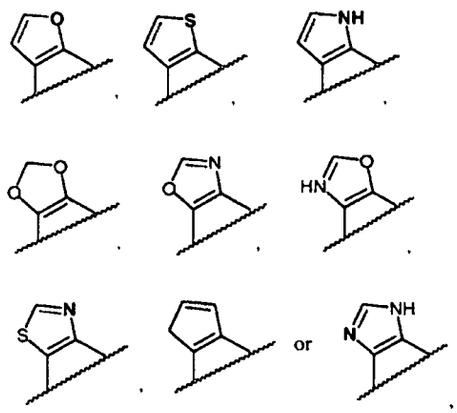
wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1.

30. The compound of claim 14, wherein ring Z can be substituted with up to 3 optional ring carbon substituents, which are the same or different, and which are selected from H, alkyl, -OH, F, Cl, -O-alkyl, $-CF_3$, $-OCF_3$ and cycloalkyl.

31. The compound of claim 15, wherein wherein ring Z is:

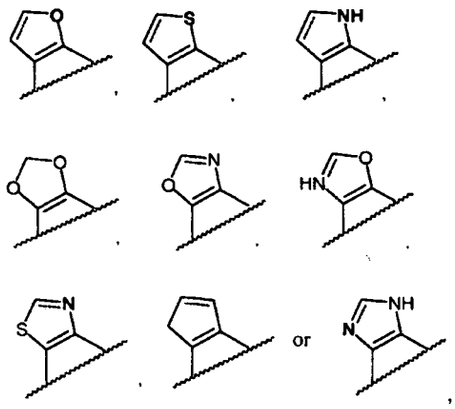


32. The compound of claim 11, wherein ring Z is



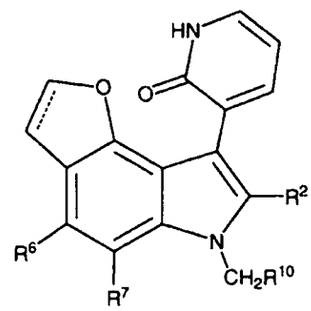
wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1.

33. The compound of claim 11, wherein ring Z is



wherein a dotted line represents an optional and additional bond, and wherein the above ring Z groups can be optionally substituted as set forth above in claim 1.

34. A compound having the formula:



(Ia)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein the dotted line indicates an optional and additional bond, and wherein:

R^2 is $-C(O)OR^9$ or $-C(O)NHSO_2R^{11}$;

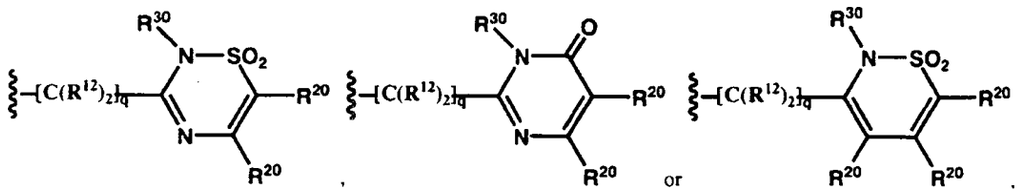
R^6 and R^7 are each independently selected from H, alkyl, F, Cl, $-CF_3$, -OH, -O-alkyl, $-OCF_3$, $-NH_2$ and $-NHSO_2$-alkyl;

R^9 is H or alkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally substituted with up to 4 substituents, which are each independently selected from H, alkyl, alkenyl, alkynyl, aryl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-cycloalkenyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkenyl, $-[C(R^{12})_2]_q$-heteroaryl, $-[C(R^{12})_2]_q$-haloalkyl, $-[C(R^{12})_2]_q$-hydroxyalkyl, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ and $-SO_2N(R^9)C(O)N(R^9)_2$; and

R^{11} is alkyl, aryl or cycloalkyl.

35. The compound of claim 34, wherein R^2 is -C(O)OH, -C(O)Oalkyl, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)NH-cycloalkyl, $-C(O)NHSO_2R^{11}$, heteroaryl ,



wherein the heteroaryl, arylthiazin-yl- or arylthiadiazol-yl- group can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl,

heteroaryl, halo, haloalkyl, hydroxyalkyl, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$; such that if Z is thiophene-yl, R^2 is other than –C(O)O-alkyl.

36. The compound of claim 35, wherein R^2 is $-C(O)NHSO_2$-alkyl, $-C(O)NHSO_2$-aryl, $-C(O)NHSO_2$-cycloalkyl or $-C(O)NHSO_2$-alkylene-cycloalkyl.

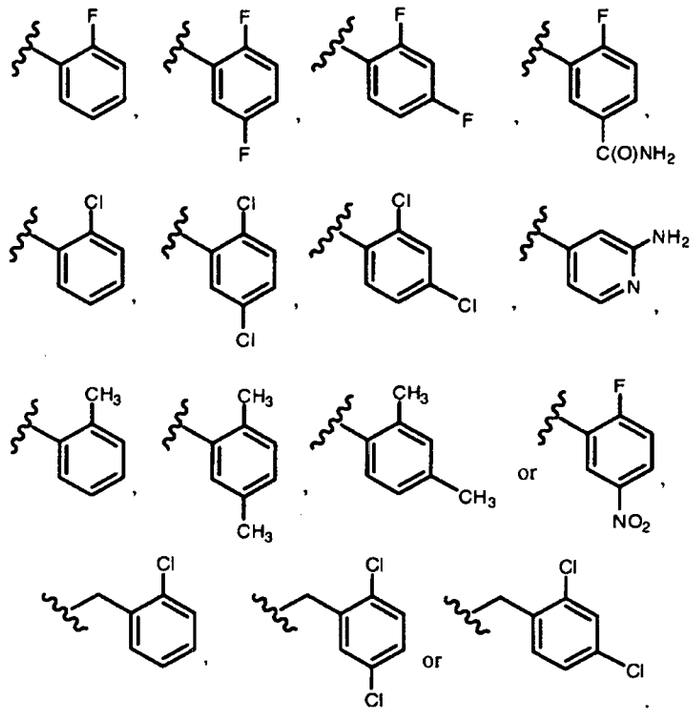
37. The compound of claim 36, wherein R^2 is $-C(O)NHSO_2$-methyl, $-C(O)NHSO_2$-ethyl, $-C(O)NHSO_2$-isopropyl, $-C(O)NHSO_2$-t-butyl, $-C(O)NHSO_2$-phenyl or $-C(O)NHSO_2$-cyclopropyl.

38. The compound of claim 35, wherein R^2 is –C(O)OH.

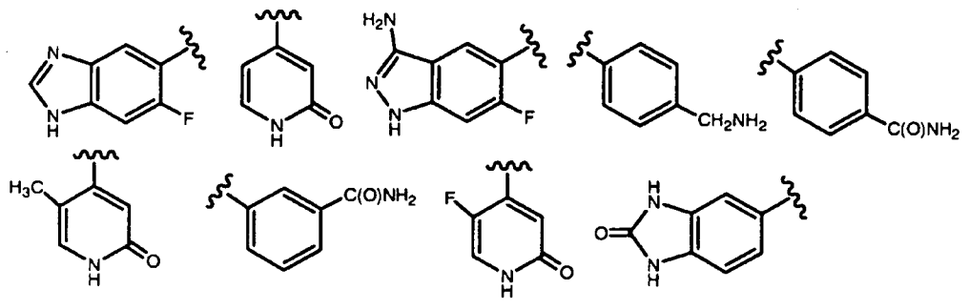
39. The compound of claim 34, wherein R^{10} is bicyclic aryl or bicyclic heteroaryl, each of which can be unsubstituted or optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, aryl, heteroaryl, halo, haloalkyl, heterocycloalkyl, heterocycloalkenyl, hydroxyalkyl, -CN, -C(O)alkyl, -C(O)Oalkyl, $-C(O)N(R^9)_2$, -alkylene-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ or $-SO_2N(R^9)_2$.

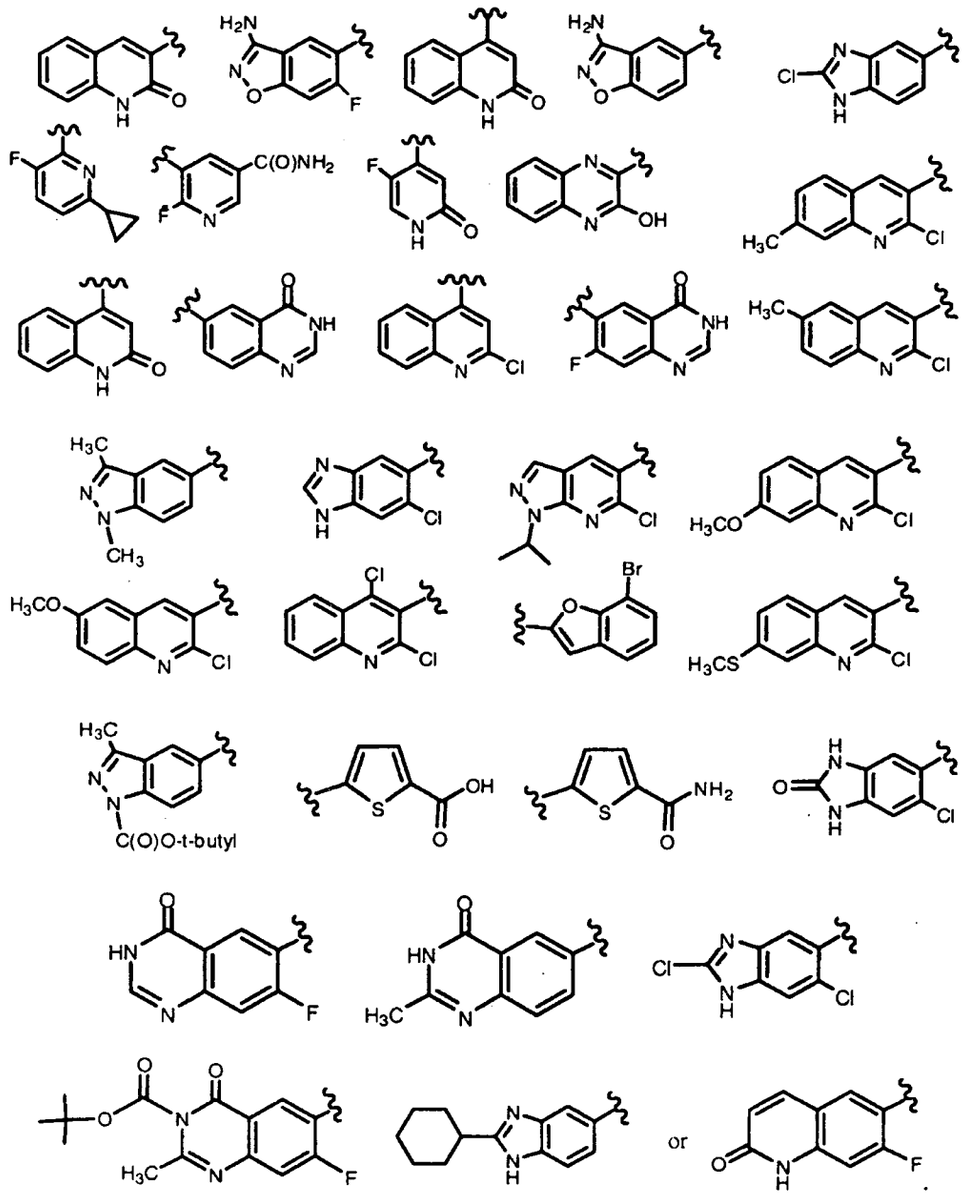
40. The compound of claim 34, wherein R^{10} is phenyl, pyridyl, benzimidazole, benzimidazolone, quinoline, quinolinone, quinoxaline, quinoxalinone, quinazoline, quinazolinone, naphthyridine, naphthyridinone, pteridine, pteridinone, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

41. The compound of claim 34, wherein R^{10} is:

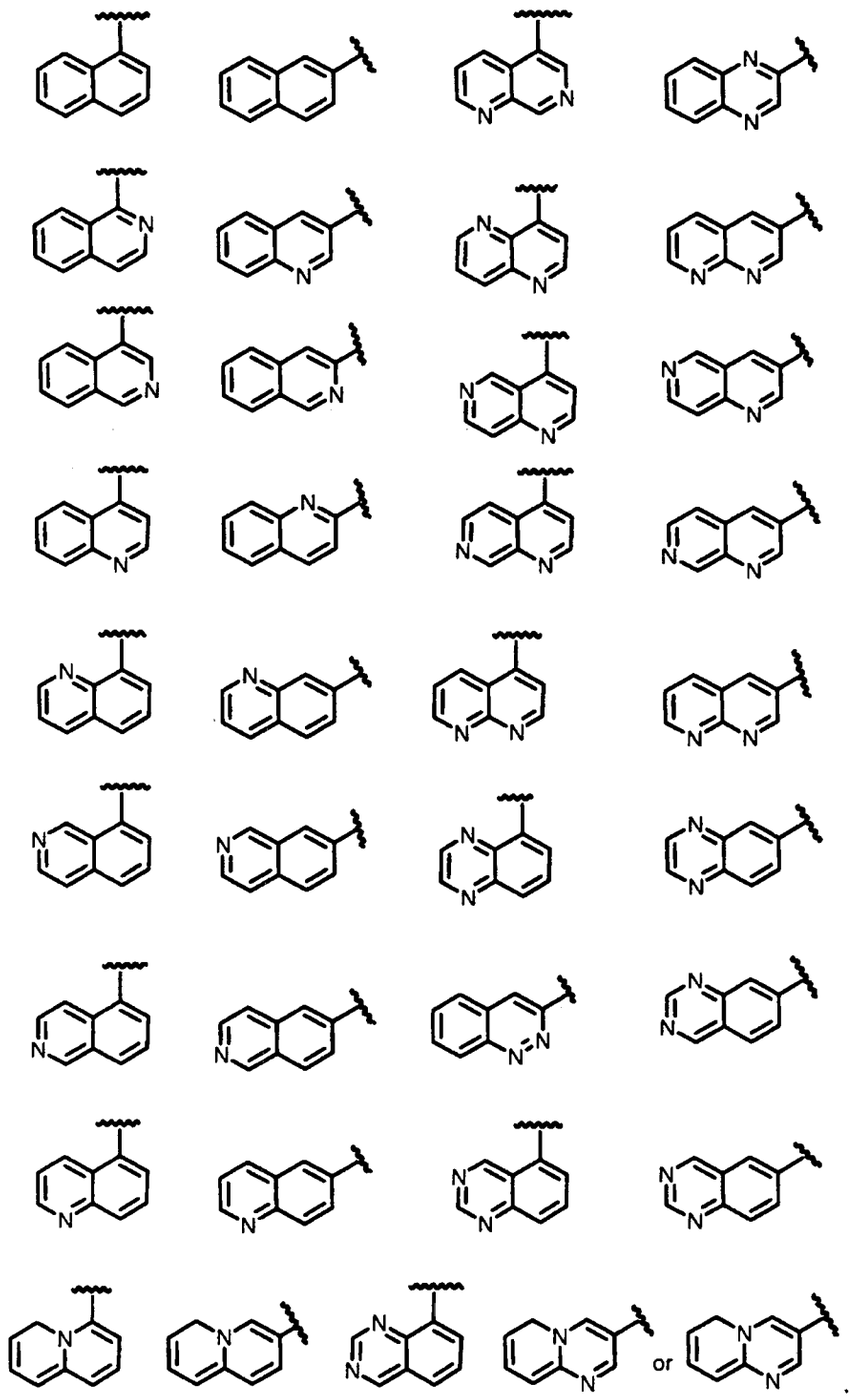


42. The compound of claim 34, wherein R^{10} is:





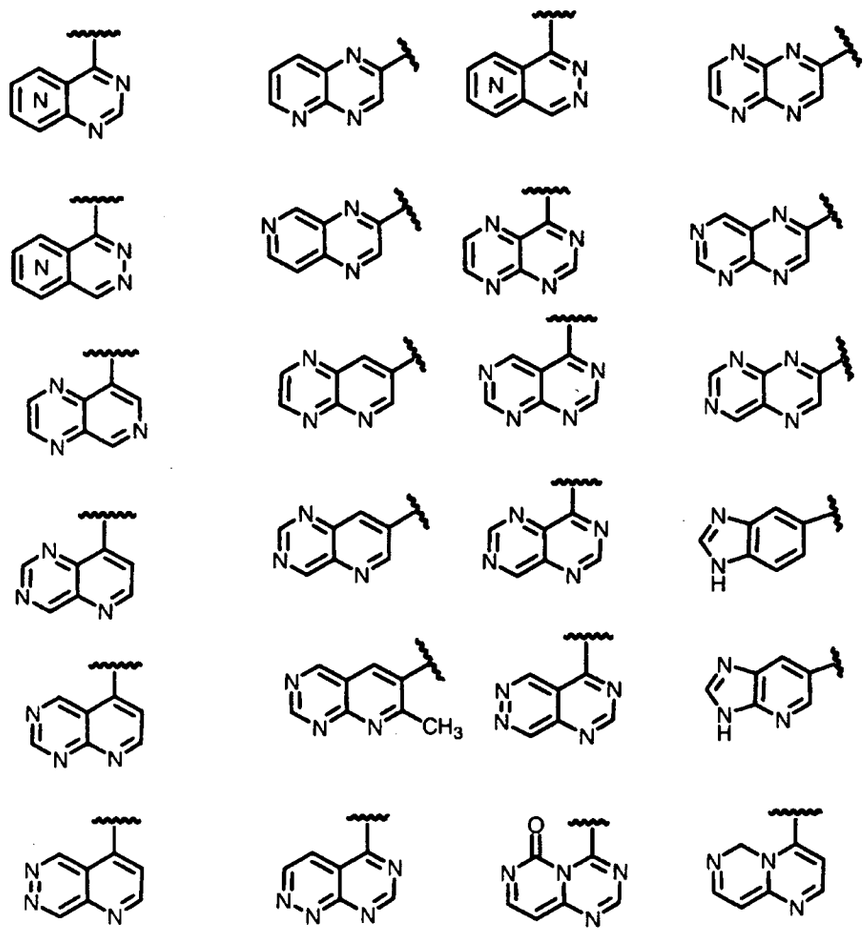
43. The compound of claim 34, wherein R^{10} is:

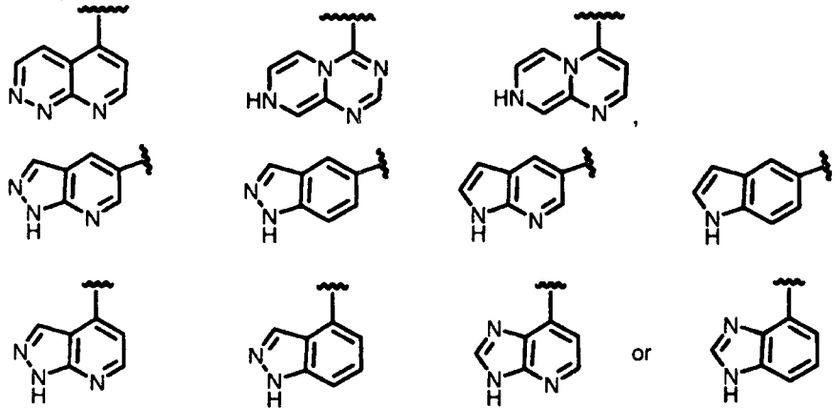


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each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl.

44. The compound of claim 34, wherein R^{10} is:





, each of which can be optionally substituted with up to 3 substituents, which are the same or different, and are selected from alkyl, cycloalkyl, heterocycloalkyl, heterocycloalkenyl, halo, haloalkyl, -O-haloalkyl, -OH, -CN, $-NH_2$, -NH-alkyl, $-N(alkyl)_2$ or $-NHSO_2$-alkyl; wherein the letter "N" inside a ring indicates that the ring has 1 or 2 ring nitrogen atoms.

45. The compound of claim 34, wherein R^6 and R^7 are each H.

46. The compound of claim 39, wherein R^2 is –C(O)OH.

47. The compound of claim 40, wherein R^2 is –C(O)OH.

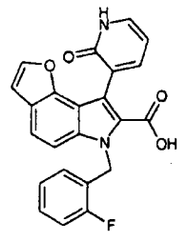
48. The compound of claim 41, wherein R^2 is –C(O)OH.

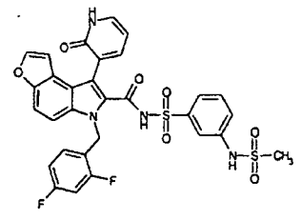
49. The compound of claim 42, wherein R^2 is –C(O)OH.

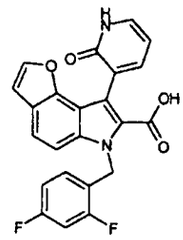
50. The compound of claim 43, wherein R^2 is –C(O)OH.

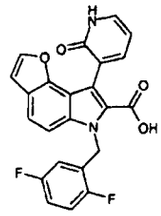
51. The compound of claim 44, wherein R^2 is –C(O)OH..

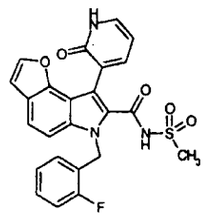
52. A compound having the structure:

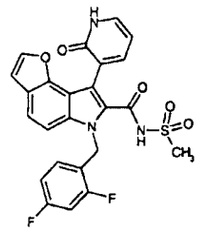
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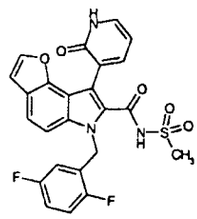
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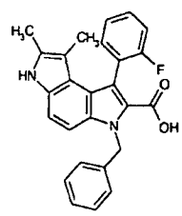
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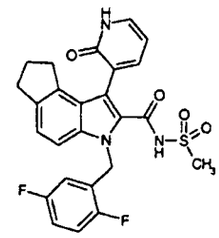
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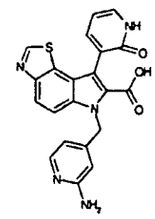
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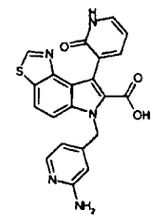
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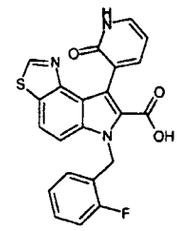
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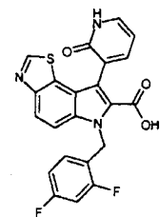
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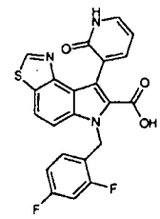
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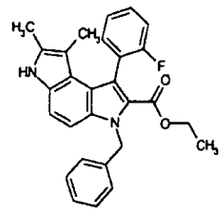
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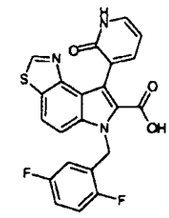
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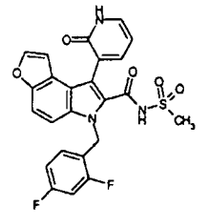
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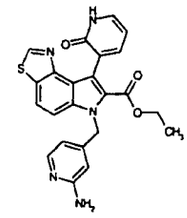
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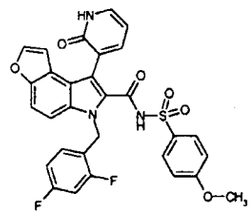
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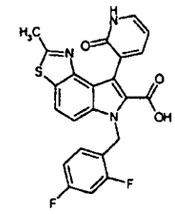
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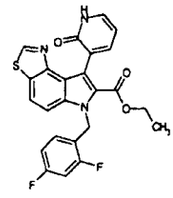
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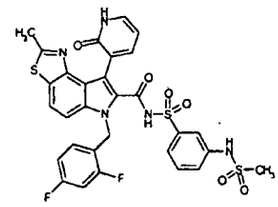
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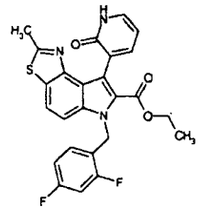
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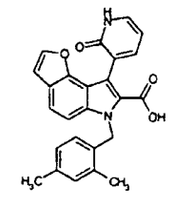
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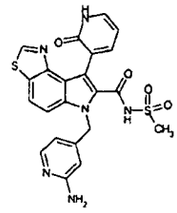
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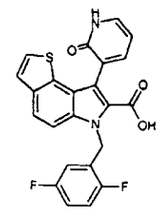
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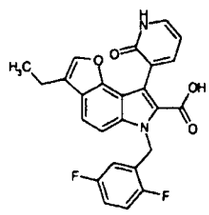
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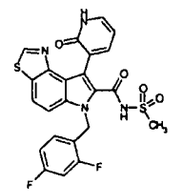
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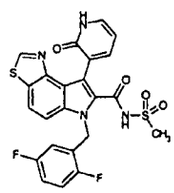
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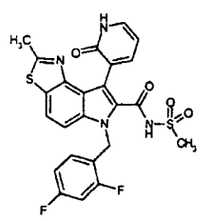
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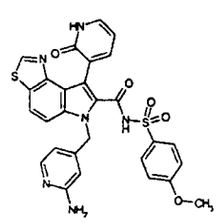
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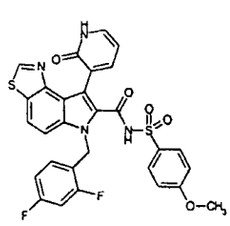
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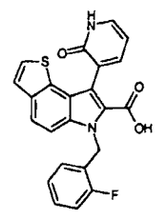
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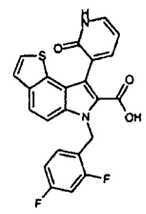
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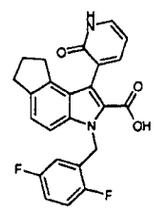
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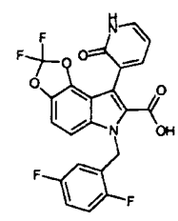
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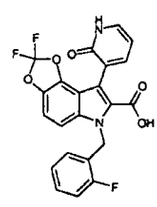
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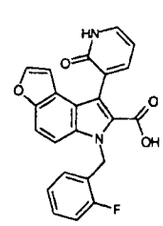
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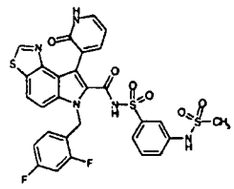
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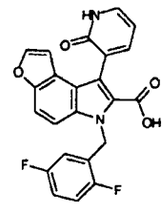
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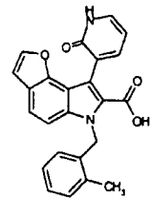
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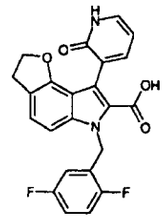
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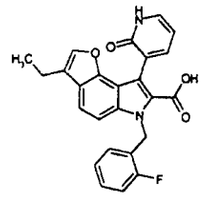


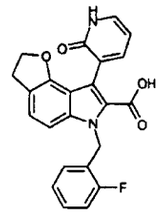
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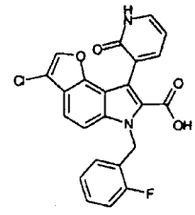


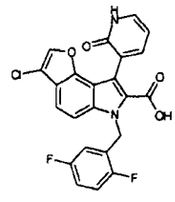
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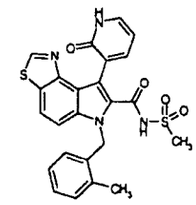
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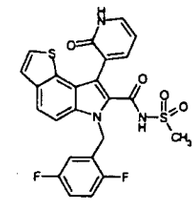
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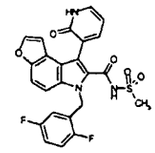
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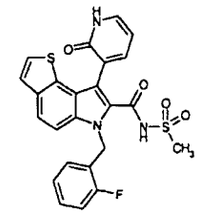
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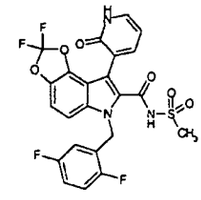
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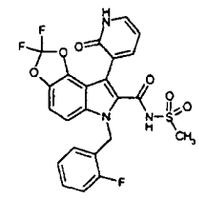
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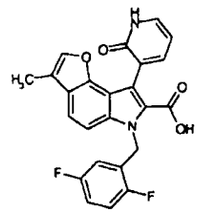
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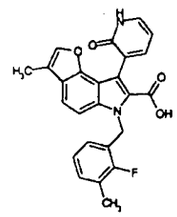
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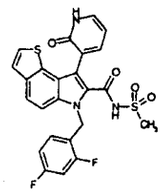
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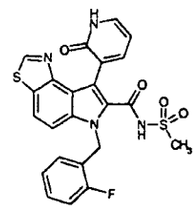
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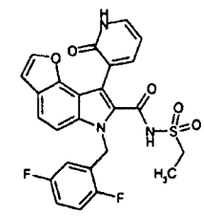
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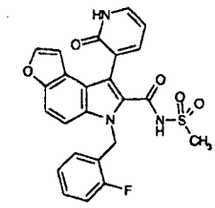
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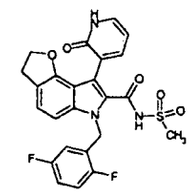
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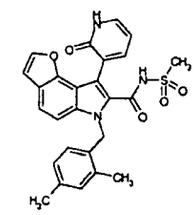
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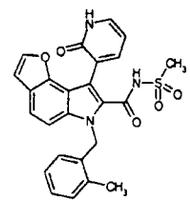
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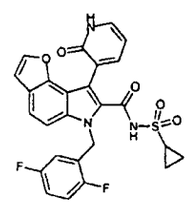
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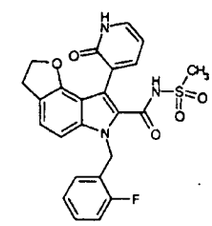
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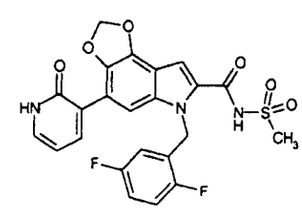
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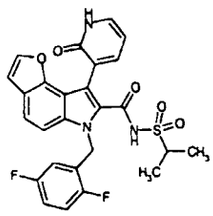
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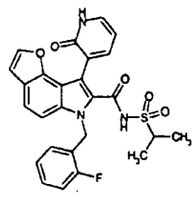
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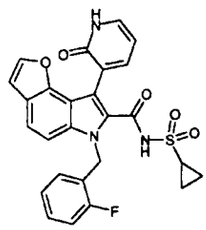
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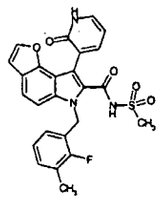
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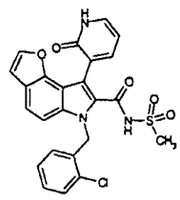
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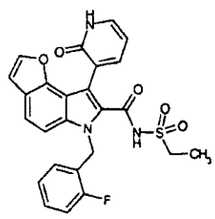
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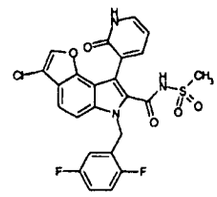
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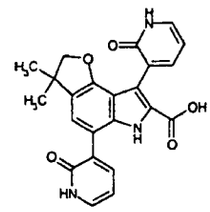
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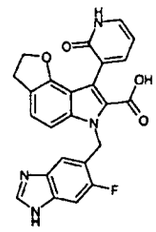
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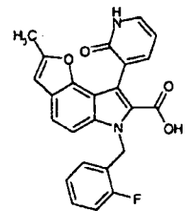
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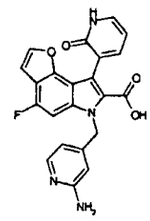
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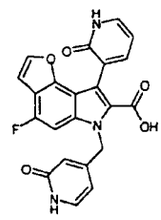
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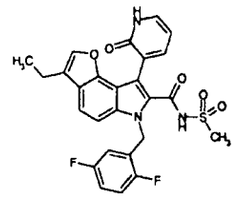
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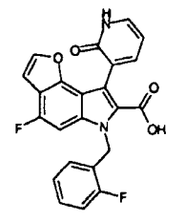
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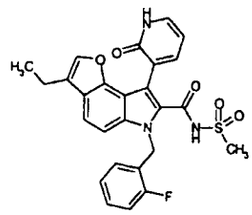
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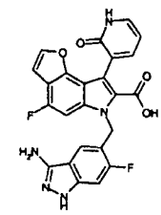
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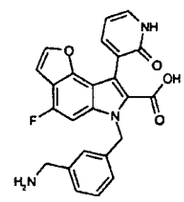
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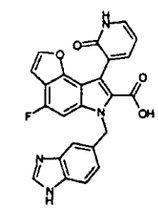
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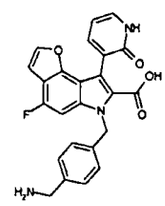
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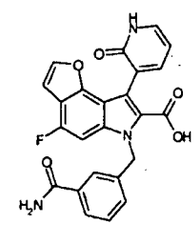
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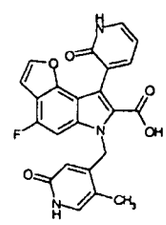
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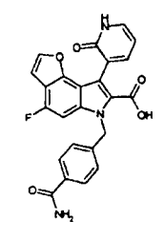
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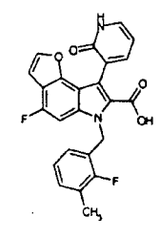
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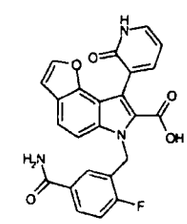
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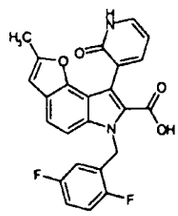
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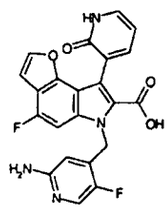
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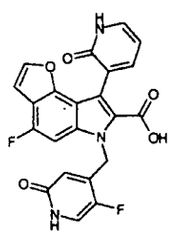
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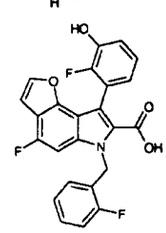
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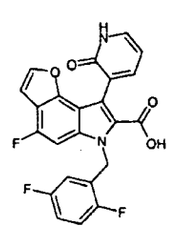
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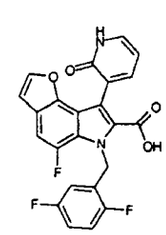
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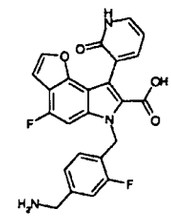
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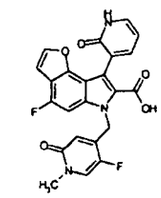
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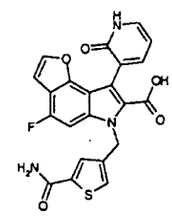
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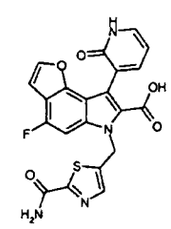
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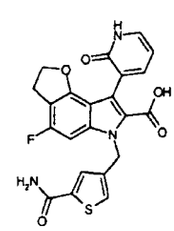
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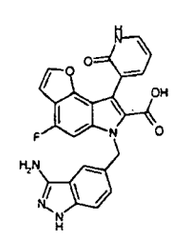
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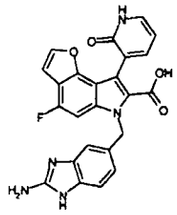
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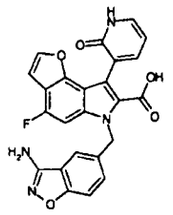
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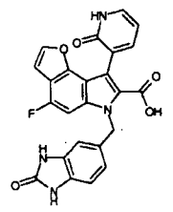
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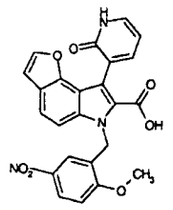
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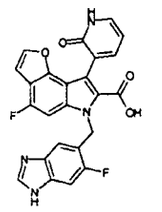
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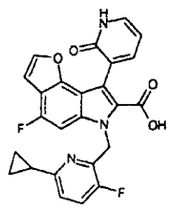
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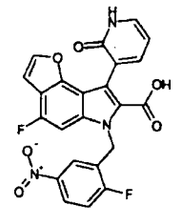
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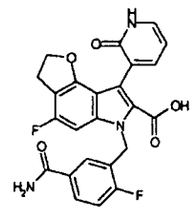
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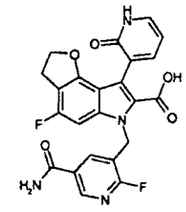
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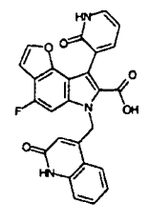
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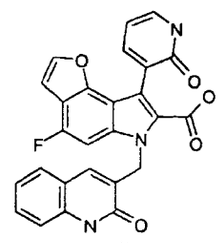
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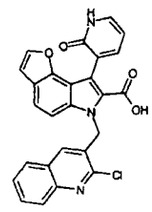
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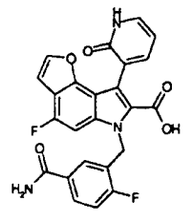
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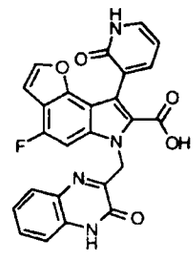
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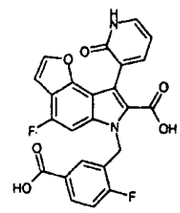
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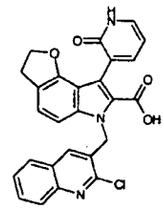
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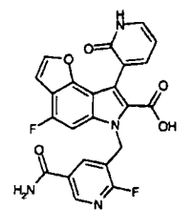
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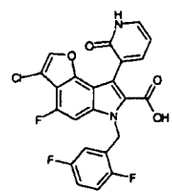
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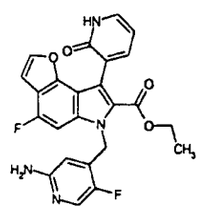
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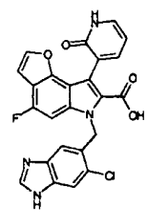
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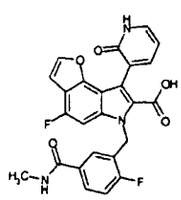
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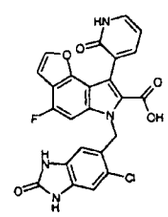
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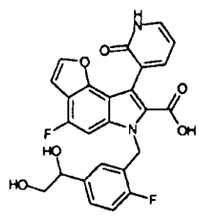
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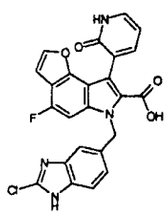
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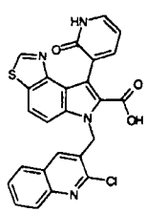
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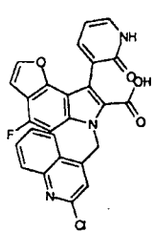
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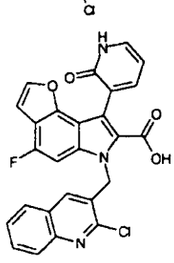
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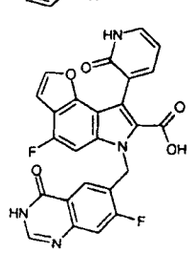
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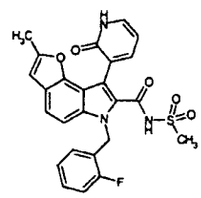
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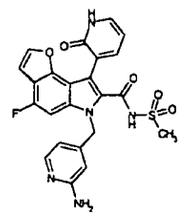
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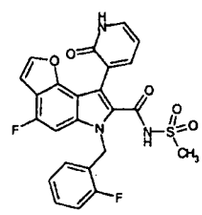
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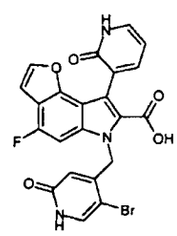
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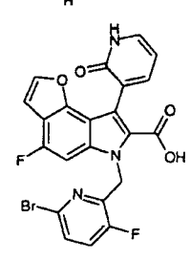
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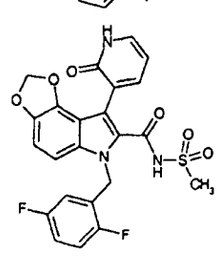
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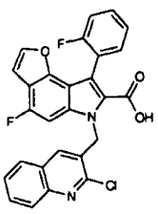
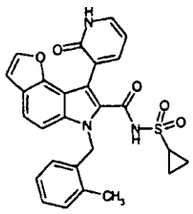
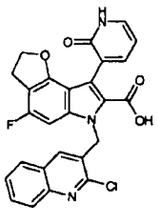
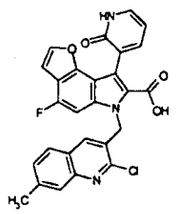
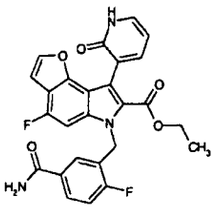
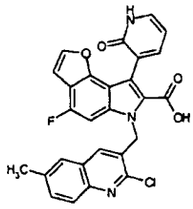
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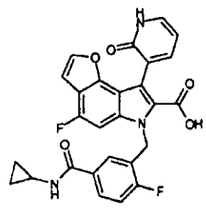
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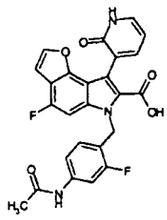
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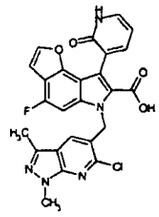
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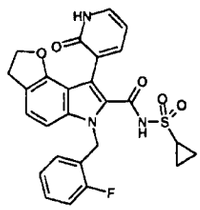
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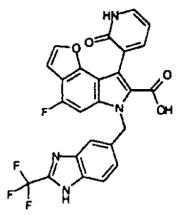
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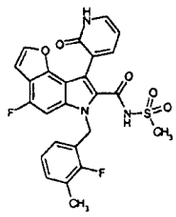
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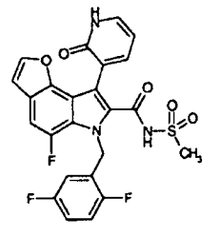
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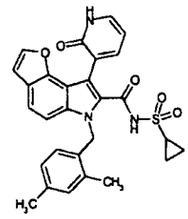
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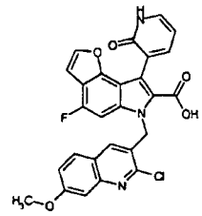
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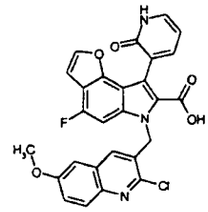
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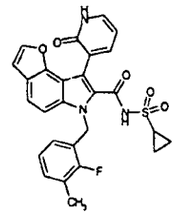
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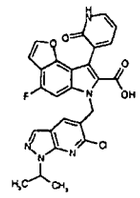
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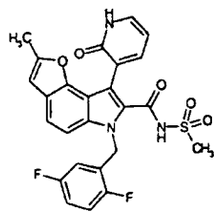
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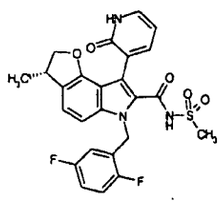
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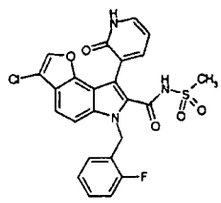
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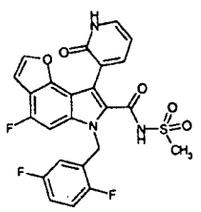
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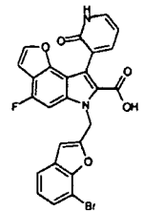
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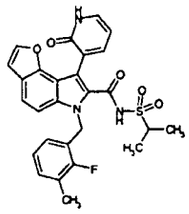
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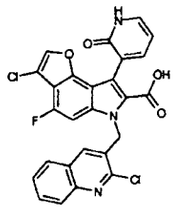
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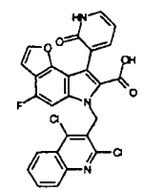
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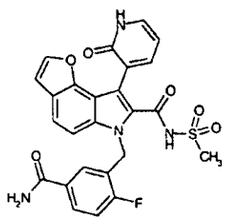
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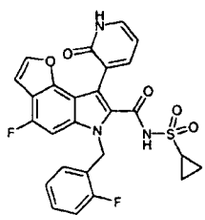
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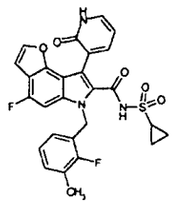
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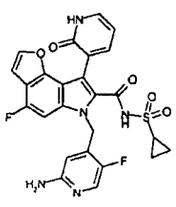
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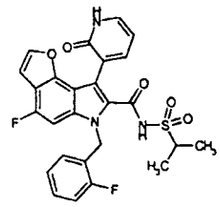
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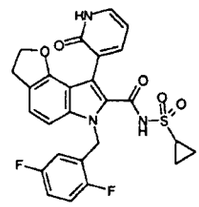
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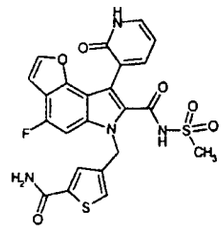
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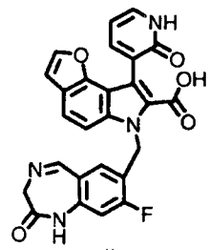
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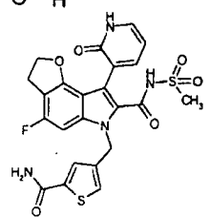
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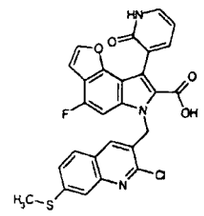
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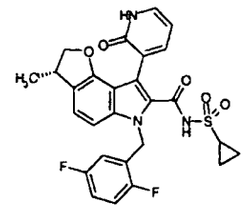
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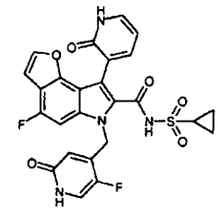
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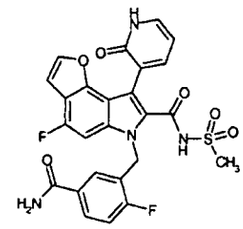
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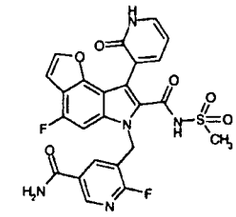
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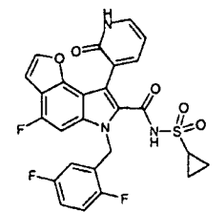
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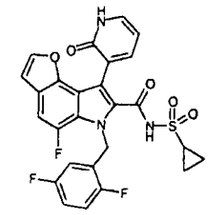
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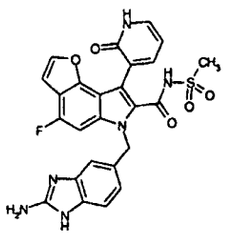
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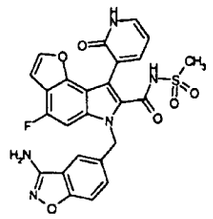
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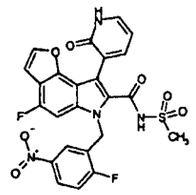
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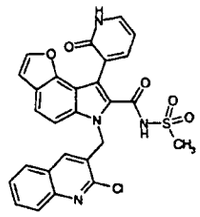
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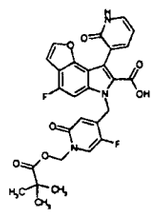
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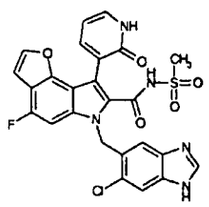
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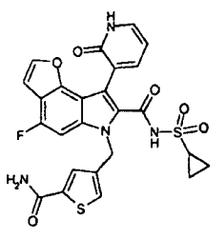
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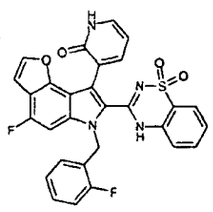
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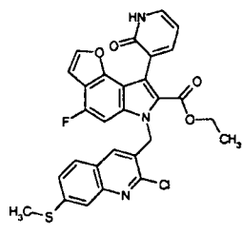
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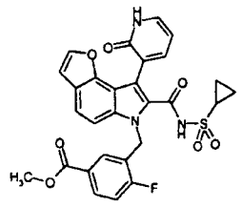
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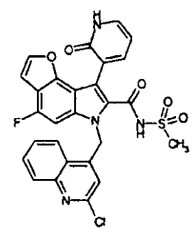
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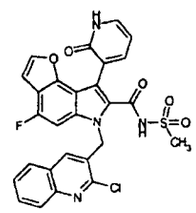
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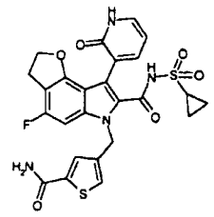
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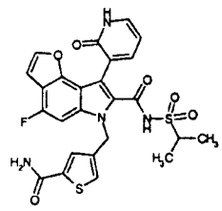
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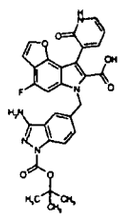
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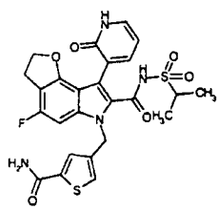
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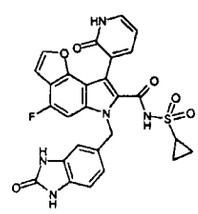
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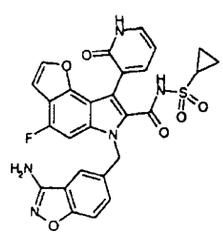
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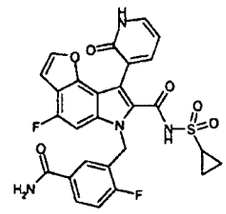
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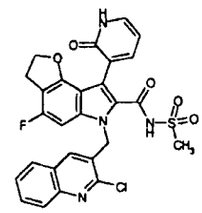
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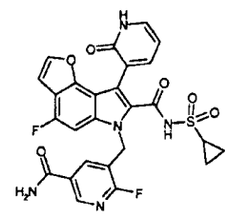
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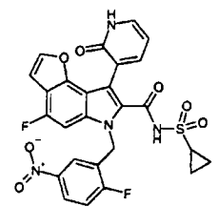
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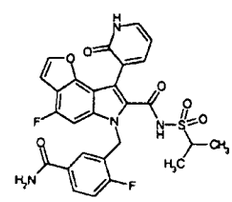
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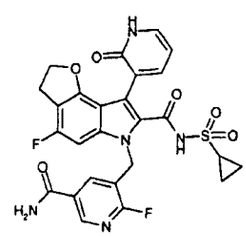
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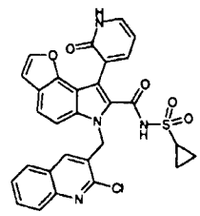
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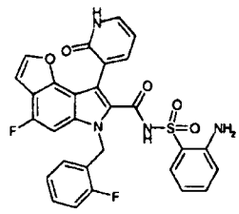
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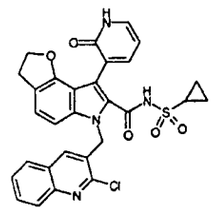
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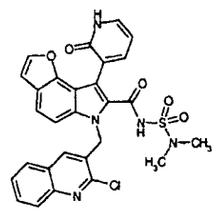
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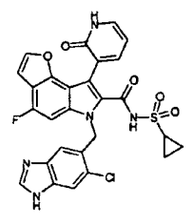
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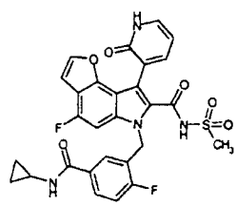
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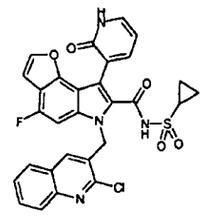
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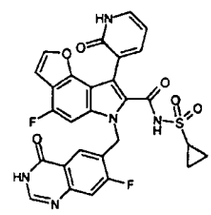
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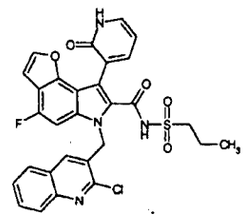
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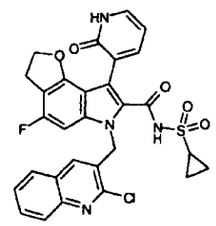
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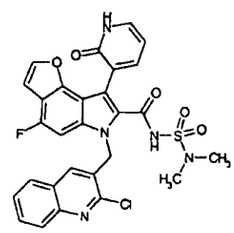
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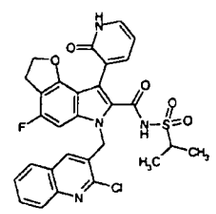
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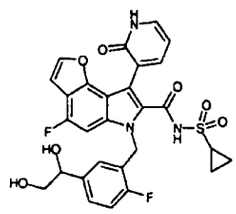
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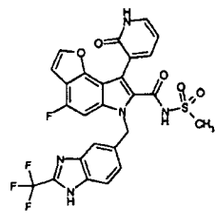
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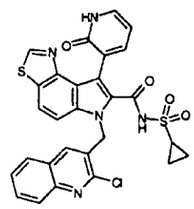
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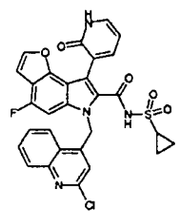
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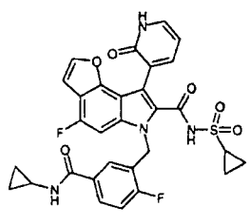
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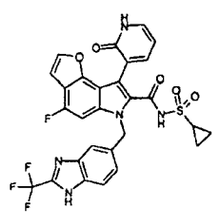
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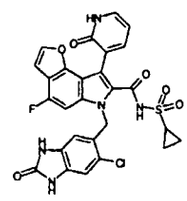
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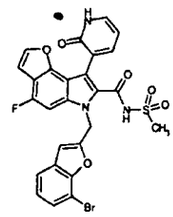
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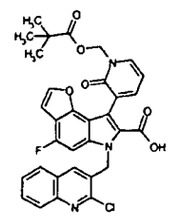
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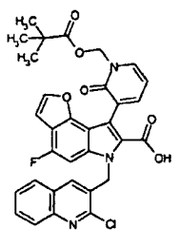
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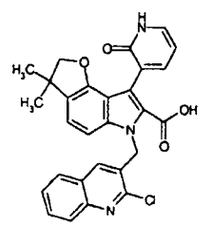
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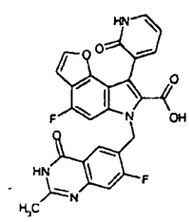
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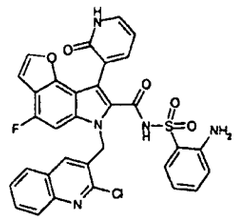
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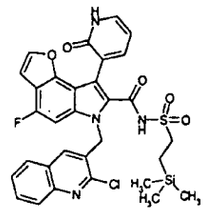
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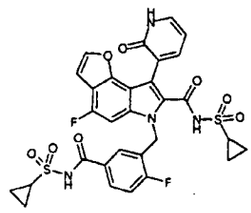
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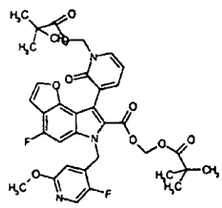
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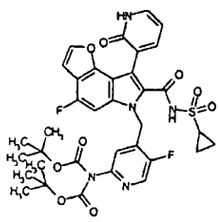
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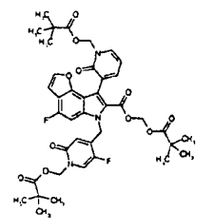
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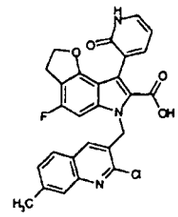
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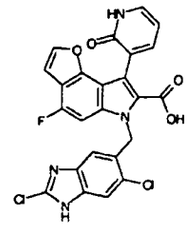
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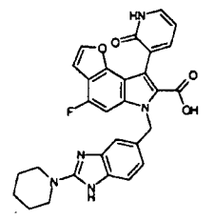
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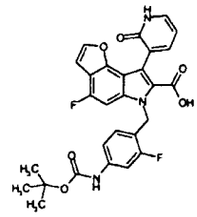
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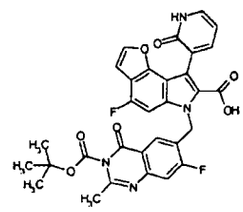
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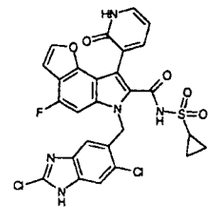
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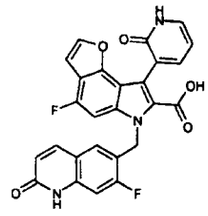
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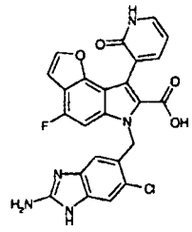
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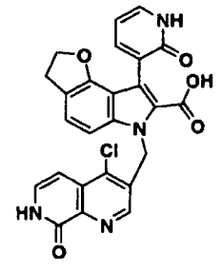
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or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

53. A pharmaceutical composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable carrier.

54. A pharmaceutical composition comprising at least one compound of claim 52 or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable carrier.

55. The pharmaceutical composition of claim 53, further comprising at least one additional antiviral agent, wherein the additional agent is not a compound of claim 1.

56. The composition of claim 55, wherein the additional antiviral agent is selected from: an HCV polymerase inhibitor; an interferon; a RNA replication inhibitor; an antisense agent; a therapeutic vaccine; a protease inhibitor; an antibody therapy (monoclonal or polyclonal); and any agent useful for treating an RNA-dependent polymerase-related disorder.

57. The composition of claim 55, wherein the additional antiviral agent is an agent useful for treating an RNA-dependent polymerase-related disorder.

58. The composition of claim 55, wherein the additional antiviral agent(s) is an interferon.

59. The composition of claim 58, wherein the interferon is interferon alfa-2a, interferon alfa-2b, inteferon alfacon-1 or a peglylated interferon.

60. The composition of claim 55, wherein the additional antiviral agent is a protease inhibitor.

61. The composition of claim 60, wherein the protease inhibitor is an HCV protease inhibitor or a NS-3 serine protease inhibitor.

62. The composition of claim 55, wherein the additional antiviral agent is an HCV polymerase inhibitor.

63. A method for treating a viral infection in a patient, the method comprising administering to the patient an effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt or solvate thereof.

64. A method for treating a viral infection in a patient, the method comprising administering to the patient an effective amount of at least one compound of claim 52 or a pharmaceutically acceptable salt or solvate thereof.

65. The method of claim 63, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is not a compound of claim 1, and wherein the amounts administered are together effective to treat a viral infection.

66. The method of claim 64, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is not a compound of claim 1, and wherein the amounts administered are together effective to treat a viral infection.

67. The method of claim 65, wherein the additional antiviral agent is selected from: an HCV polymerase inhibitor; an interferon; a RNA replication inhibitor; an antisense agent; a

therapeutic vaccine; a protease inhibitor; an antibody therapy (monoclonal or polyclonal); and any agent useful for treating an RNA-dependent polymerase-related disorder.

68. The method of claim 67, wherein the additional antiviral agent is an agent useful for treating an RNA-dependent polymerase-related disorder.

69. The method of claim 67, wherein the additional antiviral agent(s) is an interferon.

70. The method of claim 69, wherein the interferon is interferon alfa-2a, interferon alfa-2b, inteferon alfacon-1 or a peglylated interferon.

71. The method of claim 67, wherein the additional antiviral agent(s) is protease inhibitor.

72. The method of claim 71, wherein the protease inhibitor is an HCV protease inhibitor or a NS-3 serine protease inhibitor.

73. The method of claim 67, wherein the additional antiviral agent is an HCV polymerase inhibitor.

74. The method of claim 66, wherein the additional antiviral agent is selected from: an HCV polymerase inhibitor; an interferon; a RNA replication inhibitor; an antisense agent; a therapeutic vaccine; a protease inhibitor; an antibody therapy (monoclonal or polyclonal); and any agent useful for treating an RNA-dependent polymerase-related disorder.

75. The method of claim 74, wherein the additional antiviral agent is an agent useful for treating an RNA-dependent polymerase-related disorder.

76. The method of claim 74, wherein the additional antiviral agent(s) is an interferon.

77. The method of claim 76, wherein the interferon is interferon alfa-2a, interferon alfa-2b, inteferon alfacon-1 or a peglylated interferon.

78. The method of claim 74, wherein the additional antiviral agent is a protease inhibitor.

79. The method of claim 78, wherein the protease inhibitor is an HCV protease inhibitor or a NS-3 serine protease inhibitor.

80. The method of claim 74, wherein the additional antiviral agent is an HCV polymerase inhibitor.

81. The method of claim 63, wherein the viral infection is HCV infection.

82. The method of claim 64, wherein the viral infection is HCV infection.

DERIVADOS INDÓLICOS CON ANILLO UNIDO EN LAS POSICIONES 4,5 Y SUS MÉTODOS DE USO

CAMPO DE LA INVENCIÓN

La presente invención se refiere a derivados indólicos con anillo unido en las posiciones 4,5, a composiciones que comprenden por lo menos un derivado indólico con anillo unido en las posiciones 4,5 y a métodos de uso de los derivados indólicos con anillo unido en las posiciones 4,5 para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

ANTECEDENTES DE LA INVENCIÓN

El VHC es un virus de ARN monocatenario de sentido (+) que ha sido implicado como el principal agente causante de la hepatitis no A, no B (NANBH). La NANBH se distingue de otros tipos de enfermedad hepática inducida por virus, tal como el virus de la hepatitis A (VHA), el virus de la hepatitis B (VHB), el virus de la hepatitis delta (VHD), además de otras formas de enfermedad hepática tales como alcoholismo y cirrosis biliar primaria.

El virus de la hepatitis C es un miembro del género hepacivirus de la familia Flaviviridae. Es el principal agente causante de la hepatitis viral no A, no B y es la principal causa de hepatitis asociada con transfusión y representa una proporción significativa de casos de hepatitis en el mundo. Si bien la infección aguda por VHC es con frecuencia asintomática, casi 80% de los casos conducen a hepatitis crónica. Aproximadamente 60% de los pacientes desarrollan enfermedad hepática con diversas consecuencias clínicas que varían desde un estado de portador asintomático a hepatitis activa crónica y cirrosis hepática (se produce en aproximadamente 20% de los pacientes), que está fuertemente asociada con el desarrollo de carcinoma hepatocelular (se produce en aproximadamente 1-5% de los pacientes). La Organización Mundial de la Salud estima que 170 millones de

personas están infectadas en forma crónica con VHC, con un estimado de 4 millones que viven en los Estados Unidos.

El VHC se ha vinculado con la cirrosis hepática y la inducción de carcinoma hepatocelular. El pronóstico para los pacientes que sufren de la infección con VHC aún es malo ya que la infección con VHC es más difícil de tratar que otras formas de hepatitis. Los datos actuales indican una tasa de supervivencia de cuatro años inferior al 50% para los pacientes que sufren de cirrosis y una tasa de supervivencia de cinco años menor del 30% para los pacientes diagnosticados con carcinoma hepatocelular resecable localizado. Los pacientes diagnosticados con carcinoma hepatocelular resecable localizado están una peor, ya que presentan una tasa de supervivencia de cinco años menor del 1%.

El VHC es un virus de ARN con envoltura que contiene un genoma de ARN monocatenario de sentido positivo de aproximadamente 9,5 kb de longitud. El genoma de ARN contiene una región 5' no traducida (5' NTR) de 341 nucleótidos, un marco de lectura abierto (ORF) que codifica un polipéptido único de 3.010 a 3.040 aminoácidos, y una región no traducida 3' (3'-NTR) de longitud variable de aproximadamente 230 nucleótidos. El VHC es similar en cuanto a la organización de las secuencias de aminoácidos y genoma a los flavivirus y pestivirus, y en consecuencia se ha clasificado al VHC como un tercer género de la familia Flaviviridae.

La 5' NTR, una de las regiones del genoma viral más conservadas, contiene un sitio de entrada ribosómico interno (IRES) que cumple una función crucial en la iniciación de la traducción de la poliproteína viral. Un marco de lectura abierto largo único codifica una poliproteína, que es procesada en forma co- o post-traduccional en proteínas virales estructurales (núcleo, E1, E2 y p7) y no estructurales (NS2, NS3, NS4A, NS4B, NS5A y NS5B) por proteinasas celulares o virales. La 3' NTR consiste en tres regiones distintas: una región

variable de aproximadamente 38 nucleótidos que siguen al codón de detención de la poliproteína, un tramo de poliuridina de longitud variable con sustituciones de citidinas intercaladas y 98 nucleótidos (nt) en el propio extremo 3' que están altamente conservadas entre diversas cepas del VHC. Por analogía con otros virus de ARN de cadena positiva, se considera que la 3'-NTR desempeña un papel importante en la síntesis del ARN viral. El orden de los genes dentro del genoma es: NH_2-C-E1-E2-p7-NS2-NS3-NS4A-NS4B-NS5A-NS5B-COOH.

El procesamiento del núcleo de proteínas estructurales (C, por core en inglés), la proteína de envoltura 1 y (E1, E2), y la región p7 es mediado por peptidasas de señal del huésped. En contraste, la maduración de la región no estructural (NS) se obtiene por medio de dos enzimas virales. La poliproteína del VHC primero es escindida por una peptidasa señal del huésped que genera las proteínas estructurales C/E1, E1/E2, E2/p7 y p7/NS2. La proteinasa NS2-3, que es una metaloproteasa, luego se escinde en el cruce NS2/NS3. El complejo de la proteinasa NS3/4A (NS3 es una serina proteasa y NS4A actúa como cofactor de la NS3 proteasa), es entonces responsable del procesamiento de todos los cruces de ruptura restantes. Se han identificado actividades de ARN helicasa y NTPasa en la proteína NS3. Un tercio de la proteína NS3 funciona como proteasa, y se piensa que los dos tercios restantes de la molécula actúan como la helicasa/ATPasa que se considera involucrada en la replicación del VHC. La NS5A se puede fosforilar y actúa como cofactor putativo de NS5B. La cuarta enzima viral, NS5B, es una ARN polimerasa dependiente de ARN asociada a membrana (RdRp) y un componente clave responsable de la replicación del genoma de ARN viral. NS5B contiene el motivo de secuencia "GDD" que está altamente conservado entre todas las RdRp caracterizadas hasta la fecha.

Se considera que la replicación de VHC se produce en los complejos de replicación asociados a membrana. Dentro de estos, el ARN de cadena positiva

genómica se transcribe en ARN de cadena negativa, que a su vez se puede usar como molde para la síntesis de cadenas positivas genómicas hijas. Por lo menos dos enzimas virales parecen participar en esta reacción: la NS3 helicasa/NTPasa, y la ARN polimerasa NS5B dependiente de ARN. Aunque el papel de la NS3 en la replicación del ARN es menos claro, NS5B es la enzima clave responsable de la síntesis de las hebras de ARN hijas. Usando baculovirus recombinantes para expresar NS5B en células de insectos y un ARN no viral sintético como sustrato, se han identificado dos actividades enzimáticas que están asociadas con esta: una actividad RdRp dependiente del cebador y una actividad transferasa terminal (TNTasa). Posteriormente se confirmó y caracterizó adicionalmente mediante el uso del genoma de ARN del VHC como sustrato. Otros estudios han demostrado que NS5B con un truncamiento C-terminal de 21 aminoácidos expresada en Escherichia coli también es activa para la síntesis de ARN *in vitro*. En ciertos ARN moldes, se ha demostrado que NS5B cataliza la síntesis de ARN por medio de un mecanismo de iniciación *de novo*, que ha sido postulado como el modo de replicación viral *in vivo*. Se ha hallado que los moldes con extremos terminales 3' monocatenarios, en especial los que contienen un residuo citidilato 3'-terminal, dirigen la síntesis *de novo* en forma eficiente. Se ha hallado también evidencia de que NS5B utiliza di- o tri-nucleótidos como cebadores cortos para iniciar la replicación.

Está bien establecido que la infección persistente de VHC está relacionada con la hepatitis crónica y, como tal, la inhibición de la replicación del VHC es una estrategia viable para la prevención del carcinoma hepatocelular. Los enfoques actuales de tratamiento para la infección de VHC adolecen de escasa eficacia y efectos secundarios desfavorables y actualmente existe un gran esfuerzo dirigido al descubrimiento de inhibidores de la replicación del VHC que sean útiles para el tratamiento y prevención de los trastornos relacionados con el VHC. Actualmente

los nuevos abordajes de investigación incluyen el desarrollo de vacunas profilácticas y terapéuticas, la identificación de interferones con mejores características farmacocinéticas, y el descubrimiento de agentes diseñados para inhibir la función de tres importantes proteínas virales: proteasa, helicasa y polimerasa. Además, el propio genoma del ARN del VHC, en particular el elemento IRES, se está explotando activamente como blanco antiviral empleando moléculas antisentido y ribozimas catalíticas.

Las terapias particulares para la infección con VHC incluyen la monoterapia con α-interferón y terapia combinada que comprende α-interferón y ribavirina. Se ha demostrado que estas terapias son efectivas en algunos pacientes con infección por VHC crónica. También se ha propuesto el uso de oligonucleótidos antisentido para el tratamiento de la infección por VHC como así también el uso de los ácidos biliares libres, tales como ácido ursodesoxicólico y ácido quenodesoxicólico y ácidos biliares conjugados, tales como ácido tauroursodesoxicólico. También se ha propuesto a los ésteres del ácido fosfonofórmico como agentes potenciales para el tratamiento de diversas infecciones virales que incluyen el VHC. El desarrollo de vacunas, sin embargo, se ha visto dificultado por el alto grado de heterogeneidad de las cepas virales y la evasión inmune y la falta de protección contra la re-infección, aun con el mismo inóculo.

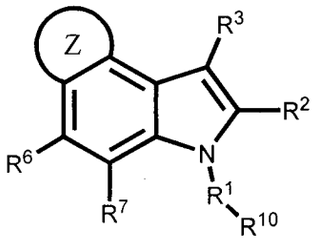
El desarrollo de inhibidores de molécula pequeña dirigidos contra blancos virales específicos se ha convertido en un foco importante de la investigación anti-VHC. La determinación de las estructuras cristalinas de la proteasa NS3, la ARN helicasa NS3 y la polimerasa NS5B, con y sin ligandos unidos, ha proporcionado importantes perspectivas estructurales útiles para el diseño racional de inhibidores específicos.

La NS5B, la ARN polimerasa dependiente de ARN, es un importante y atractivo blanco para los inhibidores de molécula pequeña. Los estudios con pestivirus han demostrado que el compuesto de molécula pequeña VP32947 (3-[((2-dipropilamino)etil)tio]-5H-1,2,4-triazino[5,6-b]indol) es un potente inhibidor de la replicación de pestivirus y que muy probablemente inhibe la enzima NS5B ya que las cepas resistentes mutan en este gen. También se ha observado la inhibición de la actividad de RdRp por parte de la (-)β-L-2',3'-didesoxi-3'-tiacitidina 5'-trifosfato (3TC; trifosfato de lamivudina) y el ácido fosfonoacético.

A pesar del intenso esfuerzo dedicado al tratamiento y prevención del VHC e infecciones virales relacionadas, es necesario en el arte hallar compuestos no peptídicos de molécula pequeña que presenten propiedades fisicoquímicas deseables o mejoradas que sean útiles para inhibir los virus y tratar infecciones virales y trastornos relacionados con virus.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

En un aspecto, la presente invención proporciona derivados indólicos con anillo unido en las posición 4,5 (en la presente memoria denominados como "Compuestos de Fórmula (I)"):



(I)

y sus sales y solvatos aceptables para uso farmacéutico,

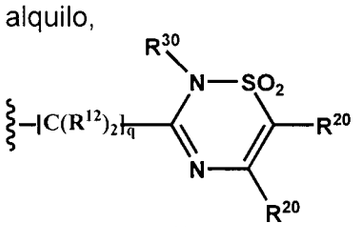
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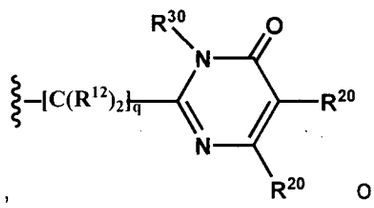
el anillo Z, de fórmula (I), es un ciclopentilo, ciclopentenilo, heterocicloalquilo de 5 miembros, anillo heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros, donde el anillo Z puede estar: (i) opcionalmente

sustituido en uno o más átomos de carbono anulares con sustituyentes, que son iguales o diferentes, y que se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$; y/o (ii) opcionalmente sustituido en átomo de nitrógeno anular con sustituyentes, que son iguales o diferentes, y que se seleccionan de alquilo, arilo, haloalquilo, heteroarilo, hidroxialquilo, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_r-OR^9$, $-[C(R^{12})_2]_r-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$;

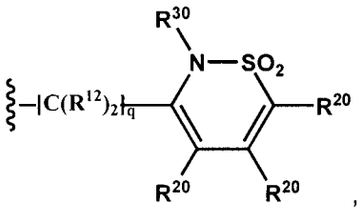
R^1 es un enlace, $-[C(R^{12})_2]_r-$, $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$, o $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$;

R^2 is $-C(O)R^9$, $-C(O)OR^9$, $-C(O)OCH_2OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)N(R^9)C=N(R^9)_2$, $-[C(R^{12})_2]_q$-arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$, alquilo,





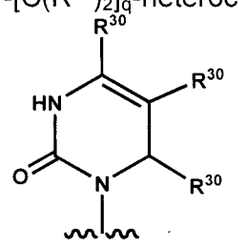
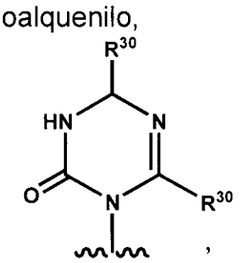
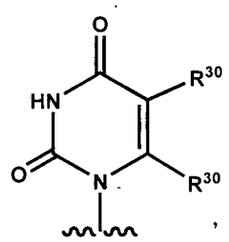
o

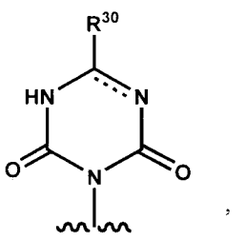
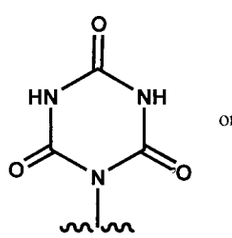
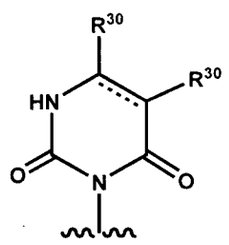


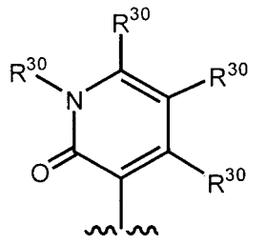
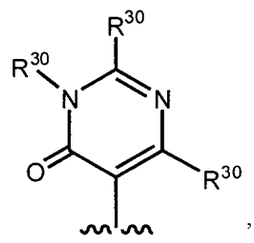
, donde un arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo, el grupo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona de alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, -

$[C(R^{12})_2]_q$-heteroarilo, -$[C(R^{12})_2]_q$-haloalquilo, -$[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ y -$SO_2N(R^9)C(O)N(R^9)_2$;

R^3 es –H, -$[C(R^{12})_2]_q$-alquilo, -$[C(R^{12})_2]_q$-arilo, -$[C(R^{12})_2]_q$-cicloalquilo, -$[C(R^{12})_2]_q$-cicloalquenilo, -$[C(R^{12})_2]_q$-heterocicloalquilo, -$[C(R^{12})_2]_q$-heteroarilo o -$[C(R^{12})_2]_q$-heterocicloalquenilo,


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or



or

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donde un grupo arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes y se seleccionan de alquilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, halo, haloalquilo, hidroxialquilo, -OH, -

CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$;

Cada uno de R^6 y R^7 son, independientemente, H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ o $-SO_2N(R^9)C(O)N(R^9)_2$;

cada aparición de R^8 es independientemente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q$-arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, haloalquilo o hidroxialquilo;

cada aparición de R^9 es independientemente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q$-arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, haloalquilo o hidroxialquilo, o dos grupos R^9 que están unidos a un átomo de nitrógeno común, junto con el átomo de nitrógeno al cual están unidas, combinar para formar un grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona de H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, -

$[C(R^{12})_2]_q$-C(O)N$(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-N$(R^9)_2$, -$[C(R^{12})_2]_q$-NHC(O)R^8, -$[C(R^{12})_2]_q$-NR^8C(O)N$(R^9)_2$, -$[C(R^{12})_2]_q$-NHSO_2R^{11}, -$[C(R^{12})_2]_q$-S$(O)_pR^{11}$, -$[C(R^{12})_2]_q$-SO_2N$(R^9)_2$ y -SO_2N(R^9)C(O)N$(R^9)_2$, de modo que cuando R^1 es un enlace, R^{10} no es H;

cada aparición de R^{11} es independientemente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona de –H, alquilo, alquenilo, alquinilo, arilo, -$[C(R^{12})_2]_q$-cicloalquilo, -$[C(R^{12})_2]_q$-cicloalquenilo, -$[C(R^{12})_2]_q$-heterocicloalquilo, -$[C(R^{12})_2]_q$-heterocicloalquenilo, -$[C(R^{12})_2]_q$-heteroarilo, -$[C(R^{12})_2]_q$-haloalquilo, -$[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-C(O)R^8, -$[C(R^{12})_2]_q$-C(O)OR^9, -$[C(R^{12})_2]_q$-C(O)N$(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-N$(R^9)_2$, -$[C(R^{12})_2]_q$-NHC(O)R^8, -$[C(R^{12})_2]_q$-NR^8C(O)N$(R^9)_2$, -$[C(R^{12})_2]_q$-NHSO_2alquilo, -$[C(R^{12})_2]_q$-NHSO_2cicloalquilo, -$[C(R^{12})_2]_q$-NHSO_2arilo, -$[C(R^{12})_2]_q$-SO_2N$(R^9)_2$ y -SO_2N(R^9)C(O)N$(R^9)_2$;

cada aparición de R^{12} es independientemente H, halo, -N$(R^9)_2$, -OR^9, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona de alquilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, -C(O)Oalquiloo, -C(O)NHalquiloo, -C(O)N$(alquilo)_2$, -O-alquilo, -NH_2, -NH(alquilo), -N$(alquilo)_2$, -NHC(O)alquilo, -NHSO_2alquilo, -SO_2alquilo o -SO_2NH-alquilo, o dos grupos R^{12} junto con los átomos de carbono a los que están unidos, se unen para formar un cicloalquilo, heterocicloalquilo o grupo C=O;

cada aparición de R^{20} es independientemente H, alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los

que están unidos, se unen para formar un grupo cicloalquilo, cicloheteroalquilo, arilo o heteroarilo donde un grupo cicloalquilo, cicloheteroalquilo, arilo o heteroarilo puede estar sustituido con hasta 4 grupos, cada uno de los cuales se selecciona de alquilo, alquenilo, alquinilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, $-[C(R^{12})_2]_q$-$C(O)R^8$, $-[C(R^{12})_2]_q$-$C(O)OR^9$, $-[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, $-[C(R^{12})_2]_q$-OR^9, $-[C(R^{12})_2]_q$-$N(R^9)_2$, $-[C(R^{12})_2]_q$-$NHC(O)R^8$, $-[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q$-$NHSO_2R^{11}$, $-[C(R^{12})_2]_q$-$S(O)_pR^{11}$, $-[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$;

cada aparición de R^{30} es independientemente H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q$-$C(O)R^8$, $-[C(R^{12})_2]_q$-$C(O)OR^9$, $-[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, $-[C(R^{12})_2]_q$-OR^9, $-[C(R^{12})_2]_q$-$N(R^9)_2$, $-[C(R^{12})_2]_q$-$NHC(O)R^8$, $-[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q$-$NHSO_2R^{11}$, $-[C(R^{12})_2]_q$-$S(O)_pR^{11}$, $-[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ o $-SO_2N(R^9)C(O)N(R^9)_2$, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los que están unidos, se unen para formar un anillo anular de 3 a 7 miembros anulares seleccionados de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

cada aparición de p es independientemente 0, 1 o 2;

cada aparición de q es independientemente un número entero que varía de 0 a 4; y

cada aparición de r es independientemente un número entero que varía de 1 a 4.

Los compuestos de fórmula (I) o sus sales, solvatos, profármacos o ésteres aceptables para uso farmacéutico pueden ser útiles para tratar o prevenir una infección viral de un paciente.

Los compuestos de fórmula (I) o sus sales, solvatos, profármacos o ésteres aceptables para uso farmacéutico pueden ser útiles para tratar o prevenir un trastorno relacionado con un virus en paciente.

También se proveen en la invención métodos para tratar o prevenir una infección viral o a trastorno relacionado con un virus en paciente, que comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de fórmula (I).

La presente invención además proporciona composiciones farmacéuticas que comprede una cantidad efectiva de por lo menos un compuesto de fórmula (I) o una sal aceptable para uso farmacéutico, solvato de esta, y un vehículo aceptable para uso farmacéutico. Las composiciones pueden ser útiles para tratar o prevenir una infección viral o un trastorno relacionado con un virus en paciente.

Los detalles de la invención se exponen en la siguiente descripción acompañante.

Si bien algunos métodos y materiales similares a los descriptos en la presente memoria se pueden usar en la práctica o ensayo de la presente invención, se describen ahora métodos y materiales ilustrativos. Otras características, objetos y ventajas de la invención serán evidentes a partir de la descripción y las reivindicaciones. Todas las patentes y publicaciones mencionadas en esta memoria descriptiva están incorporadas en la presente memoria por referencia.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención proporciona Compuestos de fórmula (I), composiciones farmacéuticas que comprenden por lo menos un compuesto de fórmula (I), y métodos de uso de los compuestos de fórmula (I) para tratamiento o

prevención de una infección viral o a trastorno relacionado con un virus en paciente.

Definiciones y abreviaturas

Los términos usados en la presente memoria tienen su significado ordinario y el significado de tales términos es independiente de cada una de de sus apariciones. No obstante y excepto que se indique de otro modo, las siguientes definiciones se aplican a lo largo de la memoria descriptiva y las reivindicaciones. Los nombres químicos, nombres comunes y estructuras químicas se pueden usar en forma indistinta para describir la misma estructura. Si un compuesto químico se menciona, se usan tanto la estructura química como el nombre común y si existe ambigüedad entre la estructura y el nombre, predomina la estructura. Estas definiciones se aplican sin tener en cuenta si un término se usa por sí mismo o en combinación con otros términos, a menos que se indique lo contrario. En consecuencia, la definición de "alquilo" aplica a "alquilo" además de las porciones de "alquilo" de "hidroxialquilo," "haloalquilo," "alcoxi," etc...

Como se usa en la presente memoria, y se aplican a lo largo de la memoria descriptiva, los siguientes términos, a menos que se indique de otro modo, se entenderá que tiene los siguientes significados:

Un “paciente” es un mamífero humano o no humano. En una realización, un paciente es un ser humano. En otra realización, un paciente es un mamífero no humano, que incluye, pero sin limitación, un mono, perro, babuino, rhesus, ratón, rata, caballo, gato o conejo. En otra realización, un paciente es un animal de compañía, que incluye, pero sin limitación un perro, gato, conejo, caballo o hurón. En una realización, un paciente es un perro. En otra realización, un paciente es un gato.

El término "alquilo" como se usa en la presente memoria, se refiere a un grupo hidrocarbonado alifático, donde uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquilo puede ser lineal o ramificado y puede contener de aproximadamente 1 a aproximadamente 20 átomos de carbono. En una realización, un grupo alquilo contiene de aproximadamente 1 a aproximadamente 12 átomos de carbono. En otra realización, un grupo alquilo contiene de aproximadamente 1 a aproximadamente 6 átomos de carbono. Los ejemplos no limitantes de grupos alquilo incluyen metilo, etilo, n-propil, isopropilo, n-butilo, sec-butilo, isobutil, ter-butilo, n-pentilo, neopentilo, isopentilo, n-hexilo, isohexilo y neohexilo. Un grupo alquilo puede estar no sustituido u opcionalmente sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona independientemente del grupo que consiste en halo, alquenilo, alquinilo, -O-arilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, ciano, -OH, -O-alquilo, -O-haloalquilo, -alquilen-O-alquilo, alquiltio, $-NH_2$, -NH(alquilo), $-N(alquilo)_2$, -NH-arilo, -NH-heteroarilo, -NHC(O)-alquilo, -NHC(O)NH-alquilo, $-NHSO_2$-alquilo, $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NH(cicloalquilo), -OC(O)-alquilo, -OC(O)-arilo, -OC(O)-cicloalquilo, -C(O)alquilo, $-C(O)NH_2$, -C(O)NH-alquilo, -C(O)OH y –C(O)O-alquilo. En una realización, un grupo alquilo está no sustituido. En otra realización, un grupo alquilo es un grupo alquilo de cadena lineal. En otra realización, un grupo alquilo es un grupo alquilo ramificado.

El término "alquenilo" como se usa en la presente memoria, se refiere a un grupo hidrocarbonado alifático que tiene por lo menos un doble enlace carbono-carbono, donde uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquenilo puede ser lineal o ramificado y puede contener de aproximadamente 2 a aproximadamente 15 átomos de carbono. En una realización, un grupo alquenilo contiene de

aproximadamente 2 a aproximadamente 10 átomos de carbono. En otra realización, un grupo alquenilo contiene de aproximadamente 2 a aproximadamente 6 átomos de carbono. Los ejemplos no limitantes de grupos alquenilo ilustrativos incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo. Un grupo alquenilo puede estar no sustituido u opcionalmente sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona independientemente del grupo que consiste en halo, alquilo, alquinilo, -O-arilo, arilo, cicloalquilo, cicloalquenilo, ciano, -OH, -O-alquilo, -O-haloalquilo, -alquilen-O-alquilo, alquiltio, $-NH_2$, -NH(alquilo), $-N(alquilo)_2$, -NH-arilo, -NH-heteroarilo, -NHC(O)-alquilo, -NHC(O)NH-alquilo, $-NHSO_2$-alquilo, $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NH(cicloalquilo), -OC(O)-alquilo, -OC(O)-arilo, -OC(O)-cicloalquilo, -C(O)alquilo, $-C(O)NH_2$, -C(O)NH-alquilo, -C(O)OH y –C(O)O-alquilo. En una realización, un grupo alquenilo está no sustituido. En otra realización, un grupo alquenilo es un grupo alquenilo de cadena lineal. En otra realización, un grupo alquilo es un grupo alquenilo ramificado.

El término "alquinilo" como se usa en la presente memoria, se refiere a un grupo hidrocarbonado alifático que tiene por lo menos un triple enlace carbono-carbono, donde uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquinilo puede ser lineal o ramificado y puede contener de aproximadamente 2 a aproximadamente 15 átomos de carbono. En una realización, un grupo alquinilo contiene de aproximadamente 2 a aproximadamente 10 átomos de carbono. En otra realización, un grupo alquinilo contiene de aproximadamente 2 a aproximadamente 6 átomos de carbono. Los ejemplos no limitantes de grupos alquinilo ilustrativos incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. Un grupo alquinilo puede estar no sustituido u opcionalmente sustituido con uno o

más sustituyentes que pueden ser iguales o diferentes, cada sustituyente se selecciona independientemente del grupo que consiste en halo, alquilo, alquenilo, -O-arilo, arilo, cicloalquilo, cicloalquenilo, ciano, -OH, -O-alquilo, -alquilen-O-alquilo, -O-haloalquilo, -alquiltio, $-NH_2$, -NH(alquilo), $-N(alquilo)_2$, -NH-arilo, -NH-heteroarilo, -NHC(O)-alquilo, -NHC(O)NH-alquilo, $-NHSO_2$-alquilo, $-NHSO_2$-arilo, $-NHSO_2$-heteroarilo, -NH(cicloalquilo), -OC(O)-alquilo, -OC(O)-arilo, -OC(O)-cicloalquilo, -C(O)alquilo, $-C(O)NH_2$, -C(O)NH-alquilo, -C(O)OH y –C(O)O-alquilo. En una realización, un grupo alquinilo está no sustituido. En otra realización, un grupo alquinilo es un grupo alquinilo de cadena lineal. En otra realización, un grupo alquinilo es un grupo alquinilo ramificado.

El término “alquileno” como se usa en la presente memoria, se refiere a un grupo alquilo, como se deficnio anteriormente, donde uno de los átomos de hidrógeno del grupo hidrocarbonado se reemplaza con un enlace. Los ejemplos ilstrativos de alquileno incluyen, pero sin limitación, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$ y $-CH_2CH_2CH(CH_3)-$. En una realización, un grupo alquileno es un grupo alquileno de cadena lineal. En otra realización, un grupo alquileno es un grupo alquileno ramificado.

"Arilo" significa un sistema anular aromático monocíclico o multicíclico que tiene de aproximadamente 6 a aproximadamente 14 átomos de carbono anulares. En una realización, un grupo arilo tiene de aproximadamente 6 a aproximadamente 10 átomos de carbono anulares. Un grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y se definen a continuación en la presente memoria. Los ejemplos no limitantes de grupos arilo ilustrativos incluyen fenilo y naftilo. En una realización, un grupo arilo está no sustituido. En otra realización, un grupo arilo es un grupo fenilo.

El término "cicloalquilo" como se usa en la presente memoria, se refiere a un sistema anular no aromático mono- o multicíclico que tiene de aproximadamente 3 a aproximadamente 10 átomos de carbono anulares. En una realización, un cicloalquilo tiene de aproximadamente 5 a aproximadamente 10 átomos de carbono anulares. En otra realización, un cicloalquilo tiene de aproximadamente 5 a aproximadamente 7 átomos de carbono anulares. Los ejemplos no limitantes de cicloalquilos monocíclicos ilustrativos incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Los ejemplos no limitantes de cicloalquilos multicíclicos ilustrativos incluyen 1-decalinilo, norbornilo, adamantilo y similares. Un grupo cicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y se definen a continuación en la presente memoria. En una realización, un grupo cicloalquilo está no sustituido.

El término "cicloalquenilo" como se usa en la presente memoria, se refiere a un sistema anular no aromático mono- o multicíclico que comprende de aproximadamente 3 a aproximadamente 10 átomos de carbono anulares y que contiene por lo menos un doble enlace endocíclico. En una realización, un cicloalquenilo contiene de aproximadamente 5 a aproximadamente 10 átomos de carbono anulares. En otra realización, un cicloalquenilo contiene 5 o 6 átomos de carbono anulares. Los ejemplos no limitantes de cicloalquenilo monocíclicos ilustrativos incluyen ciclopentenilo, ciclohexeniln, ciclohepta-1,3-dieniln y similares. Un grupo cicloalquenilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y se define a continuación en la presente memoria. En una realización, un grupo cicloalquenilo está no sustituido.

El término "cicloalquenilo de 5 miembros" como se usa en la presente memoria, se refiere a un grupo cicloalquenilo, como se definió anteriormente, que tiene 5 átomos de carbono anulares.

El término "halo" como se usa en la presente memoria, significa –F, -Cl, -Br o -I. En una realización, halo se refiere a –Cl o -F.

El término "haloalquilo" como se usa en la presente memoria, se refiere a un grupo alquilo como se definió anteriormente, donde uno o más de los átomos de hidrógeno del grupo alquilo se ha reemplazado con un halógeno. En una realización, un grupo haloalquilo tiene 1 a 6 átomos de carbono. En otra realización, un grupo haloalquilo está sustituido con 1 a 3 átomos de F. Los ejemplos no limitantes de grupos haloalquilo ilustrativos incluyen $–CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2Cl$ y $-CCl_3$.

El término "hidroxialquilo" como se usa en la presente memoria, se refiere a un grupo alquilo como se definió anteriormente, donde uno o más de los átomos de hidrógeno del grupo alquilo se ha reemplazado con un grupo –OH. En una realización, un grupo hidroxialquilo tiene de 1 a 6 átomos de carbono. Los ejemplos no limitantes de grupos hidroxialquilo ilustrativos incluyen hidroximetilo, 2-hidroxietilo, 3-hidroxipropilo, 4-hidroxibutilo y $–CH(OH)CH_2CH_3$.

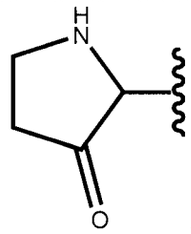
El término "heteroarilo" como se usa en la presente memoria, se refiere a un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 a aproximadamente 14 átomos anulares, donde de 1 a 4 de los átomos anulares es independientemente O, N o S y los restantes átomos anulares son átomos de carbono. En una realización, un grupo heteroarilo tiene 5 a 10 átomos anulares. En otra realización, un grupo heteroarilo es monocíclico y tiene 5 o 6 átomos anulares. En otra realización, un grupo heteroarilo es monocíclico y tiene 5 o 6 átomos anulares y por lo menos un átomo de nitrógeno. Un grupo heteroarilo puede estar opcionalmente sustituido con uno o más

"sustituyentes del sistema anular" que pueden ser iguales o diferentes, y se define a continuación en la presente memoria. Un grupo heteroarilo unido por medio de un átomo de carbono del anillo y algún átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N-óxido. El término "heteroarilo" también abarca un grupo heteroarilo, como se definió anteriormente, que se ha fusionado a un anillo de benceno. Los ejemplos no limitantes de heteroarilos ilustrativos incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, 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, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" también se refiere a residuos de heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares. En una realización, un grupo heteroarilo es un grupo heteroarilo de 6 miembros. En otra realización, un grupo heteroarilo es un grupo heteroarilo de 5 miembros.

El término "heteroarilo de 5 miembros" como se usa en la presente memoria, se refiere a un grupo heteroarilo, como se definió anteriormente, que tiene 5 átomos anulares.

El término "heterocicloalquilo" como se usa en la presente memoria, se refiere a un sistema anular no aromático saturado monocíclico o multicíclico que comprende 3 a aproximadamente 10 átomos anulares, donde de 1 a 4 de los átomos anulares son independientemente O, S o N y el resto de los átomos anulares son átomos de carbono. En una realización, un grupo heterocicloalquilo tiene de aproximadamente 5 a aproximadamente 10 átomos anulares. En otra realización, un grupo heterocicloalquilo tiene 5 o 6 átomos anulares. No existen

átomos de oxígeno y/o azufre presentes en el sistema anular. Cualquier grupo –NH de un anillo heterocicloalquilo puede existir protegido tal como, por ejemplo, como un grupo -N(Boc), -N(CBz), -N(Tos) y similares; tales grupos protegidos heterocicloalquilo se consideran parte de esta invención. Un grupo heterocicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como definen a continuación en la presente memoria. El átomo de nitrógeno o azufre del heterociclilo opcionalmente se puede oxidar al correspondiente N-óxido, S-óxido o S,S-dióxido. Los ejemplos no limitantes de anillos heterocicloalquilo monocíclico incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona y similares. Un átomo de carbono anular de un grupo heterocicloalquilo puede estar funcionalizado como grupo carbonilo. Un ejemplo ilustrativo de tal grupo heterocicloalquilo es pirrolidonilo:

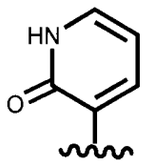


En una realización, un grupo heterocicloalquilo es un grupo heterocicloalquilo de 6 miembros. En otra realización, un grupo heterocicloalquilo es un grupo heterocicloalquilo de 5 miembros.

El término "heterocicloalquilo de 5 miembros" como se usa en la presente memoria, se refiere a un grupo heterocicloalquilo, como se definió anteriormente, que tiene 5 átomos anulares.

El término "heterocicloalquenilo" como se usa en la presente memoria, se refiere a un grupo heterocicloalquilo, como se definió anteriormente, donde el grupo heterocicloalquilo contiene de 3 a 10 átomos anulares, y por lo menos un

doble enlace endocíclico carbono-carbono o carbono-nitrógeno. En una realización, un grupo heterocicloalquilo tiene de 5 a 10 átomos anulares. En otra realización, un grupo heterocicloalquilo es monocíclico y tiene 5 o 6 átomos anulares. Un grupo heterocicloalquenilo opcionalmente puede estar opcionalmente sustituido con uno o más sustituyentes del sistema anular, donde "sustituyentes del sistema anular" son como se definió anteriormente. El átomo de nitrógeno o azufre del heterocicloalquenilo opcionalmente se puede oxidar al correspondiente N-óxido, S-óxido o S,S-dióxido. Los ejemplos no limitantes de grupos heterocicloalquenilo ilustrativos incluyen 1,2,3,4- tetrahidropiridinilo, 1,2-dihidropiridinilo, 1,4-dihidropiridinilo, 1,2,3,6-tetrahidropiridinilo, 1,4,5,6-tetrahidropirimidinilo, 2-pirrolinilo, 3-pirrolinilo, 2-imidazolinilo, 2-pirazolinilo, piridona, 2-piridona, dihidroimidazolilo, dihidrooxazolilo, dihidrooxadiazolilo, dihidrotiazolilo, 3,4-dihidro-2H-piranilo, dihidrofuranilo, fluorodihidrofuranilo, 7-oxabiciclo[2.2,1]heptenilo, piridona, 2-piridona, dihidrotiofenilo, dihidrotiopiranilo y similares. Un átomo de carbono anular de un grupo heterociclenilo puede estar funcionalizado como grupo carbonilo. Un ejemplo ilustrativo de tal grupo heterociclenilo es:

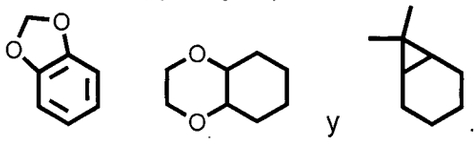


En una realización, un grupo heterocicloalquenilo es un grupo heterocicloalquenilo de 6 miembros. En otra realización, un grupo heterocicloalquenilo es un grupo heterocicloalquenilo de 5 miembros.

El término "heterocicloalquenilo de 5 miembros" como se usa en la presente memoria, se refiere a un grupo heterocicloalquenilo, como se definió anteriormente, que tiene 5 átomos anulares.

El término "sustituyente del sistema anular" como se usa en la presente memoria, se refiere a un grupo sustituyente unido a un sistema anular aromático o

no aromático, por ejemplo, reemplaza un hidrógeno disponible del sistema anular. Los sustituyentes del sistema anular 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, -OH, hidroxialquilo, -O-alquilo, -alquilen-O-alquilo, -O-arilo, aralcoxi, acilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, -OC(O)-alquilo, -OC(O)-arilo, -OC(O)-cicloalquilo, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alquilo), Y_1Y_2N-, Y_1Y_2N-alquilen-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- y -$SO_2NY_1Y_2$, donde Y_1 e Y_2 pueden ser iguales o diferentes, cada uno se selecciona independientemente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo y aralquilo. "Sustituyente del sistema anular" también puede significar un residuo único que reemplaza simultáneamente dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema anular. Los ejemplos de tal residuo son metilendioxi, etilendioxi, -$C(CH_3)_2$- y similares que forman residuos tales como, por ejemplo:



El término "sustituido" como se usa en la presente memoria, significa que uno o más hidrógenos del átomo designado está reemplazado con una selección del grupo indicado, con la condición de que no se exceda la valencia normal del átomo designado en las circunstancias existentes y que la sustitución origine un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles solo si tales combinaciones originan compuestos estables. Por

"compuesto estable' o "estructura estable" se entiende un compuesto que es suficientemente fuerte para sobrevivir al aislamiento en un grado de pureza útil a partir de una mezcla de reacción y formulación en un agente terapéutico eficaz.

El término "opcionalmente sustituido" como se usa en la presente memoria, significa la sustitución opcional con grupo, radicales o residuos específicos.

Los términos "purificado", "en forma purificada" o "en forma aislada y purificada" como se usa en la presente memoria, para un compuesto se refiere al estado físico de dicho compuesto después de aislarse de un proceso sintético (por ej., de una mezcla de reacción), o fuente natural o una combinación de estos. De este modo, el término "purificado", en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto después de obtenerse de un proceso de purificación o procesos descriptos en la presente memoria o bien conocidos por los expertos en el arte (por ej., cromatografía, recristalización y similares), en una pureza suficiente para ser caracterizable por técnicas analíticas estándares descriptas en la presente memoria o bien conocidas por los expertos en el arte.

Se debe advertir que se supone que cualquier carbono además del heteroátomo con valencias insatisfechas en el texto, esquemas, ejemplo y Tablas de la presente memoria tiene el número suficiente de átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional de un compuesto se denomina "protegido", esto significa que el grupo está en una forma modificada para impedir reacciones secundarias no deseadas en el sitio protegido cuando el compuesto se somete a una reacción. Los grupos protectores adecuados serán reconocidos por los expertos en el arte además de con referencia a los manuales estándares tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando aparece cualquier variable (por ej., arilo, heterociclo, R^{11}, etc.) más de una vez en cualquier constituyente o en la Fórmula (I) o (II), su definición en cada una de las apariciones es independiente de su definición en cada una de las otras apariciones, a menos que se indique de otro modo.

Los profármacos y solvatos de los compuestos de la invención también están contemplados en la presente memoria. Se proporciona una descripción de los profármacos en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Associación y Pergamon Press. El término "profármaco" como se usa en la presente memoria, se refiere a un compuesto (por ej., un precursor del fármaco) que se transforma *in vivo* para proporcionar un Compuesto de fórmula (I) o una sal, hidrato o solvato aceptable para uso farmacéutico del compuesto. La transformación se puede producir por varios mecanismos (por ej., por procesos metabólicos o químicos), tales como, por ejemplo, mediante hidrólisis en sangre. Una descripción del uso de los profármacos se proporciona en T. Higuchi y W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 de la A.C.S. Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

Por ejemplo, si un Compuesto de fórmula (I) o una sal, hidrato o solvato aceptable para uso farmacéutico del compuesto contiene un grupo funcional ácido carboxílico, un profármaco puede comprender un éster formado por el reemplazo del átomo de hidrógeno del grupo ácido con un grupo tal como, por ejemplo, alquilo (C_1–C_8), alcanoiloximetilo (C_2-C_{12}), 1-(alcanoiloxi)etilo que tiene de 4 a 9 átomos de carbono, 1-metilo-1-(alcanoiloxi)-etilo que tiene de 5 a 10 átomos de carbono, alcoxicarboniloximetilo que tiene de 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi)etilo que tiene de 4 a 7 átomos de carbono, 1-metilo-1-

(alcoxicarboniloxi)etilo que tiene de 5 a 8 átomos de carbono, N-(alcoxicarbonil)aminometil que tiene de 3 a 9 átomos de carbono, 1-(N-(alcoxicarbonil)amino)etilo que tiene de 4 a 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gamma-butirolacton-4-ilo, di-N,N-alquilamino-(C_1-C_2)alquilo (C_2-C_3) (tal como β-dimetilaminoetilo), carbamoil-(C_1-C_2)alquilo, N,N-dialquil(C_1-C_2)carbamoil-alquilo (C_1-C_2) y piperidino-, pirrolidino- o morfolinoalquilo (C_2-C_3) y similares.

De modo similar, si un Compuesto de fórmula (I) contiene un grupo funcional alcohol, un profármaco puede estar formado por el reemplazo del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo (C_1-C_6), 1-(alcanoiloxi(C_1-C_6))etilo, 1-metilo-1-((alcanoiloxi (C_1-C_6))etilo, alcoxicarboniloximetilo (C_1-C_6), N-(alcoxicarbonilaminometilo (C_1-C_6), succinoílo, alcanoílo (C_1-C_6), □-aminoalcanilo (C_1-C_4), arilacilo y □-aminoacilo, o □-aminoacil-□-aminoacilo, donde cada grupo □-aminoacilo se selecciona independientemente de los L-aminoácidos, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)$alquilo$)_2$ o glicosilo (el radical resultante de la eliminación de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un Compuesto de fórmula (I) incorpora un grupo funcional amina, se puede formar un profármaco por el reemplazo de un átomo de hidrógeno en el grupo amina con un grupo tal como, por ejemplo, R-carbonilo, RO-carbonilo, NRR'-carbonilo donde cada R y R' son independientemente (alquilo C_1-C_{10}, cicloalquilo (C_3-C_7), bencilo o R-carbonilo es un □-aminoacilo natural o □-aminoacilo, —$C(OH)C(O)OY^1$ donde Y^1 es H, alquilo (C_1-C_6) o bencilo —$C(OY^2)Y^3$ donde Y^2 es alquilo (C_1-C_4) y Y^3 alquilo (C_1-C_6), carboxialquilo, aminoalquilo (C_1-C_4) o mono-N—o di-N,N-alquilaminoalquilo (C_1-C_6), —$C(Y^4)Y^5$ donde Y^4 es H o metilo y Y^5 es mono-N— o di-N,N-(C_1-C_6)alquilamino morfolino, piperidin-1-ilo o pirrolidin-1-ilo, y similares.

Uno o más compuestos de la invención pueden existir además como formas solvatadas con solventes aceptables para uso farmacéutico tales como agua, etanol, y similares, y se considera que la invención abarca ambas formas solvatada y no solvatadas. "Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física incluye variados grados de enlaces iónicos y covalentes, que incluyen enlaces hidrógeno. En ciertos casos el solvato será capaz del aislamiento, por ejemplo cuando se incorporan una o más moléculas de solvente en la retícula cristalina del sólido cristalino. "Solvato" abarca tanto los solvatos en fase solución como los aislables. Los ejemplos no limitantes de solvatos ilstrativos incluyen etanolatos, metanolatos y similares. "Hidrato" es un solvato donde la molécula de solvato es H_2O.

Uno o más compuestos de la invención opcionalmente se pueden convertir en un solvato. La preparación de solvatos es generalmente conocida. De este modo, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe la preparación de los solvatos de fluconazol antifúngico en acetato de etilo además de agua. Se describen preparaciones similares de solvatos, hemisolvatos, hidratos y similares en E. C. van Tonder *et al*, *AAPS PharmSciTech.*, 5(1), article 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). Un proceso típico, no limitante incluye la disolución del compuesto de la invención en una cantidad deseada de solvente (orgánico o agua o sus mezclas) a una temperatura superior que la ambiente y enfriamiento de la solución a una velocidad suficiente para formar cristales que luego se aíslan por métodos estándares. Las técnicas analíticas tales como, por ejemplo espectroscopia I. R., muestran la presencia del, solvente (o agua) en los cristales como solvato (o hidrato)

El término "cantidad efectiva" o "cantidad terapéuticamente efectiva" se entiende que describe una cantidad de compuesto o una composición de la presente invención que es efectiva para tratar o prevenir una infección viral o un trastorno relacionado con el virus.

Los conjugados metabólicos, tales como glucurónidos y sulfatos pueden experimentar la conversión reversible a los compuestos de fórmula (I) están contemplados en la presente invención.

Los compuestos de fórmula (I) pueden formar sales y todas estas sales están contempladas dentro del alcance de esta invención. La referencia al Compuesto de fórmula (I) en la presente memoria se entiende que incluye la referencia a sus sales, a menos que se indique lo contrario. El término "sal(es)", como se emplea en la presente memoria, indica sales ácidas formadas con ácidos inorgánicos y/o orgánicos, además de sales básicas formadas con bases inorgánicas y/u orgánicas. Además, cuando un Compuesto de fórmula (I) contiene tanto un residuo básico, tal como, pero sin limitación, piridina o imidazol, como un residuo ácido, tal como, pero sin limitación, ácido carboxílico, se pueden formar zwitteriones ("sales internas") y están incluidas dentro del término "sal(es)" como se usa en la presente memoria. Se prefiere las sales aceptables para uso farmacéutico (es decir, no tóxicas, aceptables para uso fisiológico), si bien otras sales también son útiles. Las sales de los compuestos de la Fórmula I se pueden formar, por ejemplo, por la reacción de un Compuesto de fórmula (I) con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el que la sal precipita o en un medio acuoso seguido por liofilización.

Los ejemplos de sales de adición incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos,

propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos,) y similares. Adicionalmente, se describen ácidos que se consideran generalmente adecuados para la formación de sales útiles para uso farmacéutico a partir de compuestos farmacéuticos básicos, 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, *Internaciónal J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y in *The Orange Book* (Food & Drug Administración, Washington, D.C. en su sitio web). Estas descripciones están incorporadas en la presente memoria como referencias.

Los ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalinotérreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butilaminas y sales con aminoácidos tales como arginina, lisina y similares. Los grupos que contienen nitrógeno básico se pueden con agentes tales como haluros de alquilo inferior (por ej., cloruros, bromuros y yoduros de metilo, etilo y butilo), sulfatos de dialquilo (por ej., sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ej., cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (por ej., bromuros de bencilo y fenetilo), y otros.

Todas estas sales ácidas y sales básicas se consideran sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Los ésteres aceptables para uso farmacéutico incluidos en los presentes compuestos incluyen los siguientes grupos: (1) ésteres de ácido carboxílico

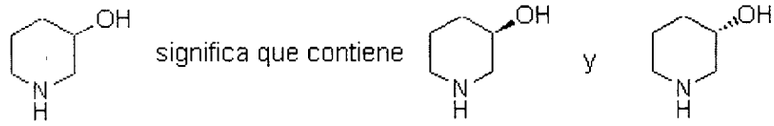
obtenidos por la esterificación de los grupos hidroxi, en los que la porción del residuo no carbonilo del grupo éster se selecciona de alquilo de cadena lineal o ramificada (por ejemplo, acetilo, n-propilo, t-butilo, o n-butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo opcionalmente sustituido con, por ejemplo, halógeno, alquilo C_{1-4}, o alcoxi C_{1-4} o amino); (2) ésteres de sulfonato, tales como alquilo o aralquilsulfonilo (por ejemplo, metansulfonilo); (3) ésteres de aminoácidos (por ejemplo, L-valilo o L-isoleucilo); (4) ésteres fosfonato y (5) ésteres de mono-, di- o trifosfato. Los ésteres de fosfato se pueden esterificar adicionalmente, por ejemplo, por un alcohol C_{1-20} o un derivado reactivo de este o por un a 2,3-diacil(C_{6-24}) glicerol.

Los compuestos de fórmula (I) pueden contener centros asimétricos o quirales y, en consecuencia existir en diferentes formas estereoisoméricas. Se onsidera que todas las formas estereoisoméricas de los compuestos de fórmula (I) además de sus mezclas, que incluyen las mezclas racémicas, forman parte de la presente invención. Además, la presente invención abarca todos los isómeros geométricos y de posición. Por ejemplo, si un Compuesto de fórmula (I) incorpora un doble enlace o un anillo fusionado, tanto las formas cis- como las trans además de sus mezclas están comprendidas dentro del alcance de la invención.

Las mezclas diastereoméricas se pueden separar en sus diastereómeros individuales sobre la base de sus diferentas fisicoquímicas por métodos bien conocidos por los expertos en el arte, tales como, por ejemplo, por cromatografía y/o cristalización fraccionada. Los enantiómeros se pueden separar por la conversión una mezcla enantiomérica en mezcla diastereomérica por la reacción con un compuesto ópticamente activo (por ej., auxiliar quiral tal como un alcohol quiral o cloruro ácido de Mosher), separación de los diastereómeros y conversión (por ej., hidrólisis) de los diastereómeros individuales a los correspondientes

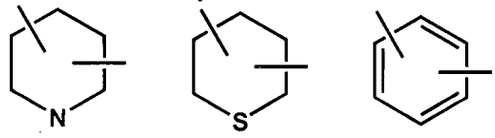
enantiómeros puros. Asimismo, algunos de los compuestos de fórmula (I) pueden ser atropisómeros (por ej., biarilos sustituidos) y se consideran parte de esta invención. Los enantiómeros también se pueden separar por el uso de la columna de HPLC quiral.

La línea recta ——— como un enlace generalmente indica una mezcla de, o cualquiera de los isómeros posibles, los ejemplos no limitantes incluyen, a los que contienen estereoquimica (R)- y (S)- Por ejemplo,



Una línea punteada (-----) representa un enlace opcional.

Las líneas dibujadas en los sistemas anulares, tales como, por ejemplo:



indican que la línea indicada (enlace) se puede unir a cualquiera de los átomos anulares sustituibles, los ejemplos no limitantes incluyen átomos anulares de carbono, nitrógeno y azufre.

Como bien se sabe el arte, un enlace dibujado desde un átomo particular en que no se grafica un residuo en el extremo terminal del enlace indica un grupo metilo unido mediante ese enlace al átomo, a menos que se indique lo contrario. Por ejemplo:



Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (que incluyen a los de las sales,

solvatos, hidratos, ésteres y profármacos de los compuestos además de las sales, solvatos y ésteres de los profármacos), tales como los que pueden existir debido a los carbonos asimétricos en varios sustituyentes, que incluyen las formas enantioméricas (que pueden existir incluso en la ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros y formas diastereoméricas, están contempladas en el alcance de esta invención, como los isómeros de posición (tales como, por ejemplo, 4-piridilo y 3-piridilo). Por ejemplo, si un Compuesto de fórmula (I) incorpora un doble enlace o un anillo fusionado, ambas formas cis y trans, así también como las mezclas, están comprendidas dentro del alcance de la invención.

Los estereoisómeros individuales de los compuestos de al invención, por ejemplo, pueden estar sustancialmente libres de otros isómeros, o se pueden mezclar, por ejemplo, como racematos o con todos los otros u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener configuración S o R definida por la recomendaciones de la *IUPAC* 1974. El uso de los términos "sal", "solvato", "éster", "profármaco" y similares, se considera que se aplica igualmente a la sal, solvato, éster y profármaco de los enantiómeros, estereoisómeros, rotámeros, isómeros de posición, racematos o profármacos de los compuestos de la invención.

La presente invención también abarca los compuestos marcados con isótopos de la presente invención que son idénticos a los mencionados en la presente memoria, excepto por el hecho que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o número másico diferente de la masa atómica o número másico usualmente hallado en la naturaleza. Tales compuestos son útiles como reactivos terapéuticos, diagnósticos o de investigación. Los ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno,

carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Ciertos compuestos fórmula (I) marcados con isótopos (por ej., los marcados con ^{3}H y ^{14}C) son útiles para los ensayos de distribución en tejido del compuesto y/o sustrato. Los isótopos tritiados (es decir, ^{3}H) y con carbono 14 (es decir, ^{14}C) son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H) puede suministrar ciertas ventajas terapéuticas debido a su mayor estabilidad metabólica (por ej., vida media in vivo aumentada o requerimientos de dosis reducidos) y por consiguiente puede ser preferida en algunas circunstancias. Los Compuestos de fórmula (I) marcados con isótopos se pueden preparar por los siguientes procedimientos análogos a los descriptos en los Esquemas y/o en los siguientes Ejemplos de la presente memoria por la sustitución de un reactivo marcado isotópicamente apropiado para un reactivo no marcado con isótopos.

Las formas polimórficas de los compuestos de fórmula (I), y de las sales, solvatos, hidratos, ésteres y profármacos de los compuestos de fórmula (I), se consideran incluidos en la presente invención.

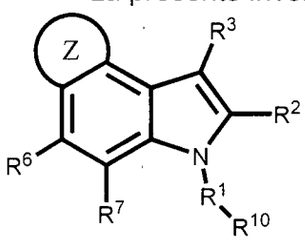
Las siguientes abreviaturas se usan a continuación y tiene los siguientes significados:

BINAP es racémico 2,2'-bis(difenilfosfino)-1,1'-binaftilo; CSA es ácido alcanforsulfónico; DBPD es 2-(Di-t-butilfosfino)bifenilo, DBU es 1,8-diazabiciclo[5.4,0]undec-7-eno, DBN es 1,5-diazabiciclo[4.3,0]non-5-eno; DCC es diciclohexilcarbodiimida; DCM es diclorometano; Dibal-H es hidruro de diisobutilaluminio; DMF es dimetilformamida; EDCI es 1-(3-dimetilaminopropil)-3-etilcarbodiimida; HATU es hexafluorofosfato N-óxido de N-(dietilamino)- 1H-1,2,3-triazolo[4,5-b]piridin-1-ilmetilen]-N-metilmetana-minio;

HOBT es 1-hidroxibenzotriazol; LAH es hidruro de litio y aluminio; LDA es diisopropilamida de litio; m-CPBA es ácido m-cloroperbenzoico; $NaBH(OAc)_3$ es triacetoxiborohidruro de sodio; $NaBH_4$ borohidruro de sodio; $NaBH_3CN$ cianoborohidruro de sodio; NaHMDS es hexametildisililazida sódica; p-TsOH es ácido p-toluensulfónico, p-TsCl es cloruro de p-toluensulfonilo; PPTS es p-toluenesulfonato de piridinio; TMAD es N,N,N',N'-tetrametilazodicarboxamida; HRMS es espectrometría de masa de alta resolución; HPLC es cromatografía líquida de alta resolución; LRMS es espectrometría de masa de baja resolución; Tr es trifenilmetilo; Tris es tris (hidroximetil)aminometano; THF es tetrahidrofurano; TFA es ácido trifluoroacético; Ci/mmol es Curie/mmol (una medida de actividad específica); y Ki representa la constante de disociación para un complejo sustrato/receptor.

Los compuestos de fórmula (I)

La presente invención proporciona Compuestos de fórmula (I):



(I)

y sus sales y solvatos aceptables para uso farmacéutico, donde R^1, R^2, R^3, R^6, R^7, R^{10} y Z se definieron anteriormente para los compuestos de fórmula (I).

En una realización, cuando R^1 es un enlace, R^{10} no es H.

En otra realización, R^1 es un enlace o $-[C(R^{12})_2]_r-$.

En otra realización, R^1 es un enlace.

En otra realización, R^1 es $-CH_2-$.

En aún otra realización, R^1 es $-[C(R^{12})_2]_r-$.

En otra realización, R^1 es $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$.

En aún otra realización, R^1 es $-[C(R^{12})_2]_r-NR^9-[C(R^{12})_2]_q-$.

En aún otra realización, R^1 es $-[C(R^{12})_2]_q-C=C-[C(R^{12})_2]_q-$.

En una realización adicional, R^1 es $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$.

En otra realización, R^1 es $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$.

En una realización, R^{10} es –H.

En otra realización, R^{10} es arilo.

En aún otra realización, R^{10} es cicloalquilo.

En aún otra realización, R^{10} es cicloalquenilo.

En una realización adicional, R^{10} es heterocicloalquilo.

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

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

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

En una realización, R^{10} es arilo o heteroarilo.

En otra realización, R^{10} es fenilo, piridilo, benzimidazol, benzimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

En otra realización, R^{10} es fenilo, piridilo, benzimidazol, benzimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de metilo, ciclopropilo, halo, -OH, $-NH_2$, $-NHCH_3$ y $-N(CH_3)_2$.

En otra realización, R^{10} es quinolina, quinolinona, pteridina o pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3

sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

En aún otra realización, R^{10} es pteridina o pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

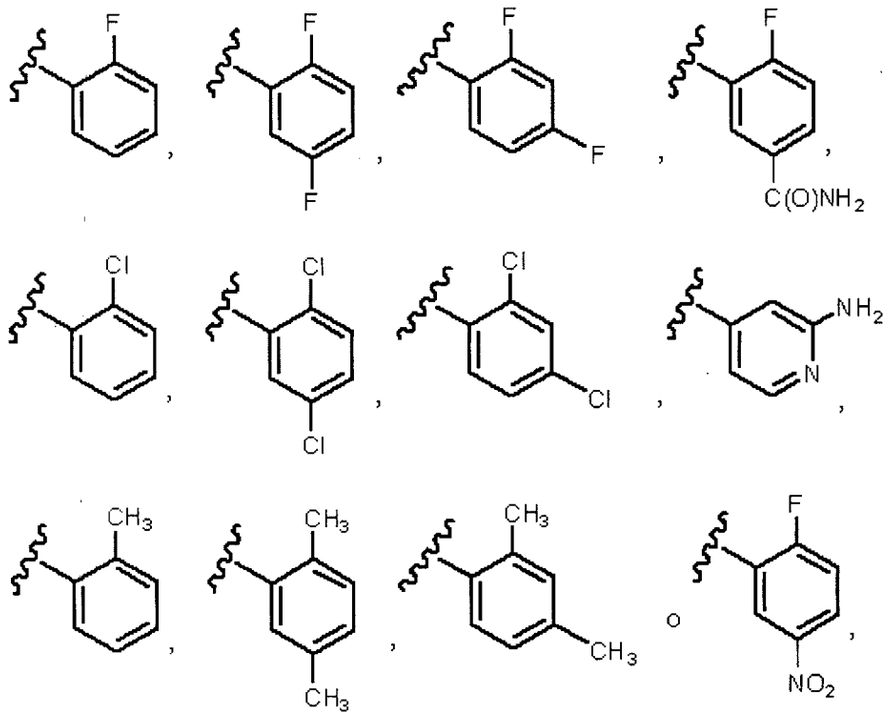
En una realización, R^{10} es quinolina o quinolinona, either of which puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

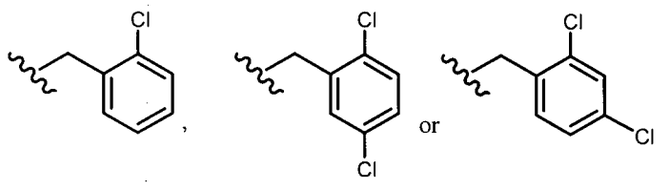
En otra realización, R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquiloo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En una realización, R^{10} es fenilo.

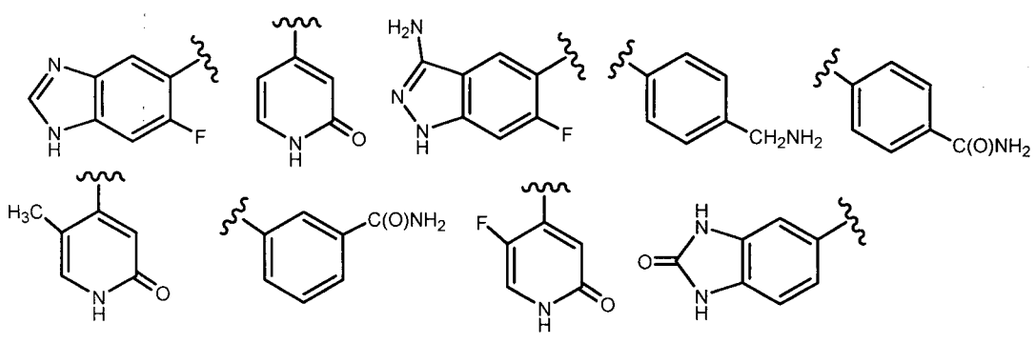
En otra realización, R^{10} es piridilo.

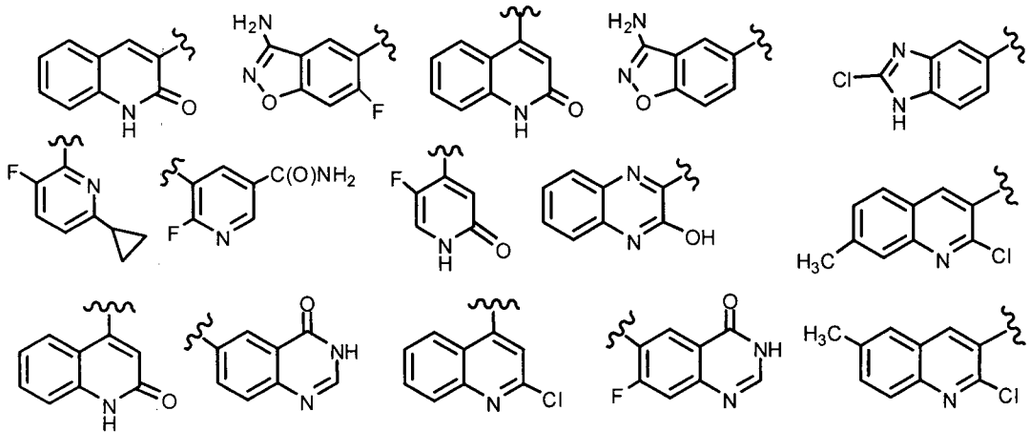
En una realización, R^{10} es:

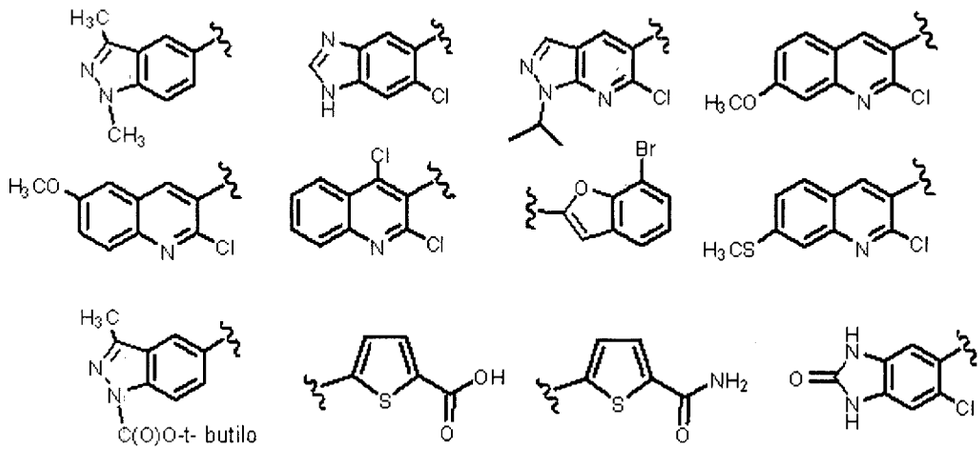


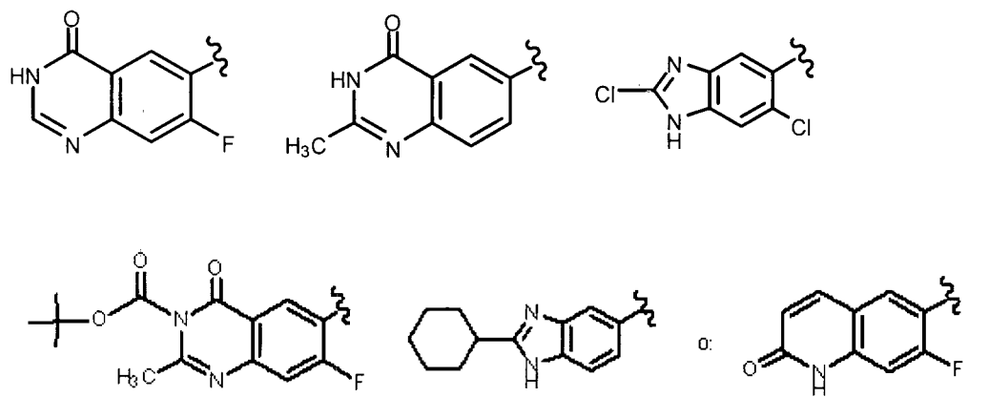


En otra realización, R^{10} es:

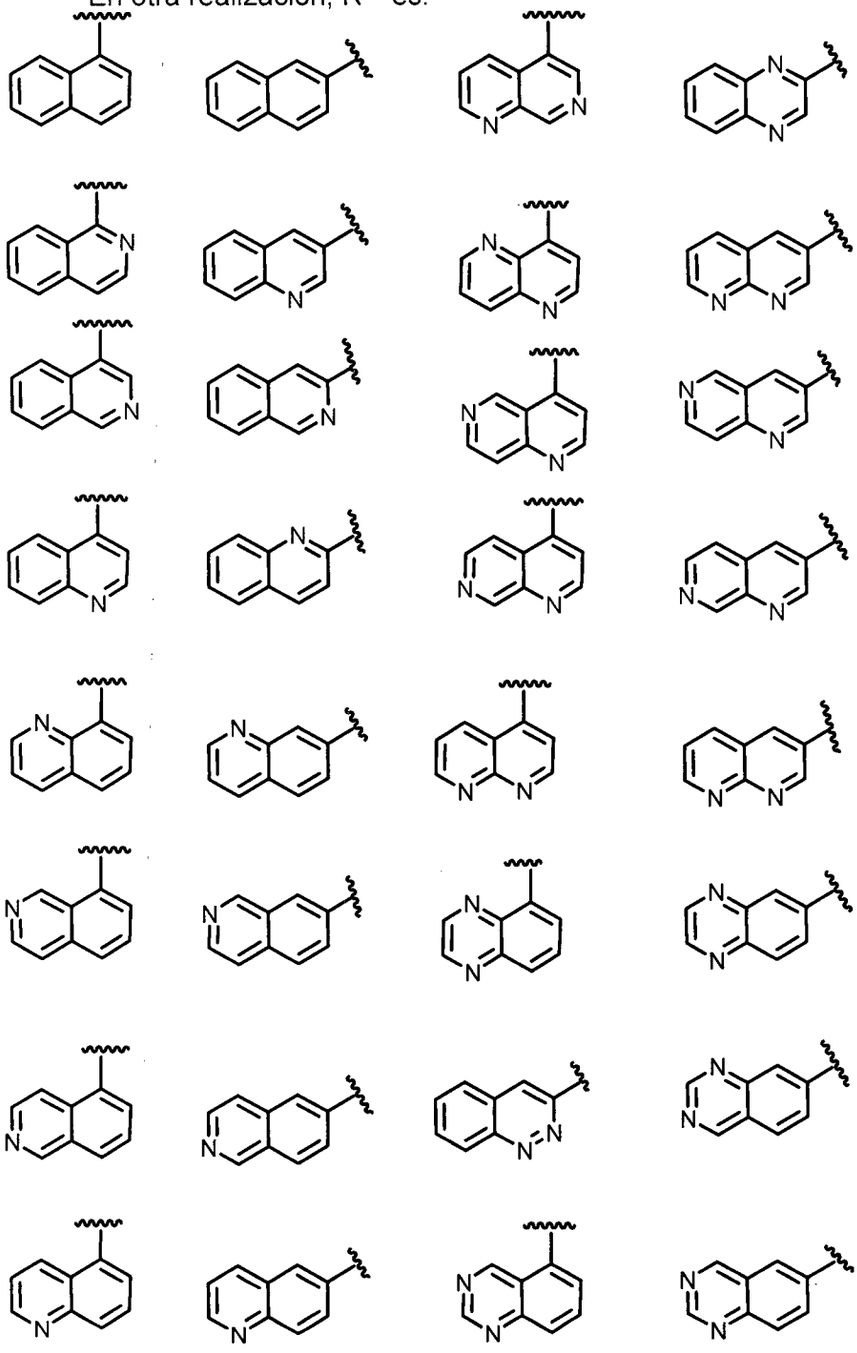


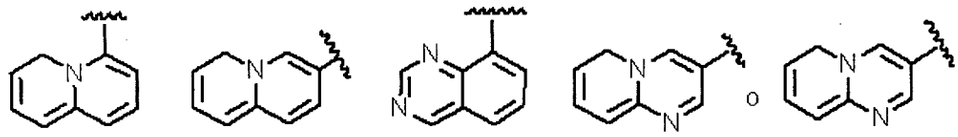



C(O)O-t- butilo



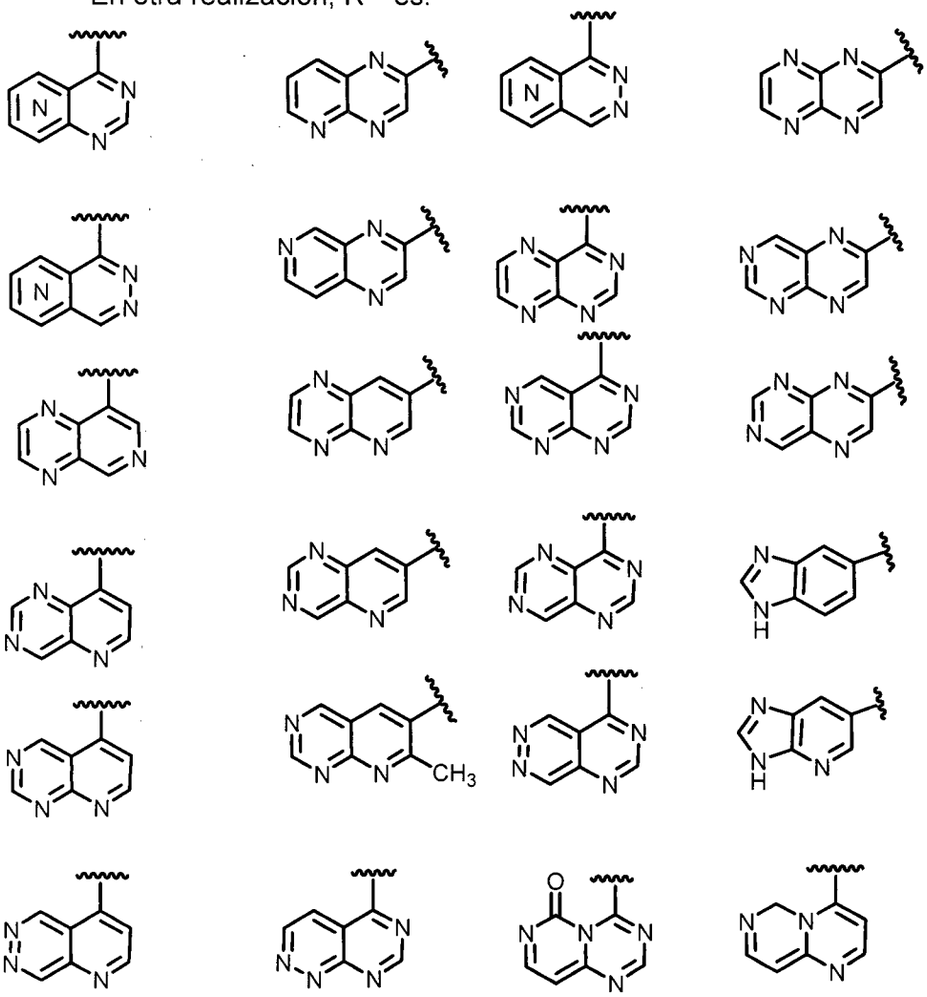
En otra realización, R^{10} es:

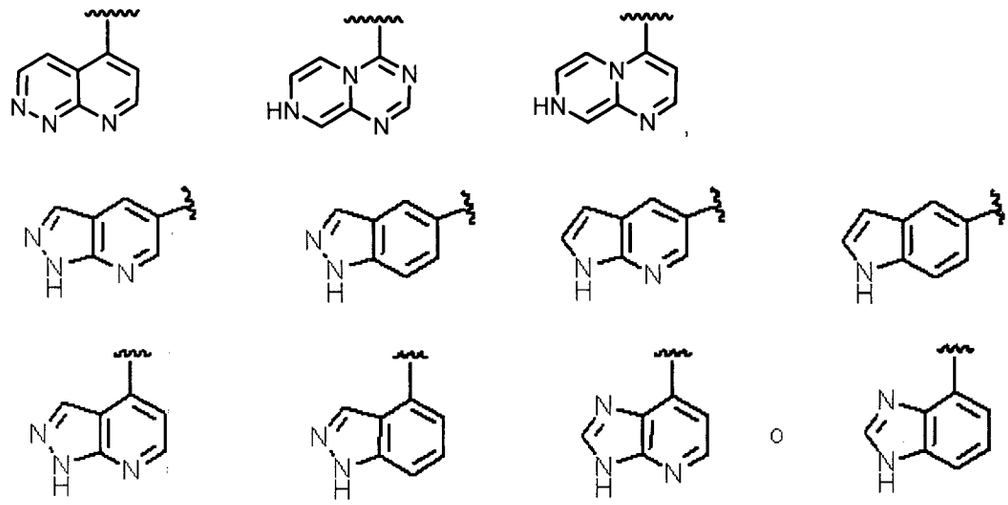




cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

En otra realización, R^{10} es:





, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro del anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

En una realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es –H.

En otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es alquilo.

En otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es arilo.

En aún otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es cicloalquilo.

En aún otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es cicloalquileno.

En una realización adicional, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es heterocicloalquilo.

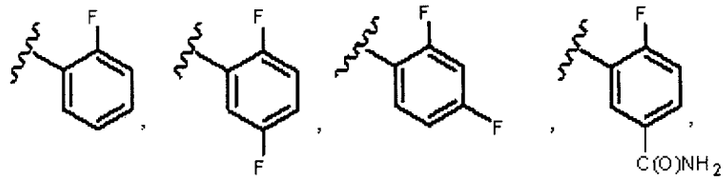
En otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es heterocicloalquileno.

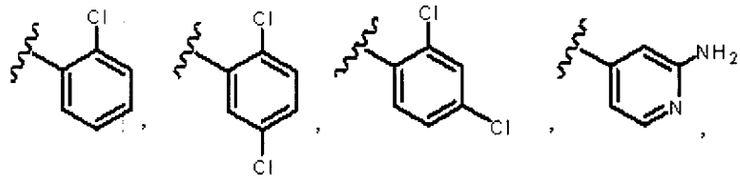
En otra realización, R^1 es $-[C(R^{12})_2]_r-$, cada aparición de R^{12} es H, y R^{10} es heteroarilo.

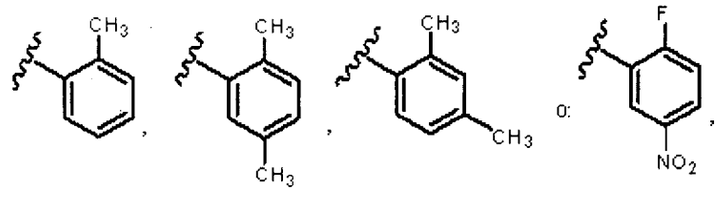
En aún otra realización, R^1 es un enlace o $-[C(R^{12})_2]_r-$, y R^{10} es fenilo, piridilo, benzimidazol, benzimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

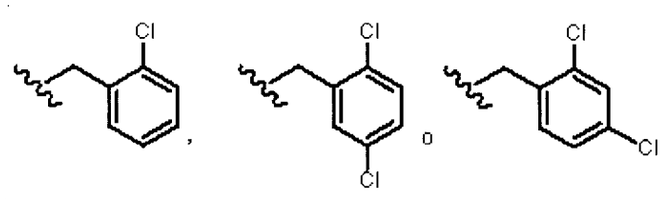
En una realización adicional, R^1 es un enlace o $-[C(R^{12})_2]_r-$, y R^{10} es fenilo, piridilo, bencimidazol, benzimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de metilo, ciclopropilo, halo, -OH, $-NH_2$, $-NHCH_3$ y $-N(CH_3)_2$.

En una realización, R^1 es $-CH_2-$ y R^{10} es:

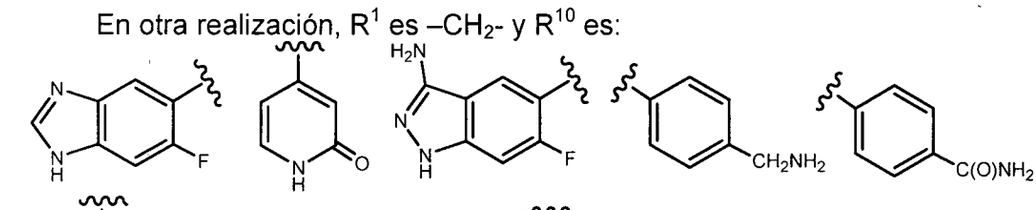


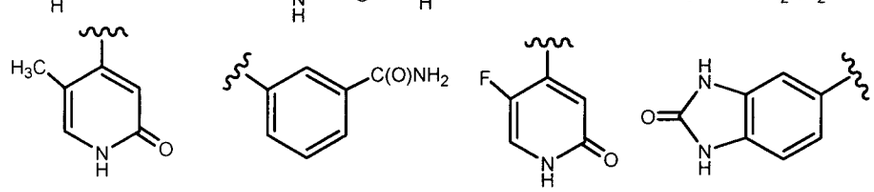


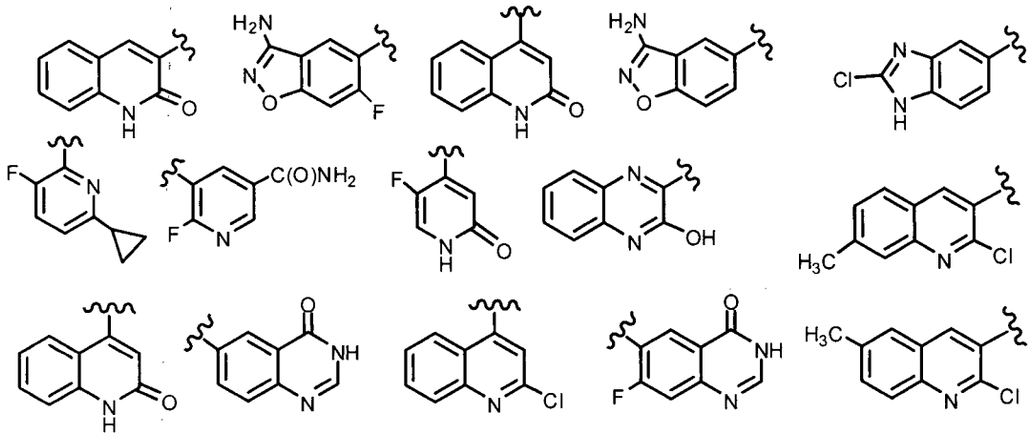


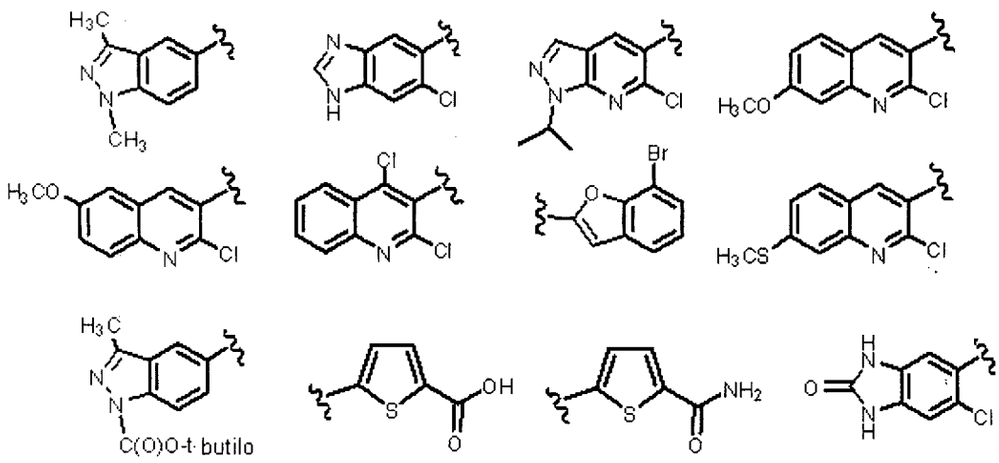


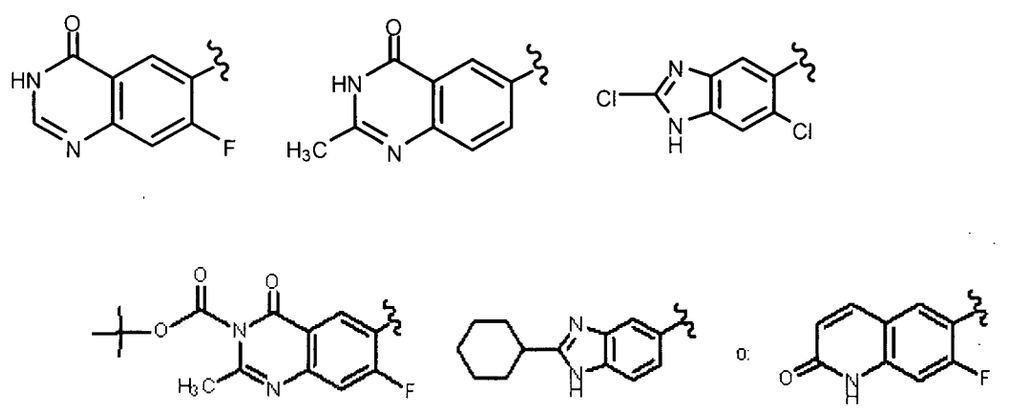
En otra realización, R^1 es $-CH_2-$ y R^{10} es:



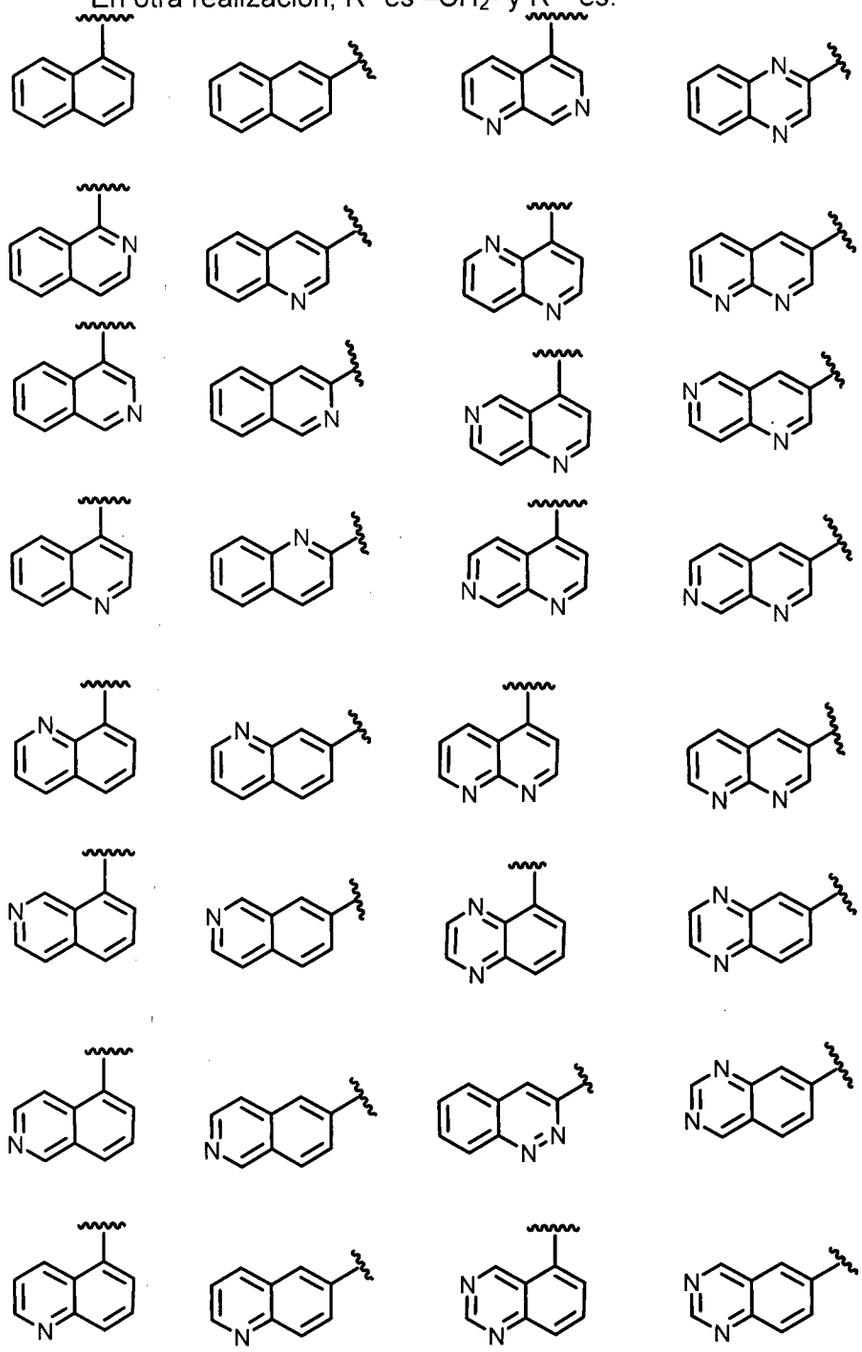


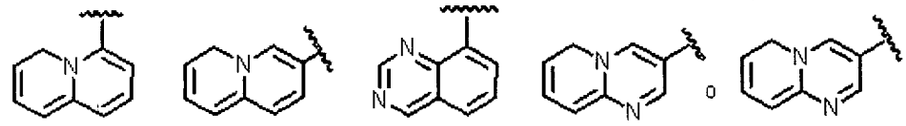



C(O)O-t-butilo



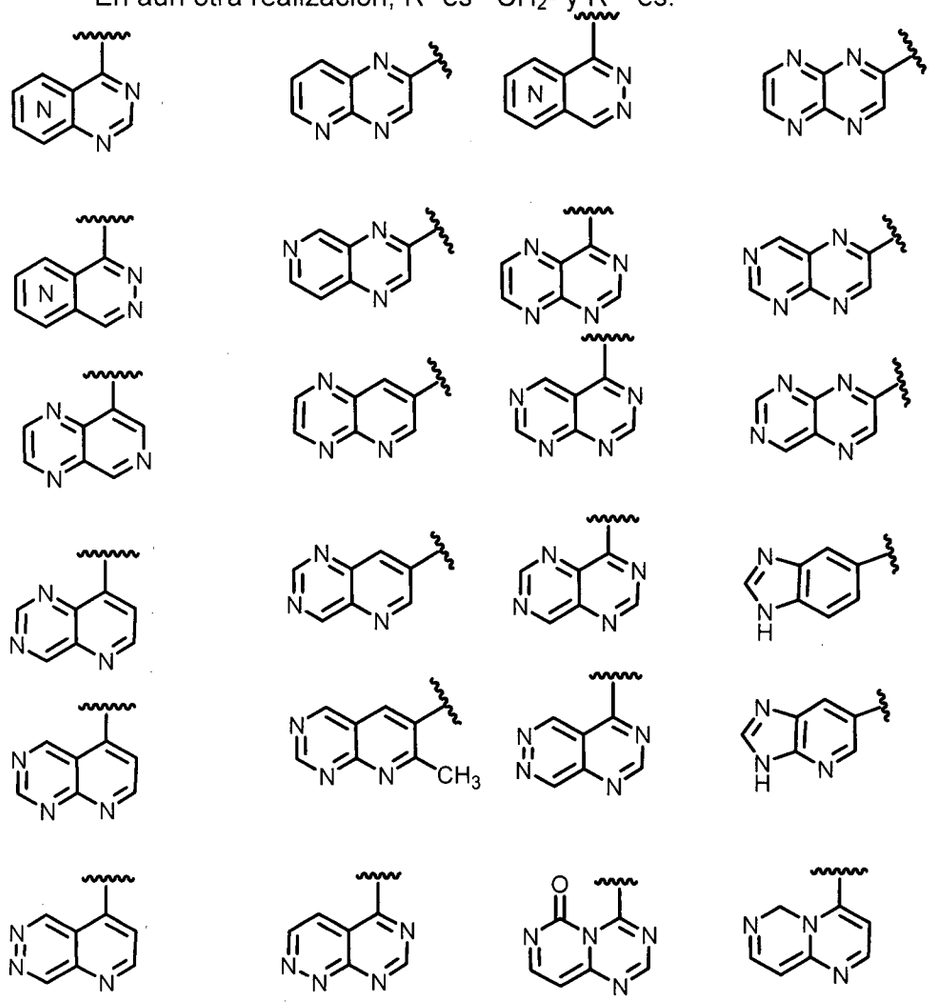
En otra realización, R^1 es $-CH_2-$ y R^{10} es:

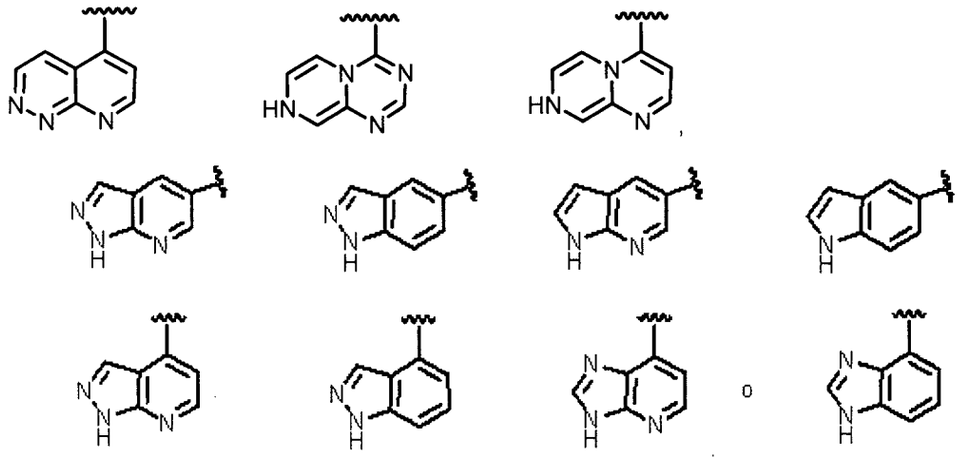




cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

En aún otra realización, R^1 es $-CH_2-$ y R^{10} es:



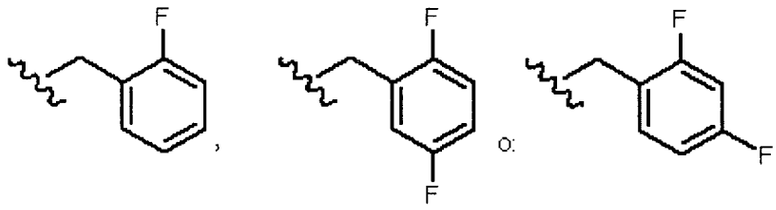


cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro del anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

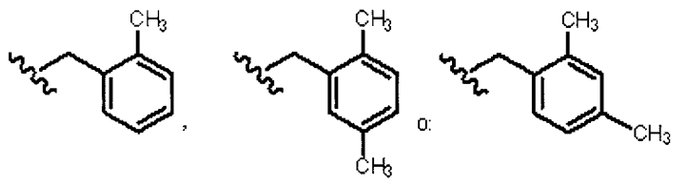
En una realización, $-R^1$-R^{10} es metilo.

En otra realización, $-R^1$-R^{10} es bencilo.

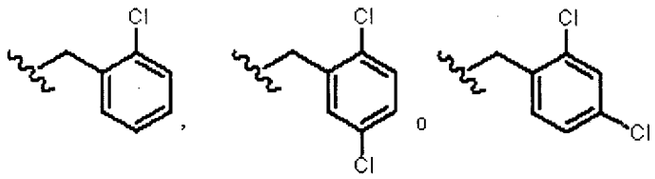
En otra realización, $-R^1$-R^{10} es:



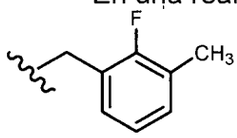
En aún otra realización, $-R^1$-R^{10} es:



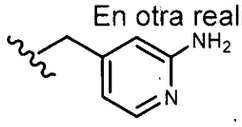
En aún otra realización, -R^1-R^{10} es:



En una realización adicional, -R^1-R^{10} es:



En otra realización, -R^1-R^{10} es:



En una realización, R^2 es –C(O)OR^9.

En otra realización, R^2 es -C(O)N(R^9)$_2$.

En otra realización, R^2 es -C(O)N(R^9)SO_2R^{11}.

En aún otra realización, R^2 es -C(O)NHSO_2R^{11}.

En otra realización, R^2 es -[C(R^{12})$_2$]$_r$–C(O)OR^9.

En otra realización, R^2 es -[C(R^{12})$_2$]$_r$-C(O)N(R^9)$_2$.

En otra realización, R^2 es -[C(R^{12})$_2$]$_r$-C(O)N(R^9)SO_2R^{11}.

En aún otra realización, R^2 es alquilo.

En una realización adicional, R^2 es -[C(R^{12})$_2$]$_q$-arilo.

En otra realización, R^2 es -[C(R^{12})$_2$]$_q$-cicloalquilo.

En otra realización, R^2 es -[C(R^{12})$_2$]$_q$-cicloalquenilo.

En otra realización, R^2 es -$[C(R^{12})_2]_q$-heterocicloalquilo.

En aún otra realización,-$[C(R^{12})_2]_q$ –heteroarilo-.

En aún otra realización, R^2 es -$[C(R^{12})_2]_q$-heterocicloalquenilo.

En una realización adicional, R^2 es -ariltiazin-ilo.

En otra realización, R^2 es ariltiadiazol-il-.

En una realización, R^2 es –C(O)OH.

En otra realización, R^2 es $-C(O)OCH_3$

En otra realización, R^2 es $-C(O)OCH_2CH_3$.

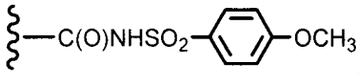
En aún otra realización, R^2 es $-C(O)NHSO_2CH_3$.

En aún otra realización, R^2 es $-C(O)NHSO_2CH_2CH_3$.

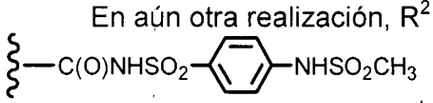
En otra realización, R^2 es $-C(O)NHSO_2$-isopropilo.

En otra realización, R^2 es $-C(O)NHSO_2$-ciclopropilo.

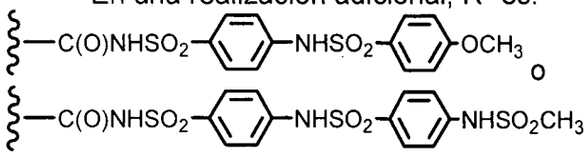
En una realización adicional, R^2 es:



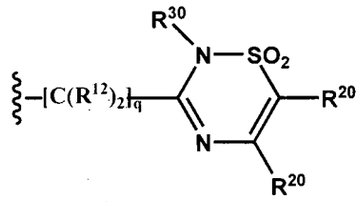
En aún otra realización, R^2 es:

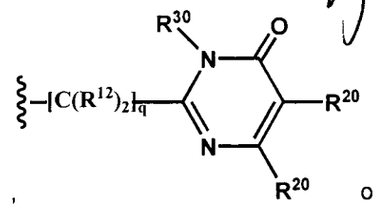


En una realización adicional, R^2 es:

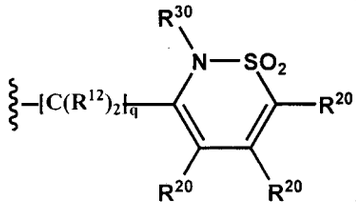


En una realización, R^2 es:

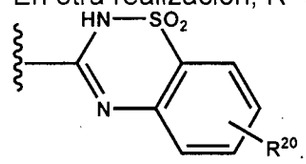




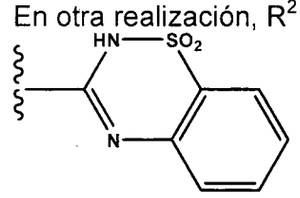
o



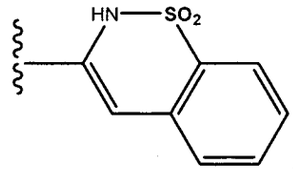
En otra realización, R^2 es:



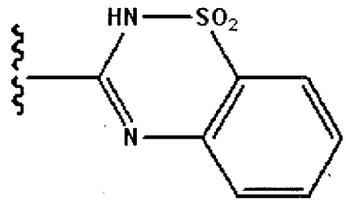
En otra realización, R^2 es:



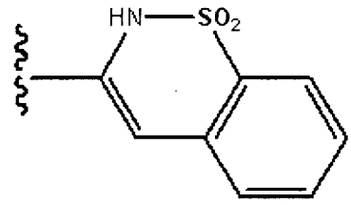
or



En aún otra realización, R^2 es -C(O)OH, -C(O)Oalquilo, -$C(O)NH_2$, -C(O)NH-alquilo, -C(O)NH-cicloalquilo, -$C(O)NHSO_2R^{11}$, heteroarilo,



o

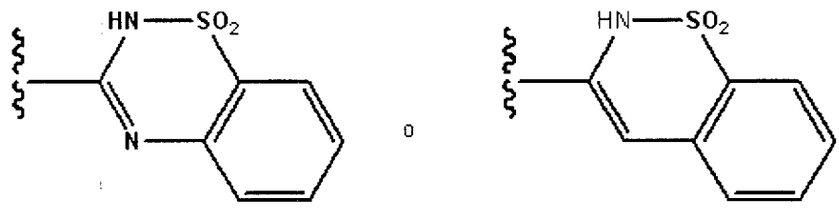


donde un grupo heteroarilo, ariltiazinilo o ariltiadiazolilo puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -$C(O)R^8$, -$C(O)OR^9$, -$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ o -$SO_2N(R^9)_2$.

En una realización, R^2 es –C(O)OH, -C(O)NHSO$_2$-alquilo, -C(O)NHSO$_2$-arilo, -C(O)NHSO$_2$-cicloalquilo o -C(O)NHSO$_2$-alquilen-cicloalquilo.

En otra realización, R^2 es –C(O)OH, -C(O)NHSO$_2$CH$_3$ o -C(O)NHSO$_2$-ciclopropilo.

En otra realización, R^2 es -C(O)OH, -C(O)Oalquiloo, -C(O)NH$_2$, -C(O)NH-alquilo, -C(O)NH-cicloalquilo, -C(O)NHSO$_2$R^{11}, heteroarilo,



donde el grupo heteroarilo, ariltiazin-il- o ariltiadiazol-il- puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)R^8, -C(O)OR^9, -C(O)N(R^9)$_2$, -[C(R^{12})$_2$]$_q$-OR^9, -[C(R^{12})$_2$]$_q$-N(R^9)$_2$, -NHC(O)R^8, -NHSO$_2$R^{11}, -S(O)$_p$R^{11} o -SO$_2$N(R^9)$_2$; de modo tal que si Z es tiofeno-ilo, R^2 es diferente de –C(O)O-alquilo.

En aún otra realización, R^2 es -C(O)NHSO$_2$-alquilo, -C(O)NHSO$_2$-arilo, -C(O)NHSO$_2$-cicloalquilo o -C(O)NHSO$_2$-alquilen-cicloalquilo.

En una realización, R^3 es –H.

En otra realización, R^3 es -[C(R^{12})$_2$]$_q$-alquilo.

En otra realización, R^3 es -[C(R^{12})$_2$]$_q$-arilo.

En aún otra realización, R^3 es -[C(R^{12})$_2$]$_q$-cicloalquilo.

En aún otra realización, R^3 es -[C(R^{12})$_2$]$_q$-cicloalquileno.

En una realización adicional, R^3 es -[C(R^{12})$_2$]$_q$-heterocicloalquilo.

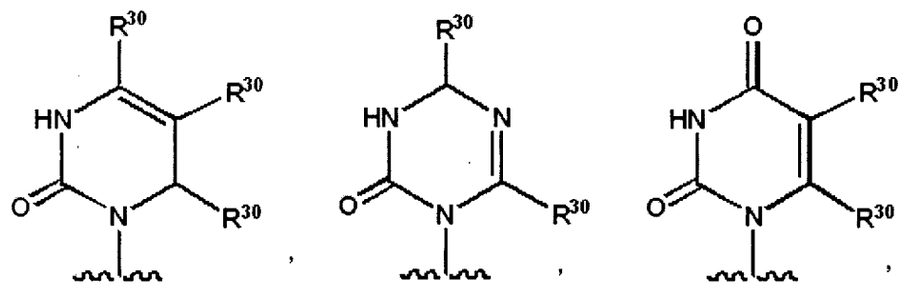
En otra realización, R^3 es -[C(R^{12})$_2$]$_q$-heterocicloalquilene.

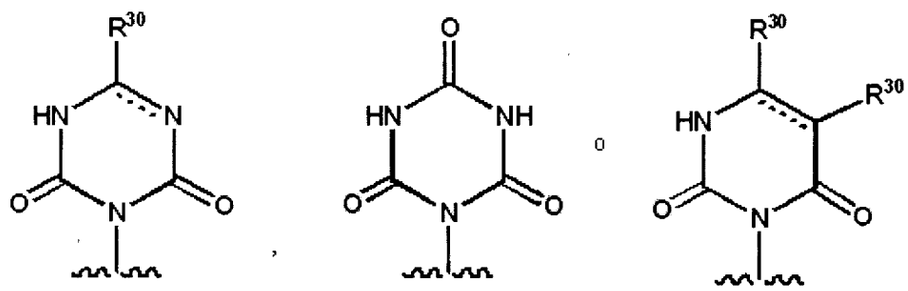
En una realización, R^3 es -[C(R^{12})$_2$]$_q$-heteroarilo.

En una realización, R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$.

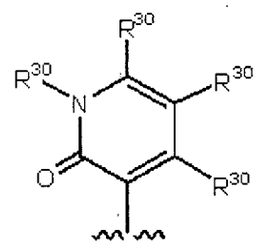
En otra realización, R^3 es piridilo o fenilo que está no sustituido u opcionalmente sustituido con 1to 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, o $-NHC(O)R^8$.

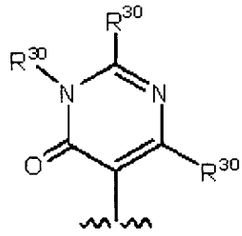
En otra realización, R^3 es:



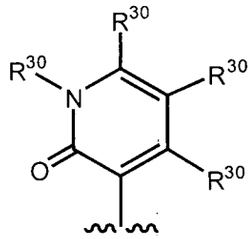


En otra realización, R^3 es:

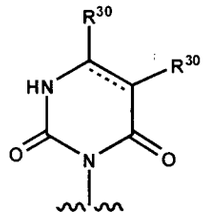


o


En aún otra realización, R^3 es:



En una realización, R^3 es:



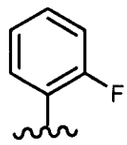
, donde ambos grupos R^{30}, junto con los átomos de carbono a los que están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo.

En otra realización, R^3 es arilo.

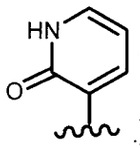
En otra realización, R^3 es fenilo.

En aún otra realización, R^3 es bencilo.

En aún otra realización, R^3 es:



En otra realización, R^3 es:



En una realización, R^6 es –H.

En otra realización, R^6 es alquilo.

En otra realización, R^6 es haloalquilo.

En otra realización, R^6 es hidroxialquilo.

En aún otra realización, R^6 es arilo.

En aún otra realización, R^6 es halo.

En una realización adicional, R^6 es -OH.

En otra realización, R^6 es –O-haloalquilo.

En una realización, R^6 es -alcoxi.

En otra realización, R^6 es -CN.

En otra realización, R^6 es $-[C(R^{12})_2]_q-OR^9$.

En otra realización, R^6 es $-[C(R^{12})_2]_q-N(R^9)_2$.

En aún otra realización, R^6 es $-C(O)R^8$.

En otra realización, R^6 es $-C(O)OR^9$.

En aún otra realización, R^6 es $-C(O)N(R^9)_2$.

En una realización adicional, R^6 es $-NHC(O)R^8$.

En otra realización, R^6 es $-NHSO_2R^{11}$.

En otra realización, R^6 es $-S(O)_pR^{11}$

En otra realización, R^6 es $-SO_2N(R^9)_2$.

En una realización, R^7 es –H.

En otra realización, R^7 es alquilo.

En otra realización, R^7 es haloalquilo.

En otra realización, $R^7$is hidroxialquilo.

En aún otra realización, R^7 es arilo.

En aún otra realización, R^7 es halo.

En una realización adicional, R^7 es -OH.

En otra realización, R^7 es –O-haloalquilo.

En una realización, R^7 es -alcoxi.

En otra realización, R^7 es -CN.

En otra realización, $R^7$is $-[C(R^{12})_2]_q$-OR^9.

En otra realización, R^7 es $-[C(R^{12})_2]_q$-$N(R^9)_2$.

En aún otra realización, R^7 es -$C(O)R^8$.

En otra realización, R^7 es -$C(O)OR^9$.

En aún otra realización, R^7 es -$C(O)N(R^9)_2$.

En una realización adicional, R^7 es -$NHC(O)R^8$.

En otra realización, R^7 es -$NHSO_2R^{11}$.

En otra realización, R^7 es $-S(O)_pR^{11}$

En otra realización, R^7 es -$SO_2N(R^9)_2$.

En una realización, cada R^6 y R^7 son –H.

En otra realización, uno, pero no ambos R^6 y R^7 es –H.

En otra realización, cada uno de R^6 y R^7 son diferentes de –H.

En una realización adicional, cada uno de R^6 y R^7 se seleccionan independientemente de H, alquilo, F, Cl, -CF_3, -OH, -O-alquilo, -OCF_3, -NH_2 o -$NHSO_2$-alquilo.

En una realización, el anillo Z es ciclopentenilo.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros.

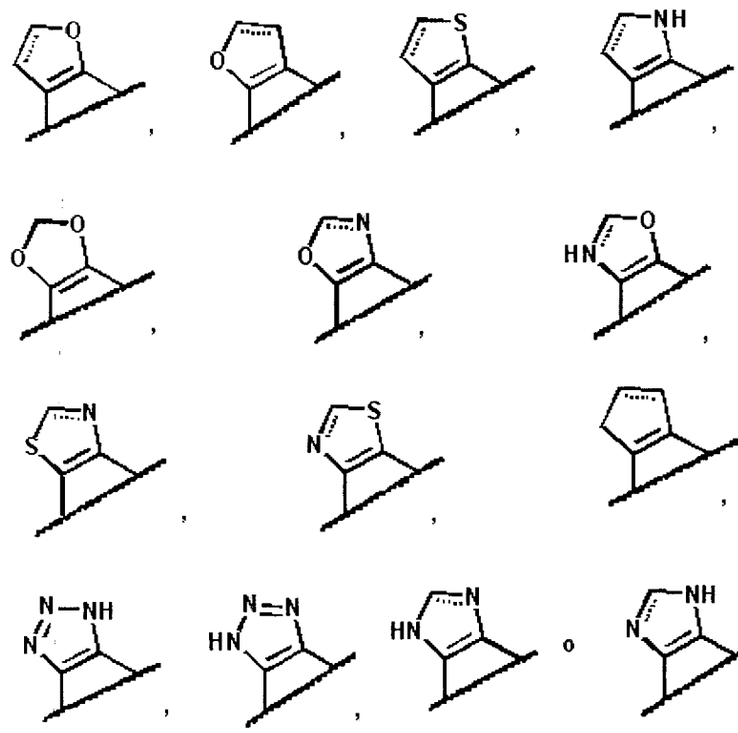
En otra realización, el anillo Z es un heterocicloalquilo de 5 miembros.

En aún otra realización, el anillo Z es un heterocicloalquenilo de 5 miembros.

En aún otra realización, el anillo Z es un heteroarilo de 5 miembros.

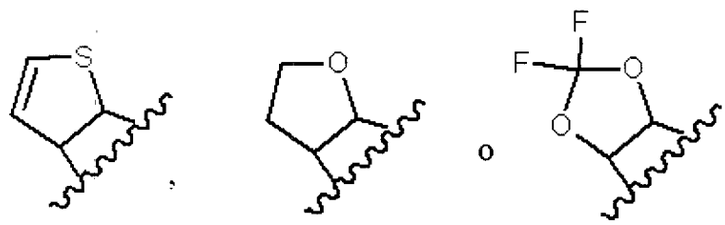
En otra realización, el anillo Z es un ciclopentilo.

En una realización, el anillo Z es:

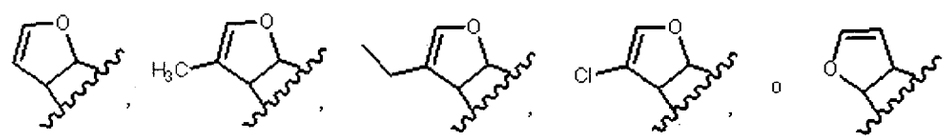


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I).

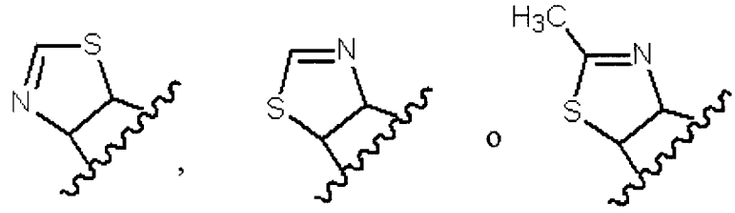
En otra realización, el anillo Z es:



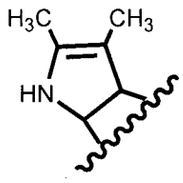
En otra realización, el anillo Z es:



En otra realización, el anillo Z es:



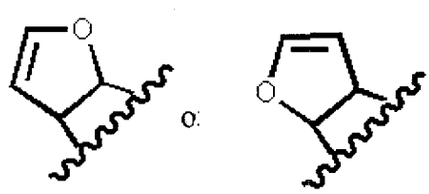
En otra realización, el anillo Z es:



En una realización, el anillo Z es un heterocicloalquilo de 5 miembros, -R^1-R^{10} es alquilo, -alquilen-arilo o –alquilen-heteroarilo, R^2 es –C(O)OR^8 o -C(O)$NHSO_2R^{11}$, y R^3 es arilo o heterocicloalquenilo.

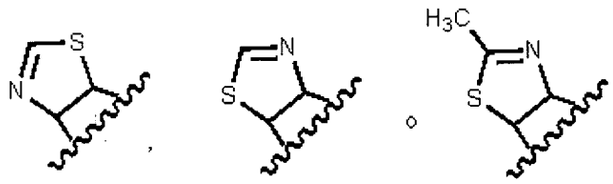
En otra realización, el anillo Z es un heterocicloalquenilo de 5 miembros o a heteroarilo de 5 miembros, -R^1-R^{10} es alquilo, -$(alquilen)_q$-arilo o -$(alquilen)_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)$NHSO_2R^{11}$, y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es



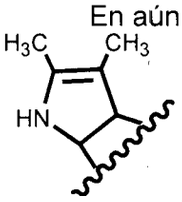
-R^1-R^{10} es alquilo, -$(alquilen)_q$-arilo o -$(alquilen)_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)$NHSO_2R^{11}$, y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es



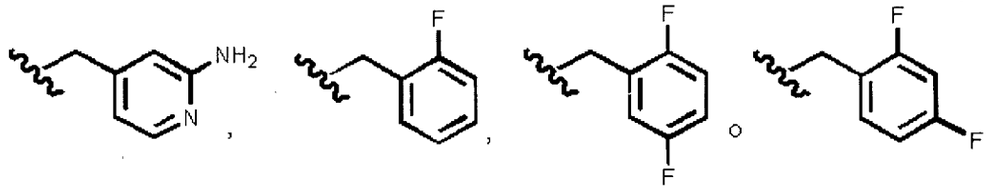
-R^1-R^{10} es alquilo, -(alquilene)$_q$-arilo o -(alquilene)$_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)NHSO_2R^{11}, y R^3 es arilo o heterocicloalquenilo.

En aún otra realización, el anillo Z es



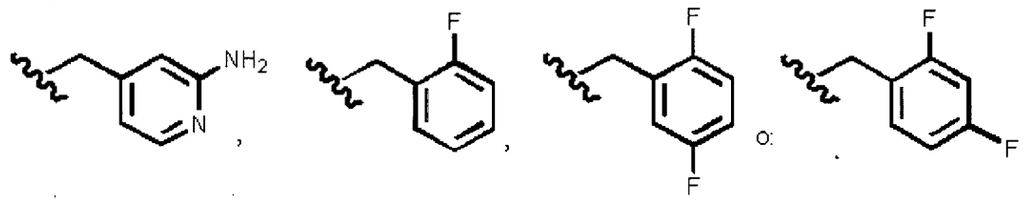
-R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilene)$_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)NHSO_2R^{11}, y R^3 es arilo o heterocicloalquenilo.

En una realización, el anillo Z es un grupo ciclopentilo o ciclopentenilo, -R^1-R^{10} es:



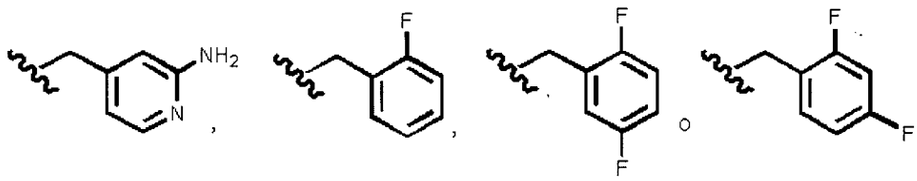
R^2 es –C(O)OR^8 o -C(O)NHSO_2R^{11}, y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es un grupo heterocicloalquilo de 5 miembros, -R^1-R^{10} es:



R^2 es –C(O)OR^8 o -C(O)NHSO_2R^{11}, y R^3 es arilo o heterocicloalquenilo.

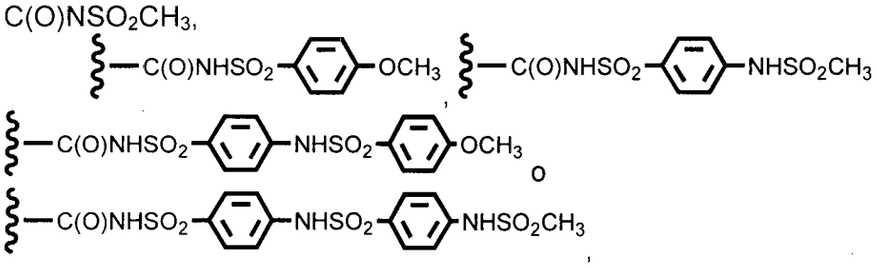
En otra realización, el anillo Z es un grupo heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros, -R^1-R^{10} es:



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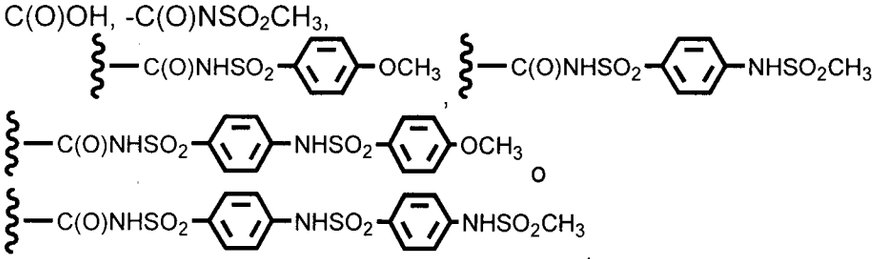
R^2 es –C(O)OR^8 o -C(O)$NHSO_2R^{11}$, y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es un grupo ciclopentilo o ciclopentenilo, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es –C(O)OH, -$C(O)NSO_2CH_3$,



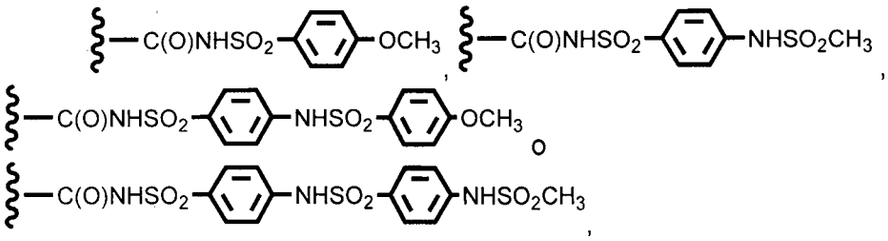
y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es un grupo heterocicloalquilo de 5 miembros, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es –C(O)OH, -$C(O)NSO_2CH_3$,



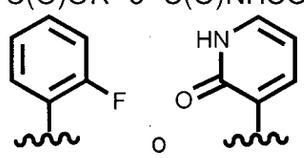
y R^3 es arilo o heterocicloalquenilo.

En otra realización, el anillo Z es un grupo heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es –C(O)OH, -$C(O)NSO_2CH_3$,

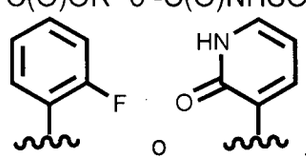


y R^3 es arilo o heterocicloalquenilo.

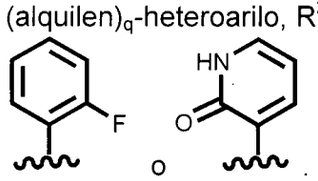
En aún otra realización, el anillo Z es un grupo ciclopentilo o ciclopentenilo, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es R^2 es –C(O)OR^8 o -C(O)NHSO$_2$$R^{11}$, y R^3 es



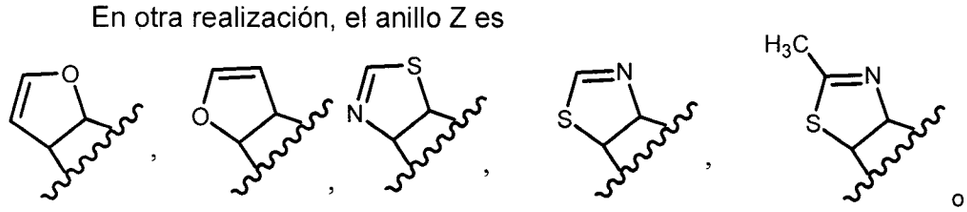
En aún otra realización, el anillo Z es un grupo heterocicloalquilo de 5 miembros, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)NHSO$_2$$R^{11}$, y R^3 es

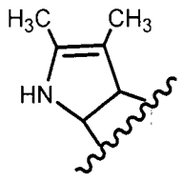


En aún otra realización, el anillo Z es un grupo heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros, -R^1-R^{10} es alquilo, -(alquilen)$_q$-arilo o -(alquilen)$_q$-heteroarilo, R^2 es –C(O)OR^8 o -C(O)NHSO$_2$$R^{11}$, y R^3 es



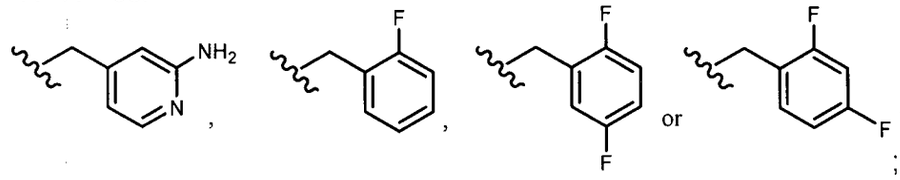
En otra realización, el anillo Z es





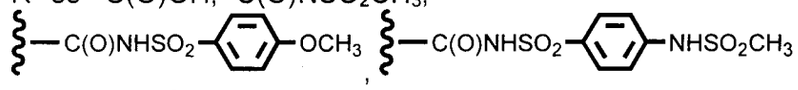
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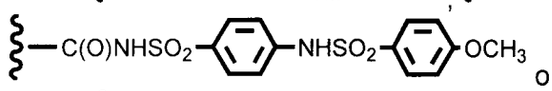
-R^1-R^{10} es:



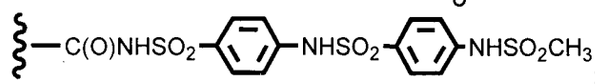
;

R^2 es –C(O)OH, -$C(O)NSO_2CH_3$,



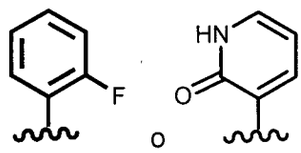


o

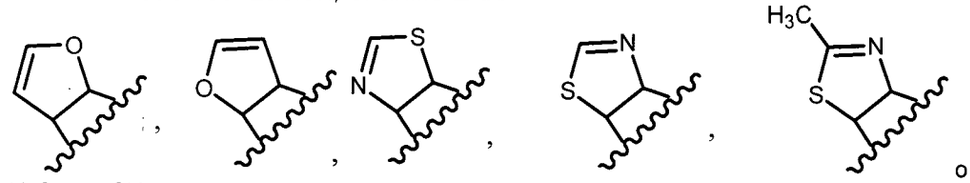


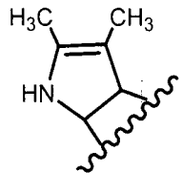
; y

R^3 es:



En otra realización, el anillo Z es

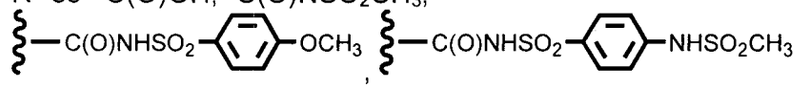


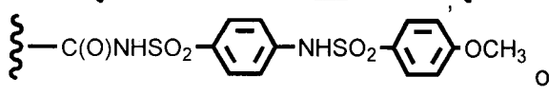


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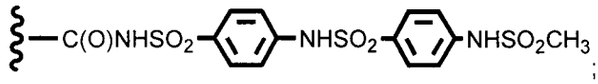
R^{10} es un heteroarilo bicíclico;

R^2 es –C(O)OH, -$C(O)NSO_2CH_3$,



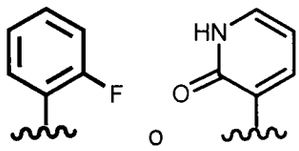


o



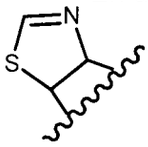
; y

R^3 es:

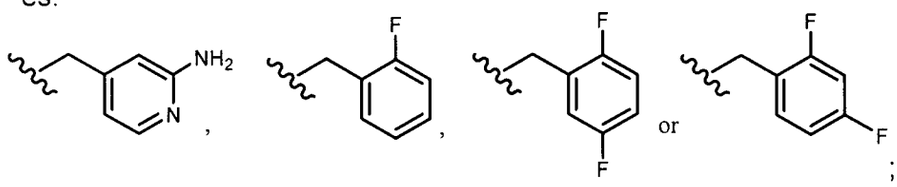


o

En una realización adicional, el anillo Z es

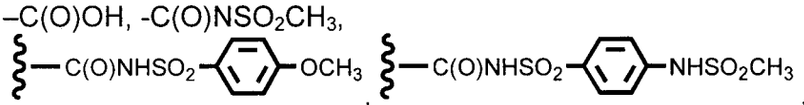


$-R^1-R^{10}$ es:

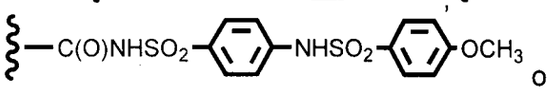


;

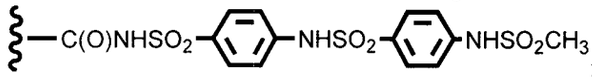
R^2 es –C(O)OH, $-C(O)NSO_2CH_3$,



,

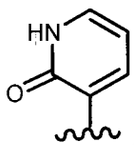


o



; y

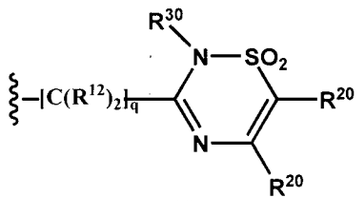
R^3 es:

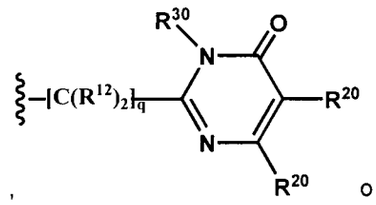


En una realización, R^1 es un enlace o $-[C(R^{12})_2)]_r-$, y R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo,

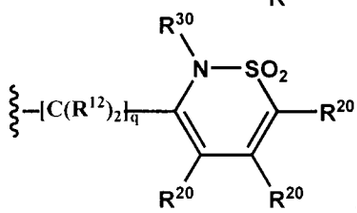
-OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquiloo, -C(O)N(R^9)$_2$, -alquilen-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO_2R^{11}, -S(O)$_p R^{11}$ o -SO_2N(R^9)$_2$.

En otra realización, R^1 es un enlace o -[C(R^{12})$_2$)]$_r$-, y R^2 es -C(O)OH, -C(O)Oalquiloo, -C(O)NH_2, -C(O)NH-alquilo, -C(O)NH-cicloalquilo, -C(O)NHSO_2R^{11},





o



En otra realización, R^1 es un enlace o -[C(R^{12})$_2$)]$_r$-, y R^2 es -C(O)NHSO_2-alquilo, -C(O)NHSO_2-arilo, -C(O)NHSO_2-cicloalquilo o -C(O)NHSO_2-(alquilen)$_q$-cicloalquilo.

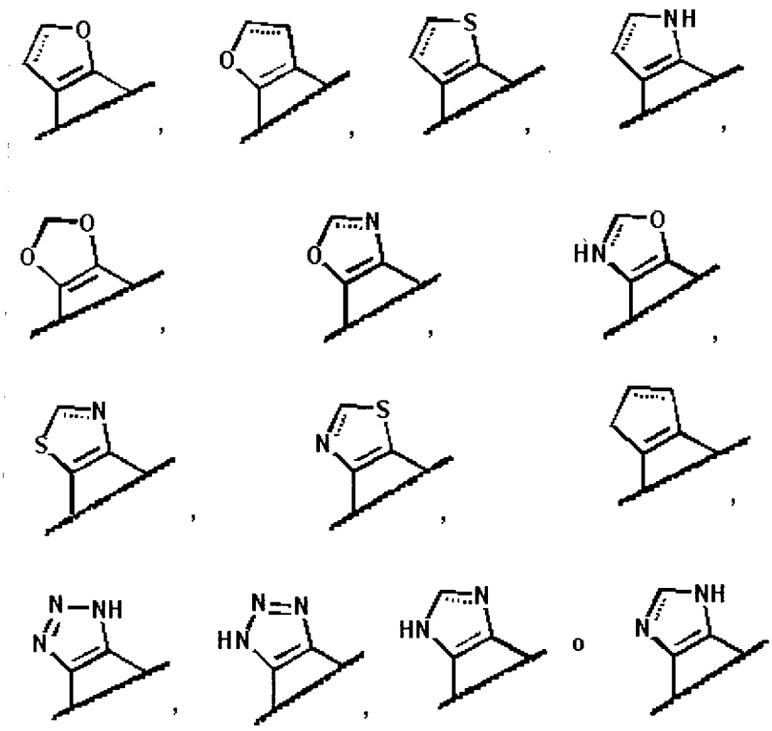
En otra realización, R^1 es un enlace o -[C(R^{12})$_2$)]$_r$-, y R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, -C(O)N(R^9)$_2$, -N(R^9)$_2$, -O-haloalquilo, -NHC(O)NH_2, -NHC(O)NH-alquilo, -NHSO_2R^{11}, -S(O)$_2 R^{11}$ o -SO_2NHR^{11}.

En aún otra realización, R^1 es un enlace o -[C(R^{12})$_2$)]$_r$-, y R^3 es piridilo, donde el grupo piridilo puede estar no sustiuido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, haloalquilo, hidroxialquilo, halo, -OH, -CN, -C(O)CH_3, -C(O)NH_2, -C(O)NHalquilo,

-O-hidroxialquilo, $-NH_2$, -NHalquil, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$alquil o $-SO_2$NHalquilo.

En aún otra realización, R^1 es un enlace o $-[C(R^{12})_2)]_r-$, y el anillo Z es un grupo heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros.

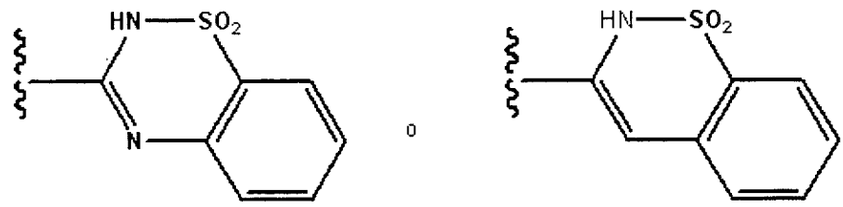
En una realización adicional, R^1 es un enlace o $-[C(R^{12})_2)]_r-$, y el anillo Z es uno de los siguientes:



donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I).

En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es $-C(O)OH$, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,

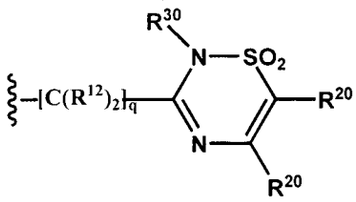


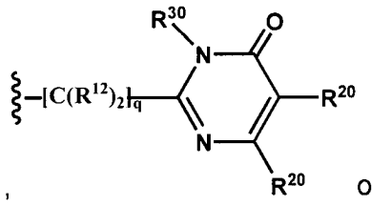
R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$; el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

Cada uno de R^6 y R^7 se seleccionan independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

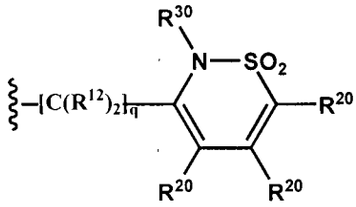
R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, -C(O)O-alquilo, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,





o



;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

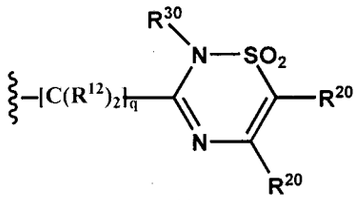
el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

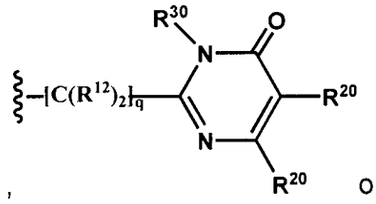
Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

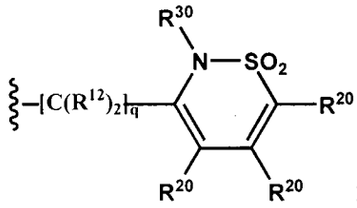
En aún otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, -C(O)O-alquilo, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,





o



;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

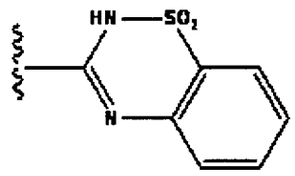
el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

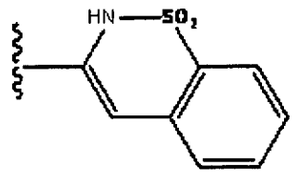
R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,

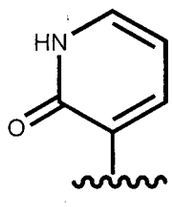


α



;

R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

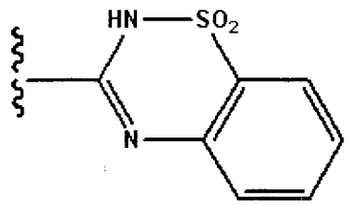
el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquiló, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

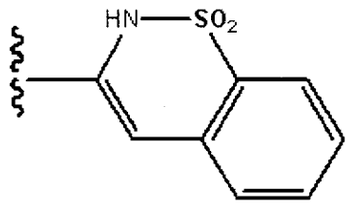
R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,

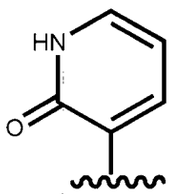


o:



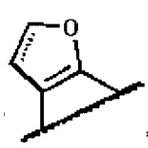
;

R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

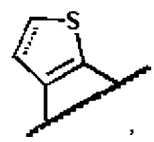
el anillo Z es:



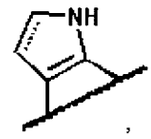
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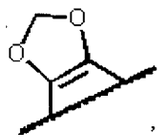
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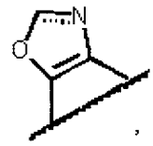
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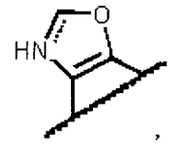
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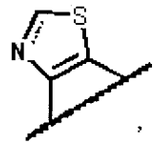
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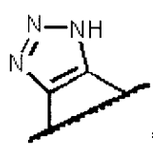
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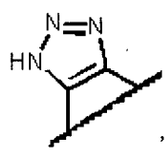
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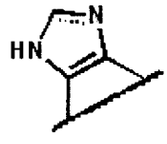
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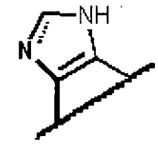
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o:



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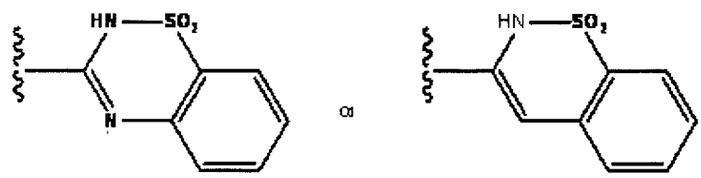
donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I);

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

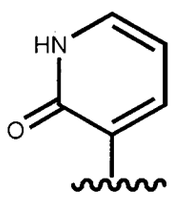
En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,



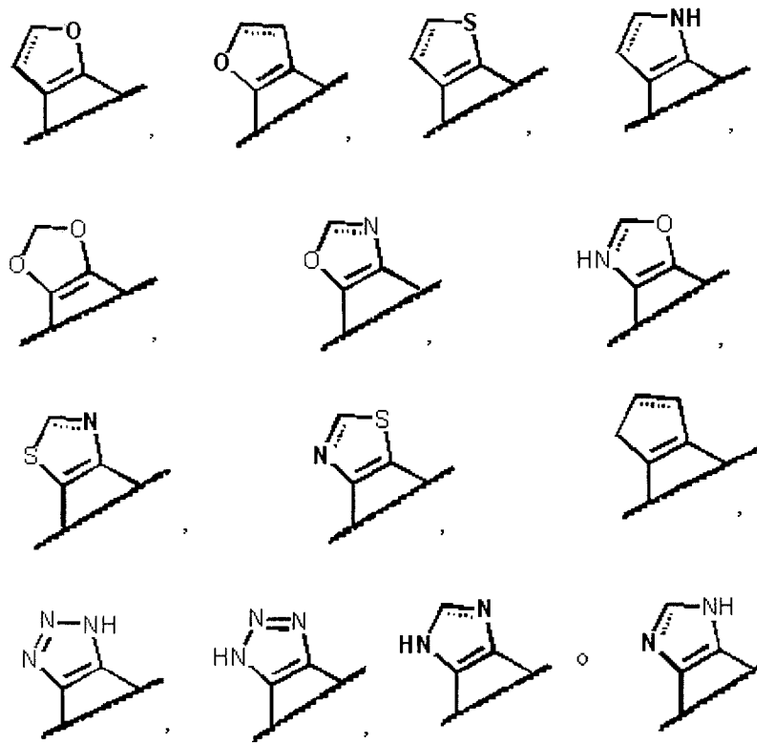
;

R^3 es:



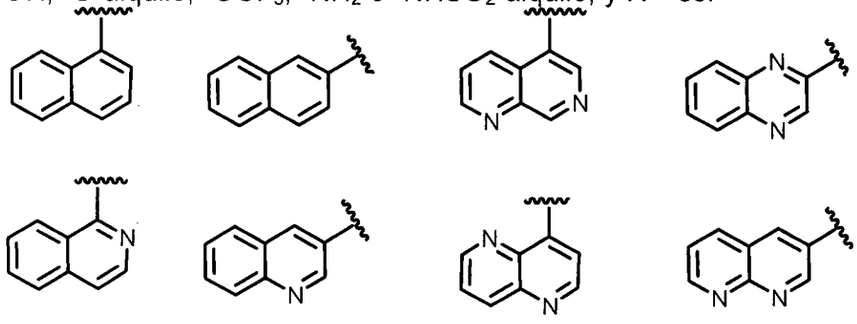
, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

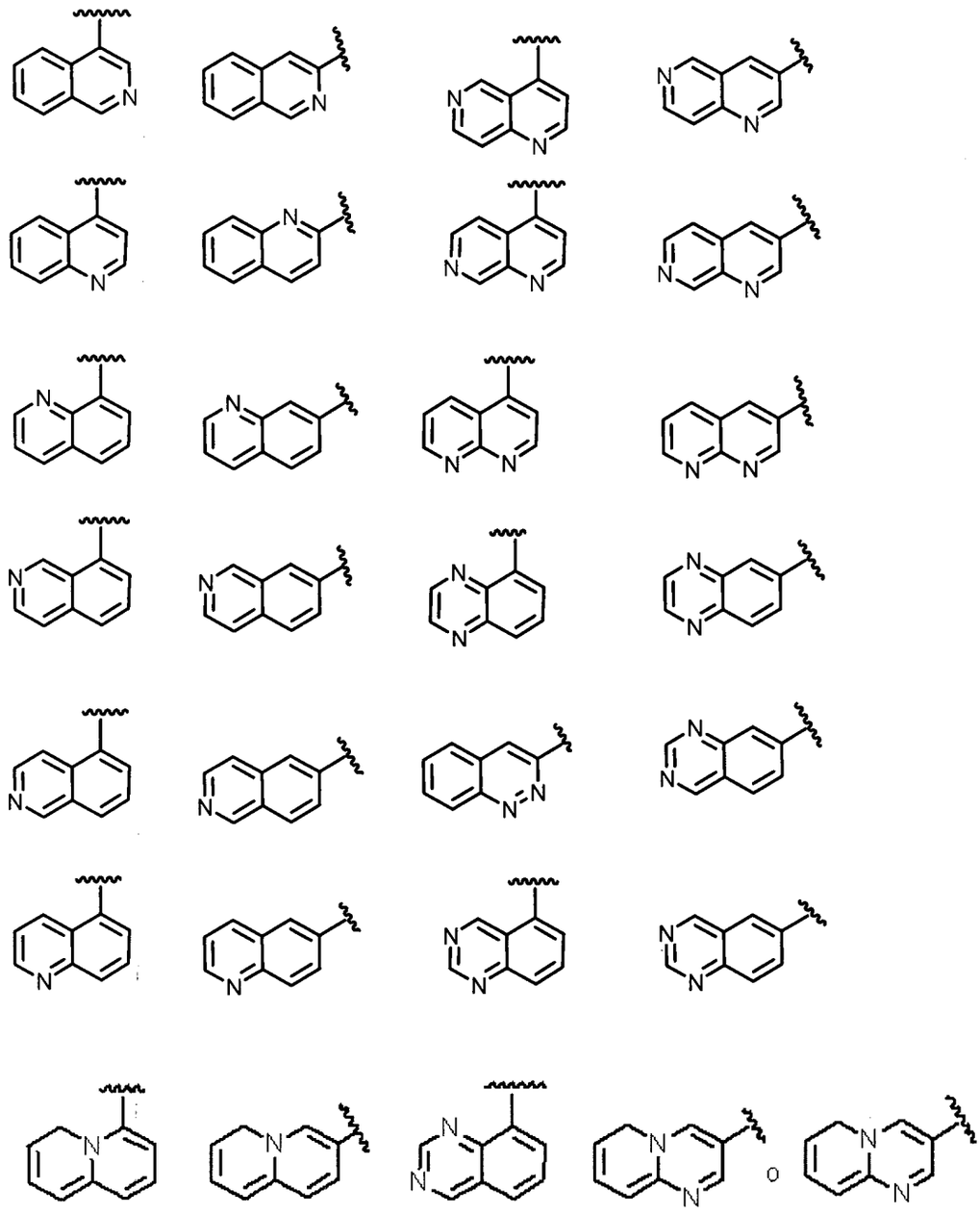
el anillo Z es:



donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I);

cada R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y R^{10} es:

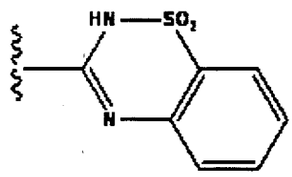




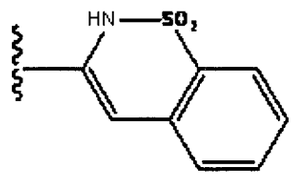
, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo;

En una realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

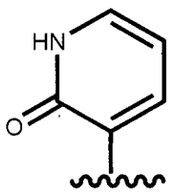
R^2 es -C(O)OH, -C(O)NH_2, -C(O)NH-alquilo, -C(O)$NHSO_2R^{11}$,



o



R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, -CF_3, -C(O)CH_3, -C(O)NH_2, -C(O)NHalquilo, -F, -Cl, -OH, -OCF_3, -NH_2, -NHalquilo, -NHC(O)NH_2, -NHC(O)NH-alquilo, -$NHSO_2$alquilo, -$S(O)_2$-alquilo o -SO_2NHalquilo;

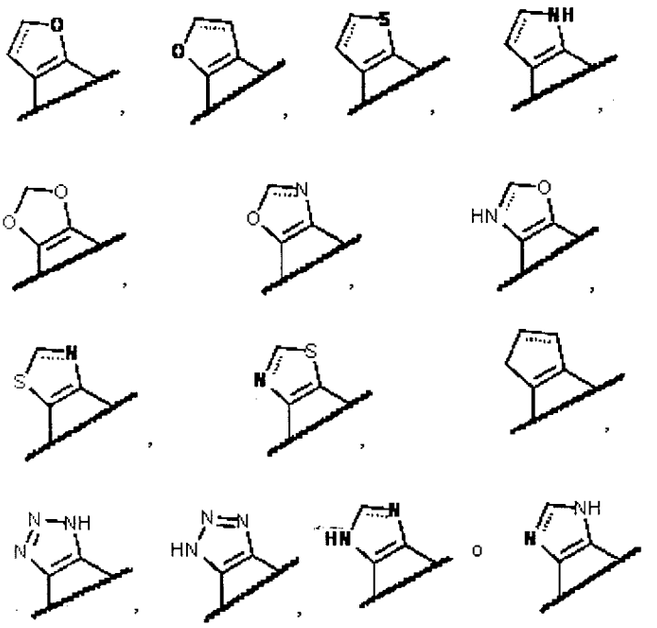
el anillo Z es:

PATENTE DE INVENCION

09-63496

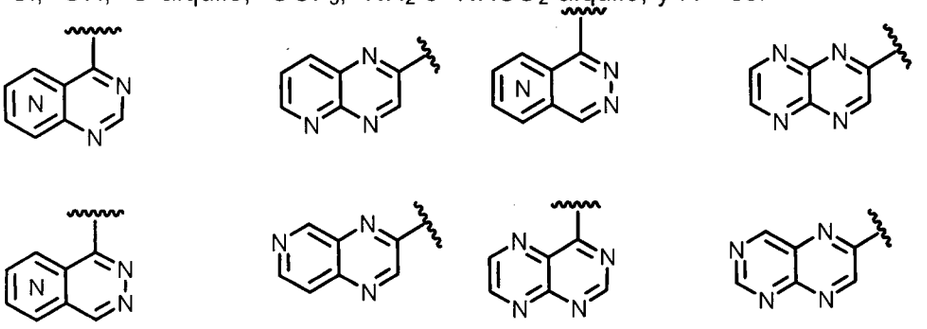
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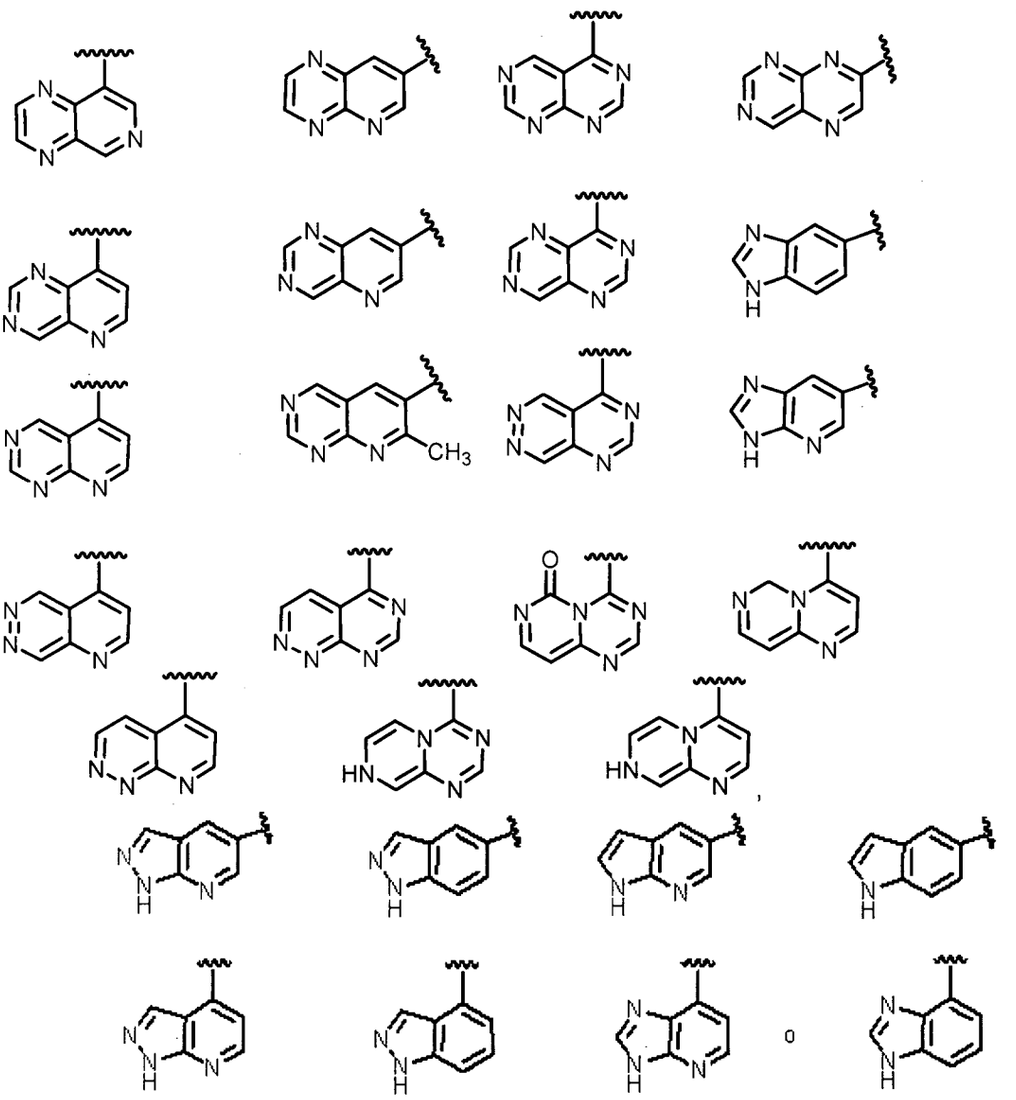
Organización y Digitalización CSJN



donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I);

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, -OCF_3, -NH_2 o -$NHSO_2$-alquilo; y R^{10} es:

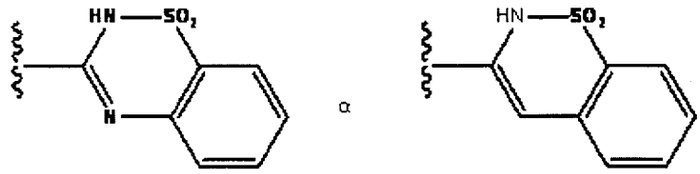




,cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro del anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

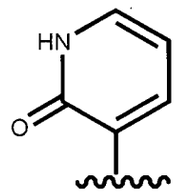
En una realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, -C(O)NH_2, -C(O)NH-alquilo, -C(O)$NHSO_2R^{11}$,



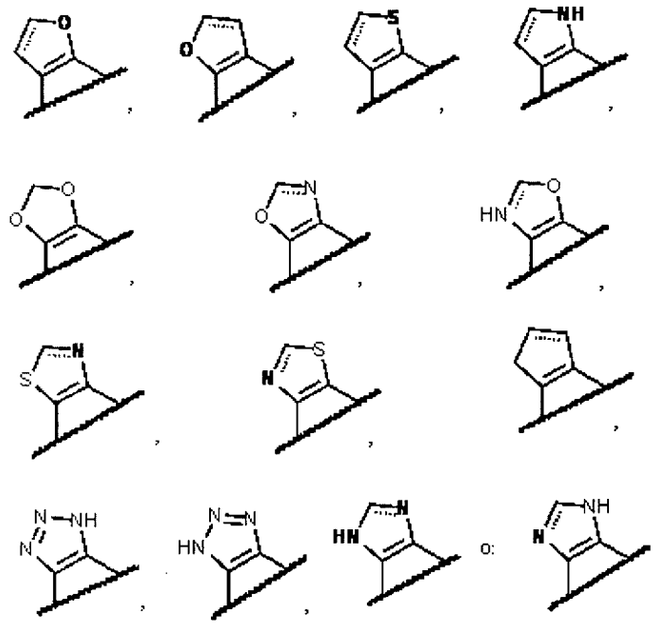
;

R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, -CF_3, -C(O)CH_3, -C(O)NH_2, -C(O)NHalquilo, -F, -Cl, -OH, -OCF_3, -NH_2, -NHalquilo, -NHC(O)NH_2, -NHC(O)NH-alquilo, -$NHSO_2$alquilo, -$S(O)_2$-alquilo o -SO_2NHalquilo;

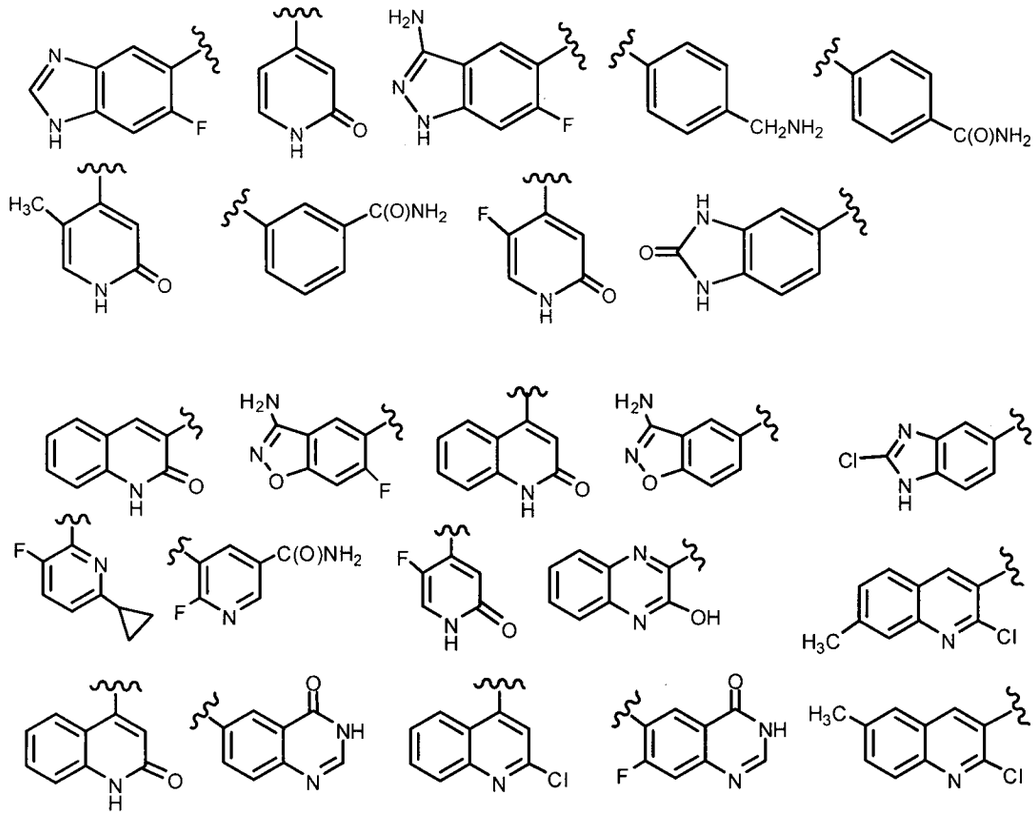
el anillo Z es:

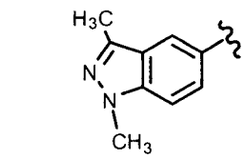
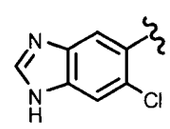
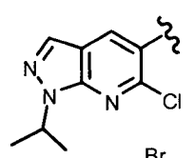
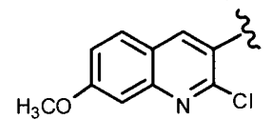
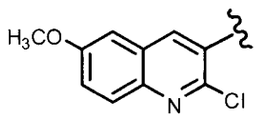
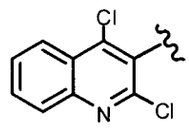
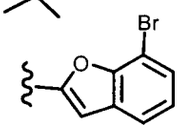
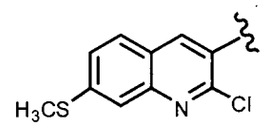
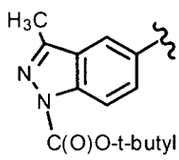
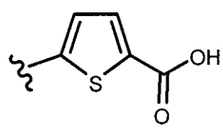
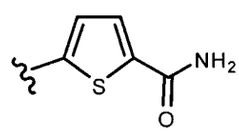
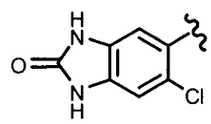
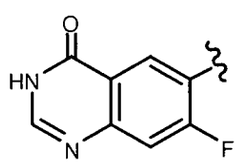
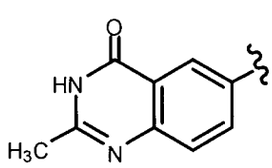
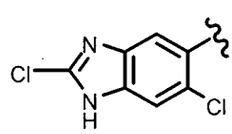
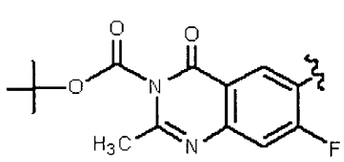
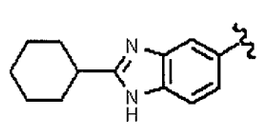
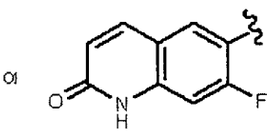


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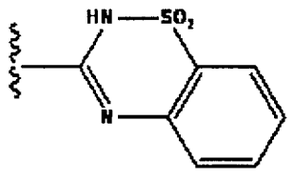
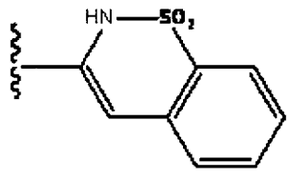
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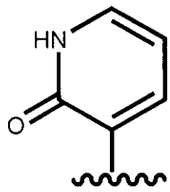



















En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono;

R^2 es -C(O)OH, -$C(O)NH_2$, -C(O)NH-alquilo, -$C(O)NHSO_2R^{11}$,

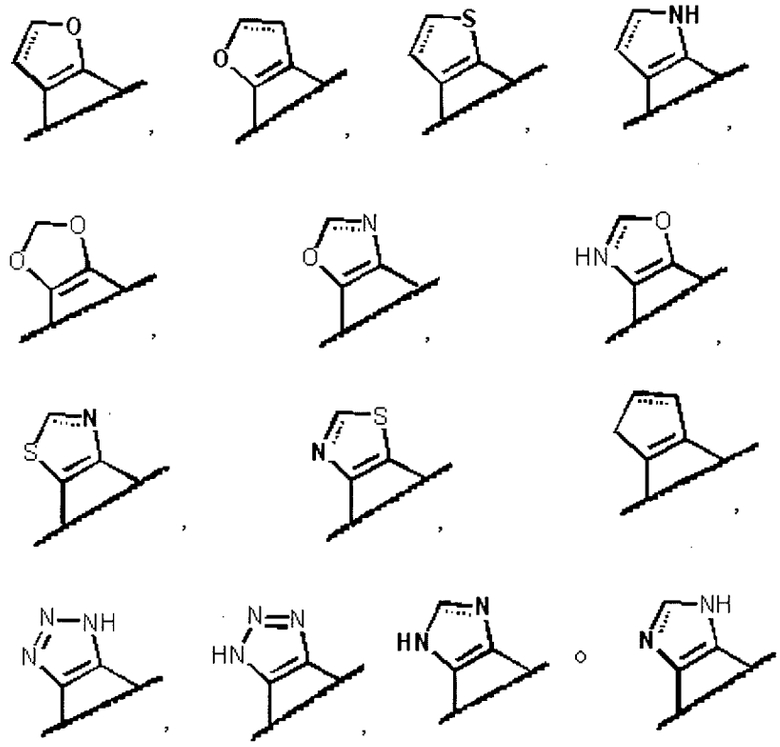



R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

el anillo Z es:



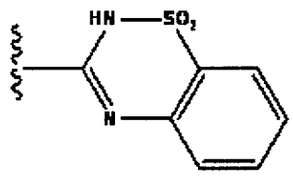
donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I);

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

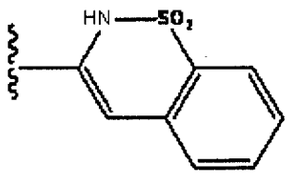
R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono,

R^2 es $-C(O)OH$, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,

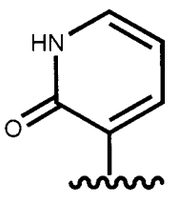


o



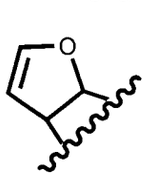
;

R^3 es:

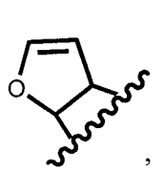


, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, -F, -Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

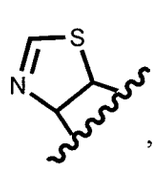
el anillo Z es:



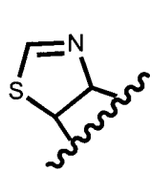
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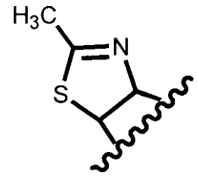
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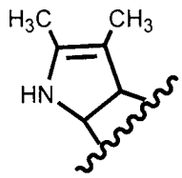
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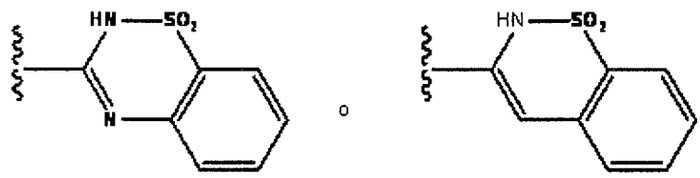
donde el anillo Z puede estar opcionalmente sustituido en uno o más átomos de carbono anulares con alquilo, -OH, -F, -Cl, -O-alquilo, $-CF_3$, cicloalquilalquilo, arilo o cicloalquilo.

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

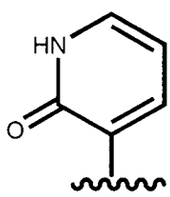
En una realización adicional, R^1 es un enlace, o un grupo alquilo que tiene de 1-6 átomos de carbono,

R^2 es $-C(O)OH$, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$,



;

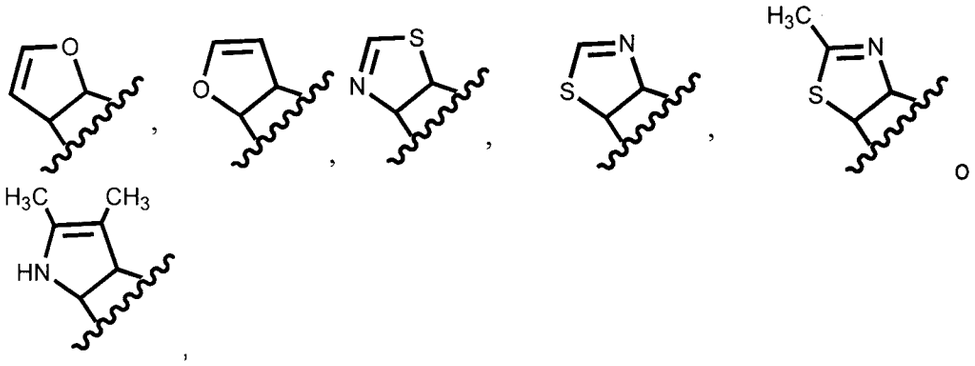
R^3 es:



, que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, CN, $-CF_3$,

-C(O)CH_3, -C(O)NH_2, -C(O)NHalquilo, -F, -Cl, -OH, -OCF_3, -NH_2, -NHalquilo, -NHC(O)NH_2, -NHC(O)NH-alquilo, -$NHSO_2$alquilo, -$S(O)_2$-alquilo o -SO_2NHalquilo;

el anillo Z es:



donde el anillo Z puede estar opcionalmente sustituido en uno o más átomos de carbono anulares con alquilo, -OH, -F, -Cl, -O-alquilo, -CF_3, cicloalquilalquilo, arilo o cicloalquilo.

Cada uno de R^6 y R^7 se selecciona independientemente de –H, alquilo, -F, -Cl, -OH, -O-alquilo, -OCF_3, -NH_2 o -$NHSO_2$-alquilo; y

R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, -C(O)N(R^9)$_2$, -alquilen-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ o -SO_2N(R^9)$_2$.

En otra realización, la invención proporciona los Compuestos de fórmula (I), donde R^1 es un enlace o -[C(R^{12})$_2$]$_r$-; y R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, -C(O)N(R^9)$_2$, -alquilen-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ o -SO_2N(R^9)$_2$.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde

el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, heteroarilo, o $-C(O)NHSO_2R^{11}$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

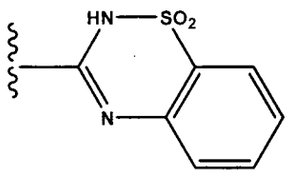
R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -(alquilen)-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En aún otra realización, la invención proporciona Compuestos de fórmula (I), donde

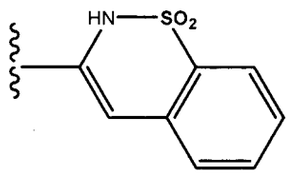
el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, $-C(O)NH_2$, -C(O)NH-alquilo, $-C(O)NHSO_2R^{11}$;



or



donde el grupo heteroarilo, ariltiazin-il- o ariltiadiazol-il- puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)$alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, $-C(O)$alquilo, $-C(O)O$alquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

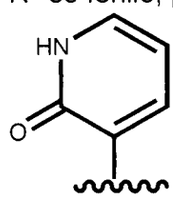
En aún otra realización, la invención proporciona Compuestos de fórmula (I), donde

El anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, heteroarilo, o $-C(O)NHSO_2R^{11}$;

R^3 es fenilo, piridilo o



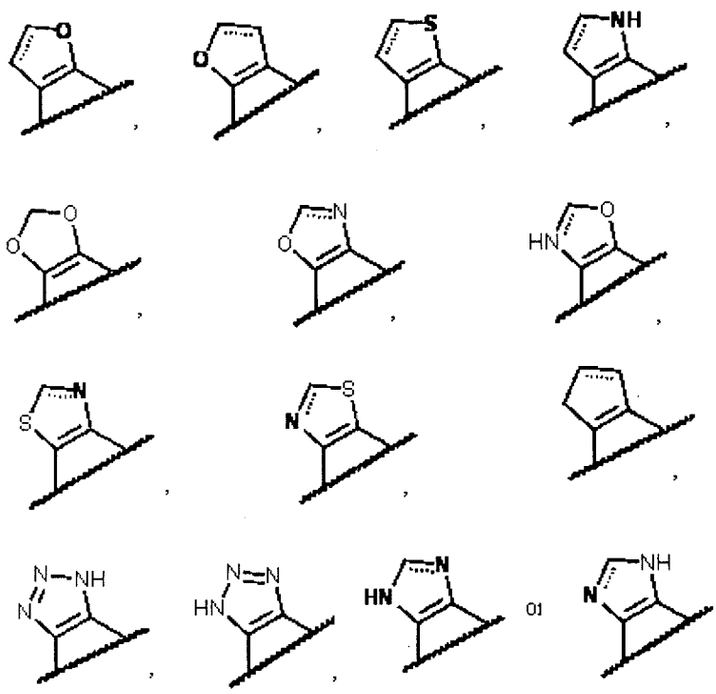
, cada uno de los cuales puede estar opcionalmente sustituido con uno a 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En una realización adicional, la invención proporciona Compuestos de fórmula (I), donde

el anillo Z es:



donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente para los compuestos de fórmula (I);

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, heteroarilo, o $-C(O)NHSO_2R^{11}$;

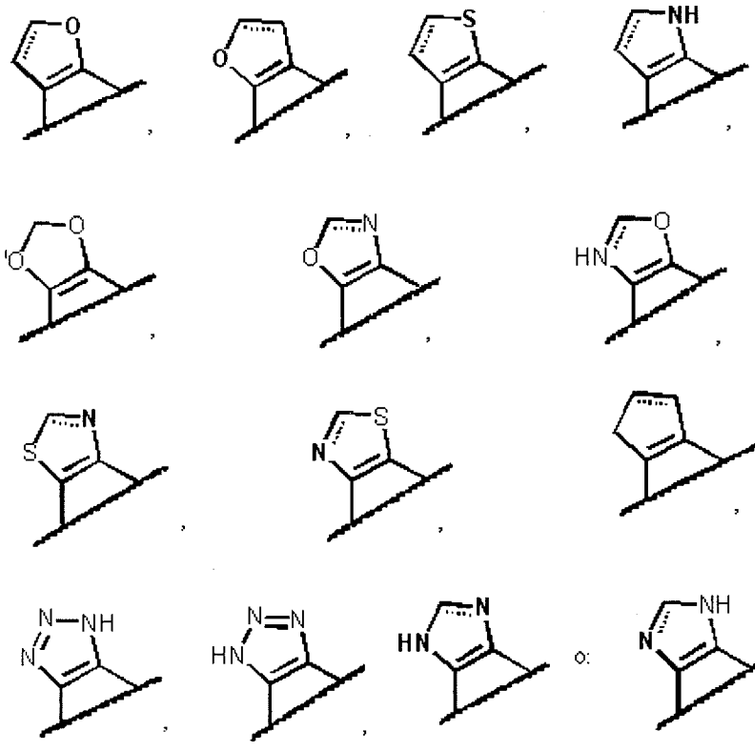
R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En una realización, la invención proporciona Compuestos de fórmula (I), donde

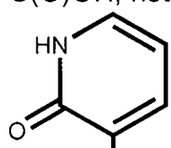
el anillo Z es:



donde el anillo Z can be sustituido con hasta 3 sustituyentes opcionales de carbono del anillo, que son iguales o diferentes, y que se seleccionan de H, alquilo, -OH, F, Cl, -O-alquilo, $-CF_3$, $-OCF_3$ y cicloalquilo;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, heteroarilo, o -C(O)$NHSO_2R^{11}$;



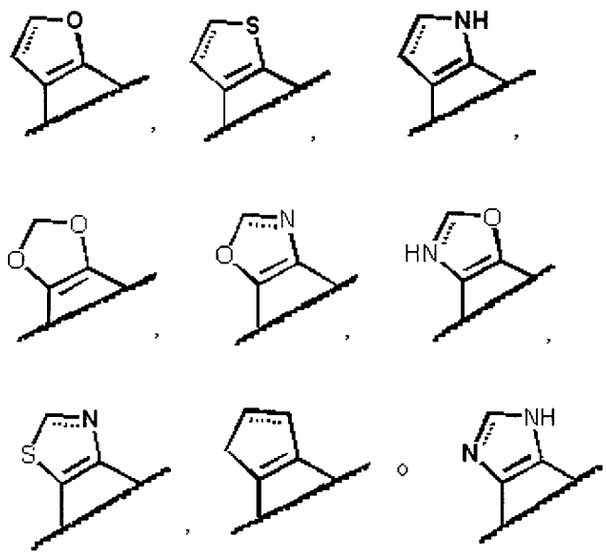
R^3 es: ;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, -CF_3, -OH, -O-alquilo, -OCF_3, -NH_2 o -$NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, -C(O)$N(R^9)_2$, -alquilen-OR^9, -OR^9, -$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ o -$SO_2N(R^9)_2$.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde

el anillo Z es:



donde ring Z can be sustituido con hasta 3 sustituyentes opcionales de carbono anular, que son iguales o diferentes, y que se seleccionan de H, alquilo, -OH, F, Cl, -O-alquilo, $-CF_3$, $-OCF_3$ y cicloalquilo;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH, heteroarilo, o $-C(O)NHSO_2R^{11}$;

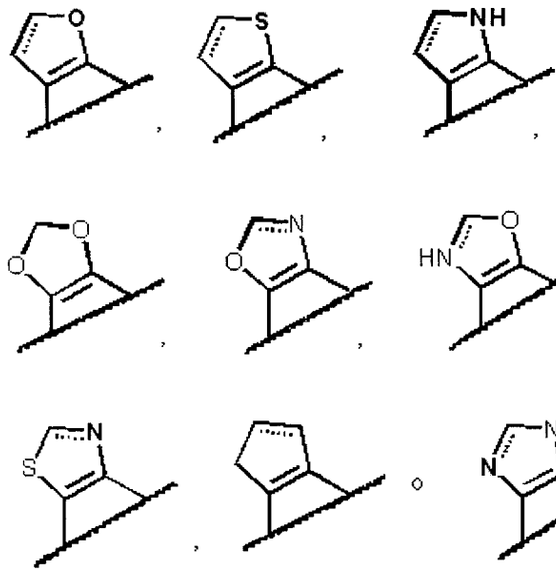
R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde

el anillo Z es

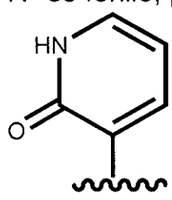


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es fenilo, piridilo o



, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son

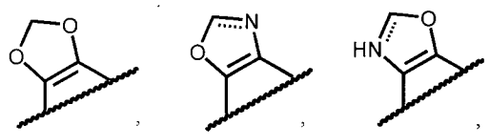
iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

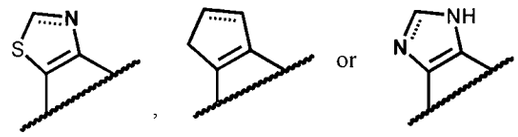
Cada uno de R^6 y R^7 se seleccionan independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, F, Cl, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, $-OR^9$, $-NH_2$, $-NHCH_3$, $-NHC(O)R^8$, $-NHSO_2CH_3$, $-SO_2CH_3$ o $-SO_2NH_2$.

En una realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es







donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-CH_2-$;

R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son

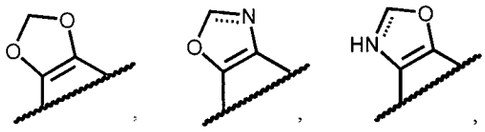
iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

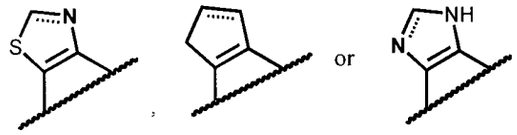
Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, F, Cl, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, $-OR^9$, $-NH_2$, $-NHCH_3$, $-NHC(O)R^8$, $-NHSO_2CH_3$, $-SO_2CH_3$ o $-SO_2NH_2$.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es





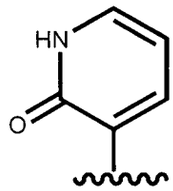


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-CH_2-$;

R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es fenilo, piridilo o

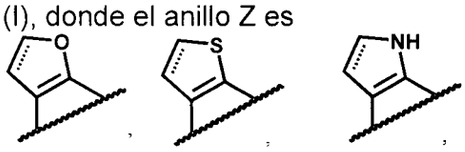


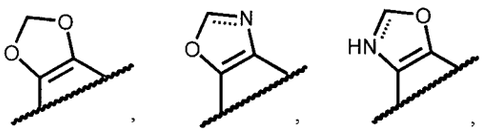
, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquil, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

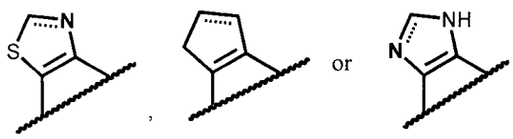
Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, F, Cl, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, $-OR^9$, $-NH_2$, $-NHCH_3$, $-NHC(O)R^8$, $-NHSO_2CH_3$, $-SO_2CH_3$ o $-SO_2NH_2$.

En aún otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es





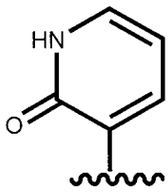


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-CH_2-$;

R^2 es -C(O)OH o -C(O)$NHSO_2R^{11}$;

R^3 es



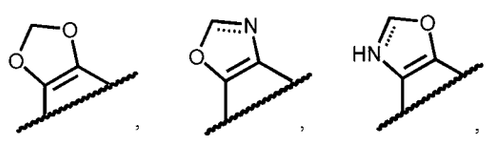
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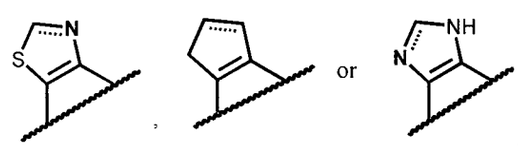
Cada R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, -CF_3, -OH, metoxi, -OCF_3, -NH_2 o -$NHSO_2CH_3$; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, F, Cl, -CF_3, -CN, -C(O)alquilo, -C(O)NH_2, -OR^9, -NH_2, -$NHCH_3$, -$NHC(O)R^8$, -$NHSO_2CH_3$, -SO_2CH_3 o -SO_2NH_2.

En una realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es







donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o –CH_2-;

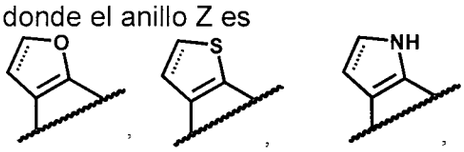
R^2 es -C(O)OH o -C(O)$NHSO_2R^{11}$;

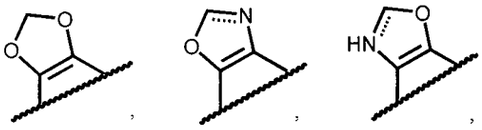
R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

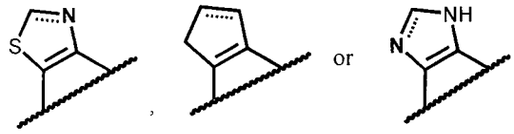
Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y

R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es





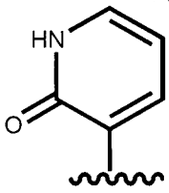


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-CH_2-$;

R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es fenilo, piridilo o

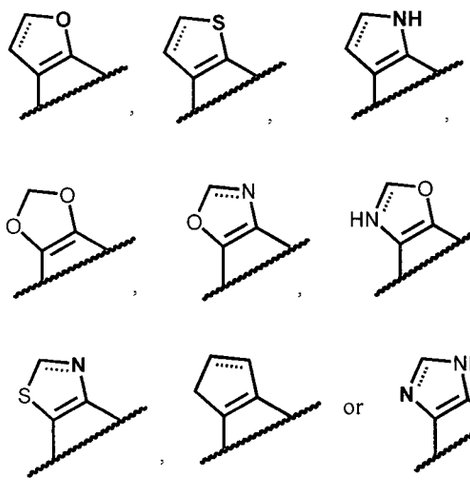


, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, $-C(O)CH_3$, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo;

Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y

R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En aún otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es

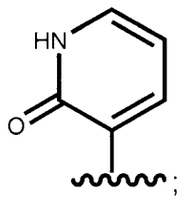


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

R^1 es un enlace o $-CH_2-$;

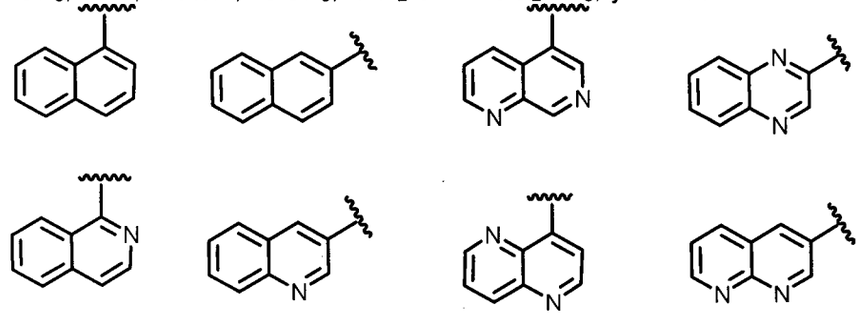
R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es

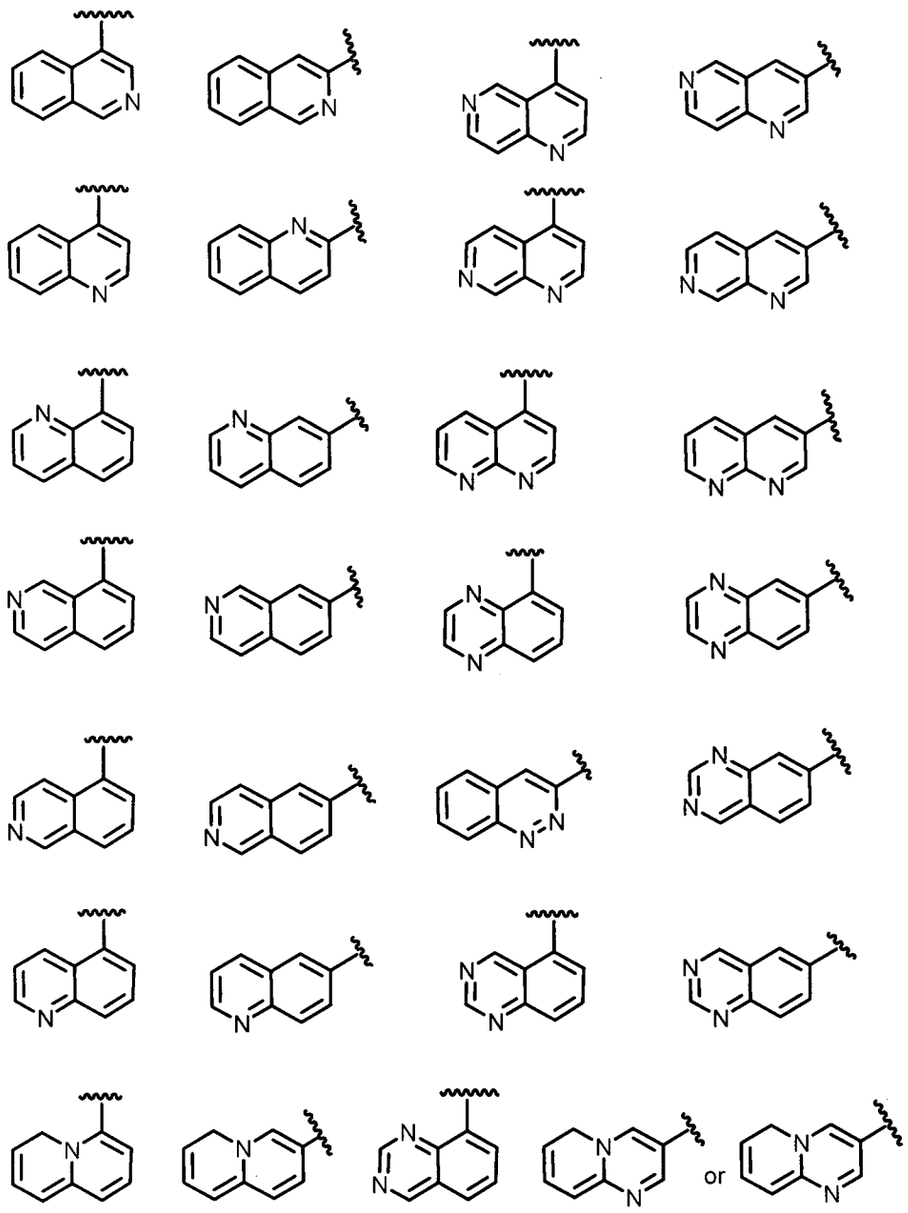


;

Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y R^{10} es :

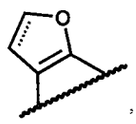
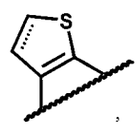
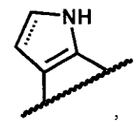


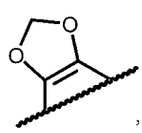
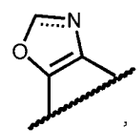
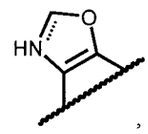
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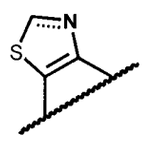
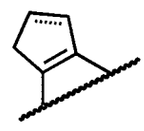
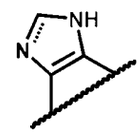


cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo;

En una realización adicional, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es

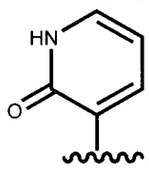


or


donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

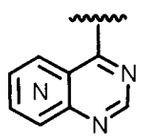
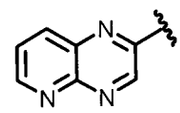
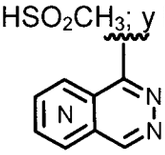
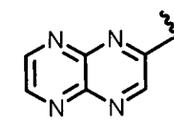
R^1 es un enlace o $-CH_2-$;

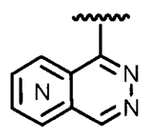
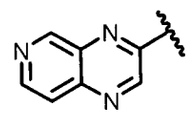
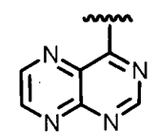
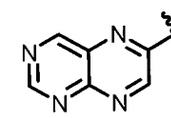
R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

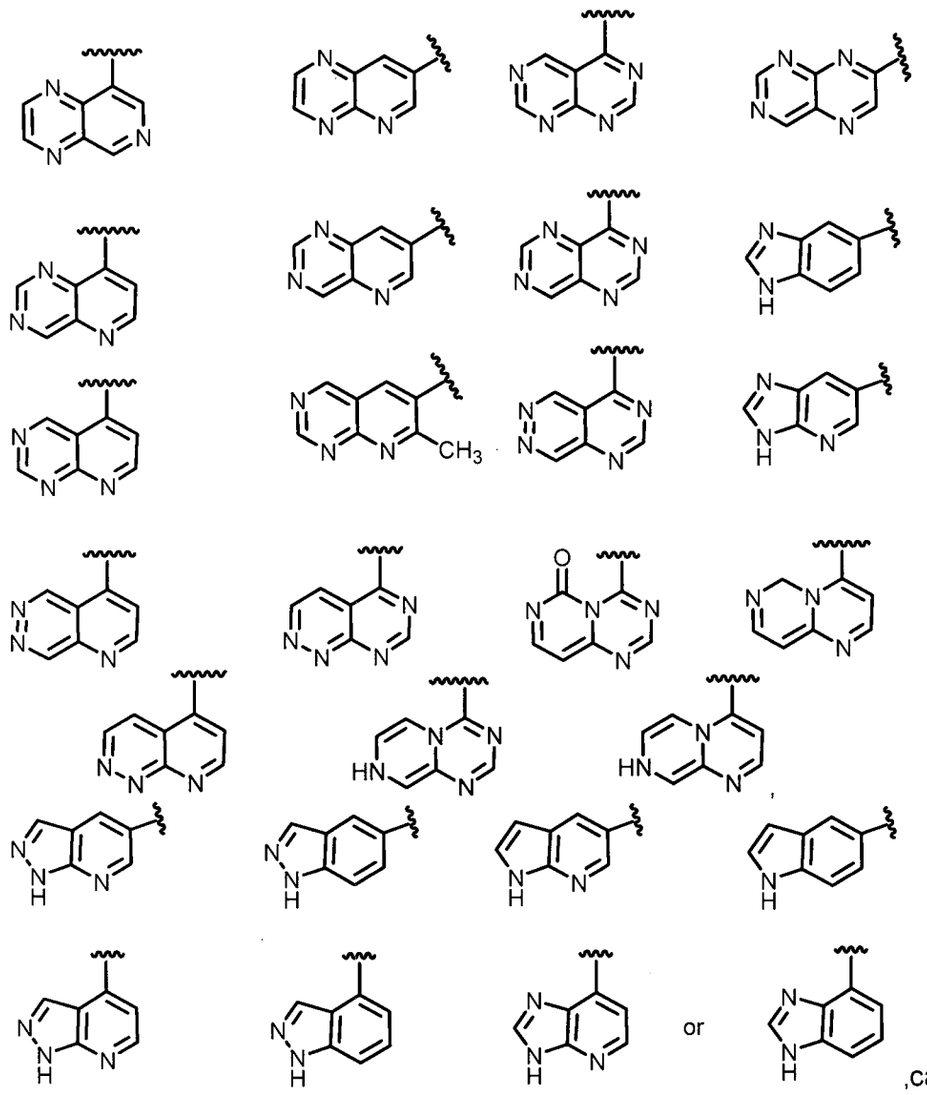
R^3 es


;

Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y R^{10} es:

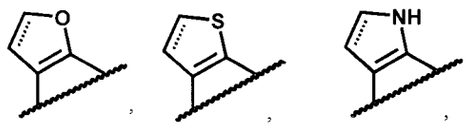
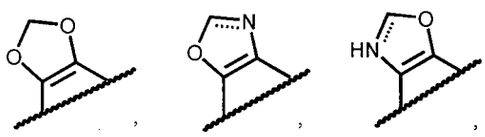
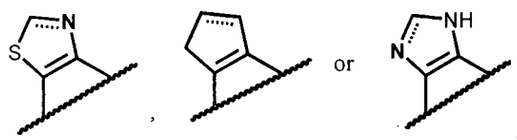







or

,cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro del anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

En aún otra realización, la invención proporciona Compuestos de fórmula (I), donde el anillo Z es

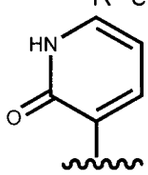




donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1;

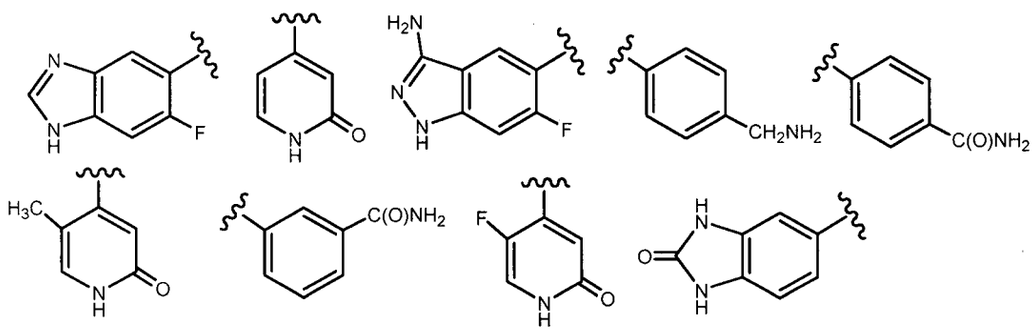
R^1 es un enlace o $-CH_2-$;

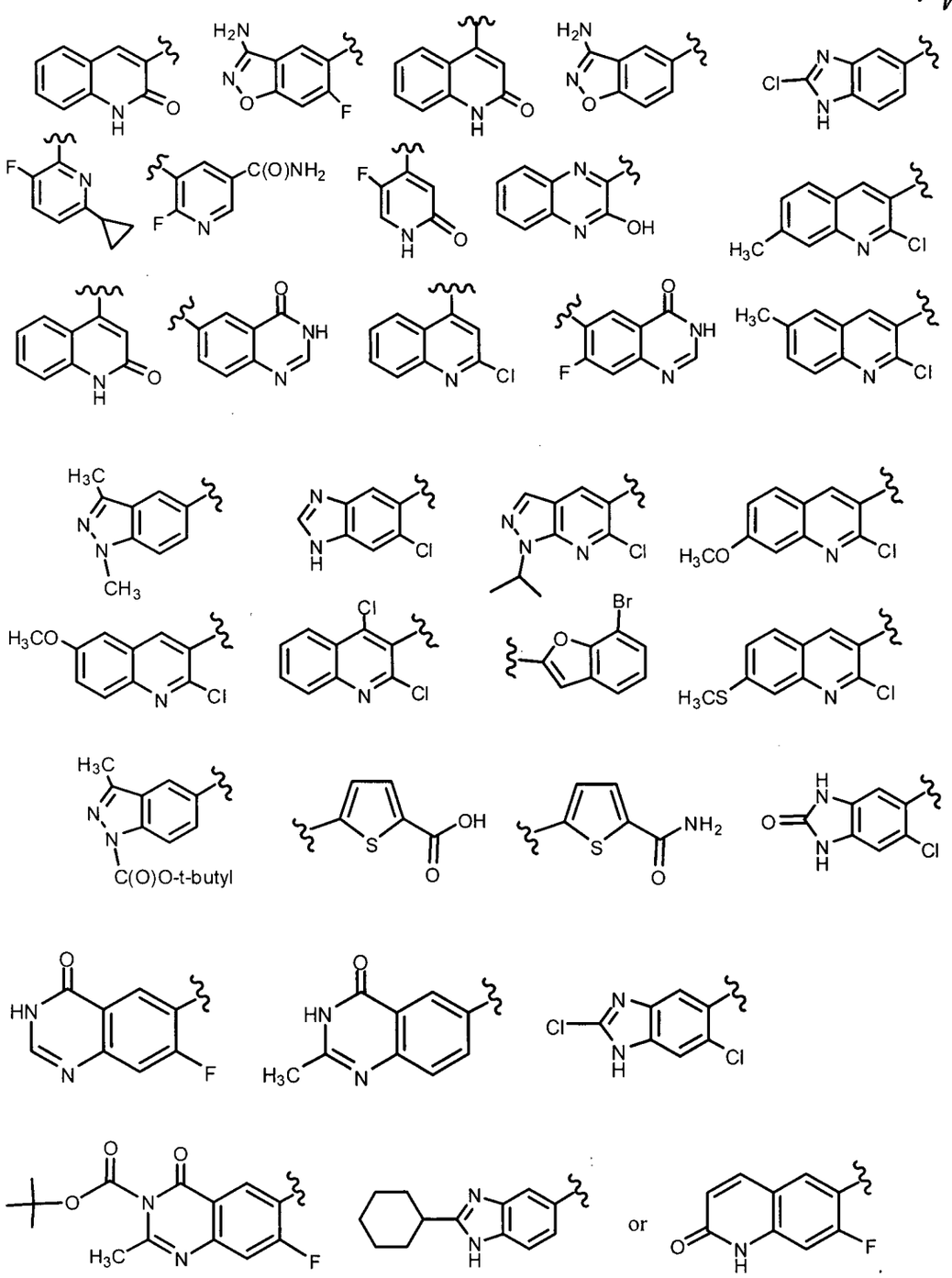
R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es


;

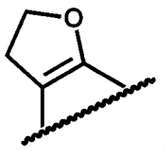
Cada uno de R^6 y R^7 se selecciona independientemente de H, metilo, F, Cl, $-CF_3$, -OH, metoxi, $-OCF_3$, $-NH_2$ o $-NHSO_2CH_3$; y R^{10} es :





En una realización, la invención proporciona Compuestos de fórmula (I), donde

el anillo Z es:



que puede estar sustituido con hasta 3 sustituyentes opcionales de carbono anular, que son iguales o diferentes, y que se seleccionan de H, alquilo, -OH, F, Cl, -O-alquilo, $-CF_3$, $-OCF_3$ y cicloalquilo;

R^1 es un enlace o $-[C(R^{12})_2]_r-$;

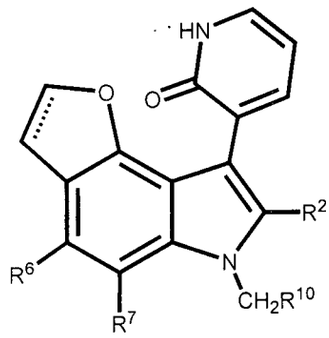
R^2 es -C(O)OH o $-C(O)NHSO_2R^{11}$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

Cada uno de R^6 y R^7 se seleccionan independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En una realización, los compuestos de fórmula (I) tiene la fórmula (Ia):



(Ia)

donde la línea punteada indica un enlace opcional y adicional;

R^2 es $-C(O)OR^9$ o $-C(O)NHSO_2R^{11}$;

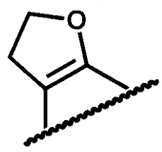
Cada uno de R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ y $-NHSO_2$-alquilo;

R^9 es H o alquilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona de H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$; y

R^{11} es alquilo, arilo o cicloalquilo.

En una realización, el anillo Z es:



En otra realización, R^2 es -C(O)OH.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$.

En aún otra realización, R^2 es $-C(O)NHSO_2R^{11}$, donde R^{11} es alquilo, arilo o cicloalquilo.

En aún otra realización, R^2 es $-C(O)NHSO_2R^{11}$, donde R^{11} es metilo, etilo, isopropilo, t-butilo, fenilo o ciclopropilo.

En otra realización, cada uno de R^6 y R^7 es H.

En una realización adicional, R^6 es diferentes de H y R^7 es H.

En una realización, R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

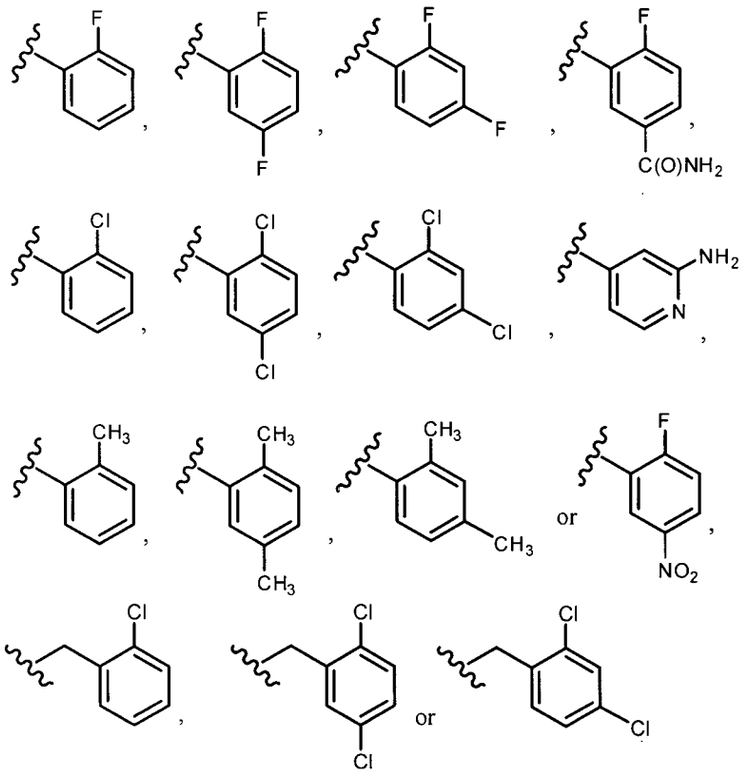
En aún otra realización, R^{10} es heteroarilo bicíclico, which puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -(alquilene)-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

En otra realización, R^{10} es quinolina, quinolinona, pteridine o pteridinone, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3

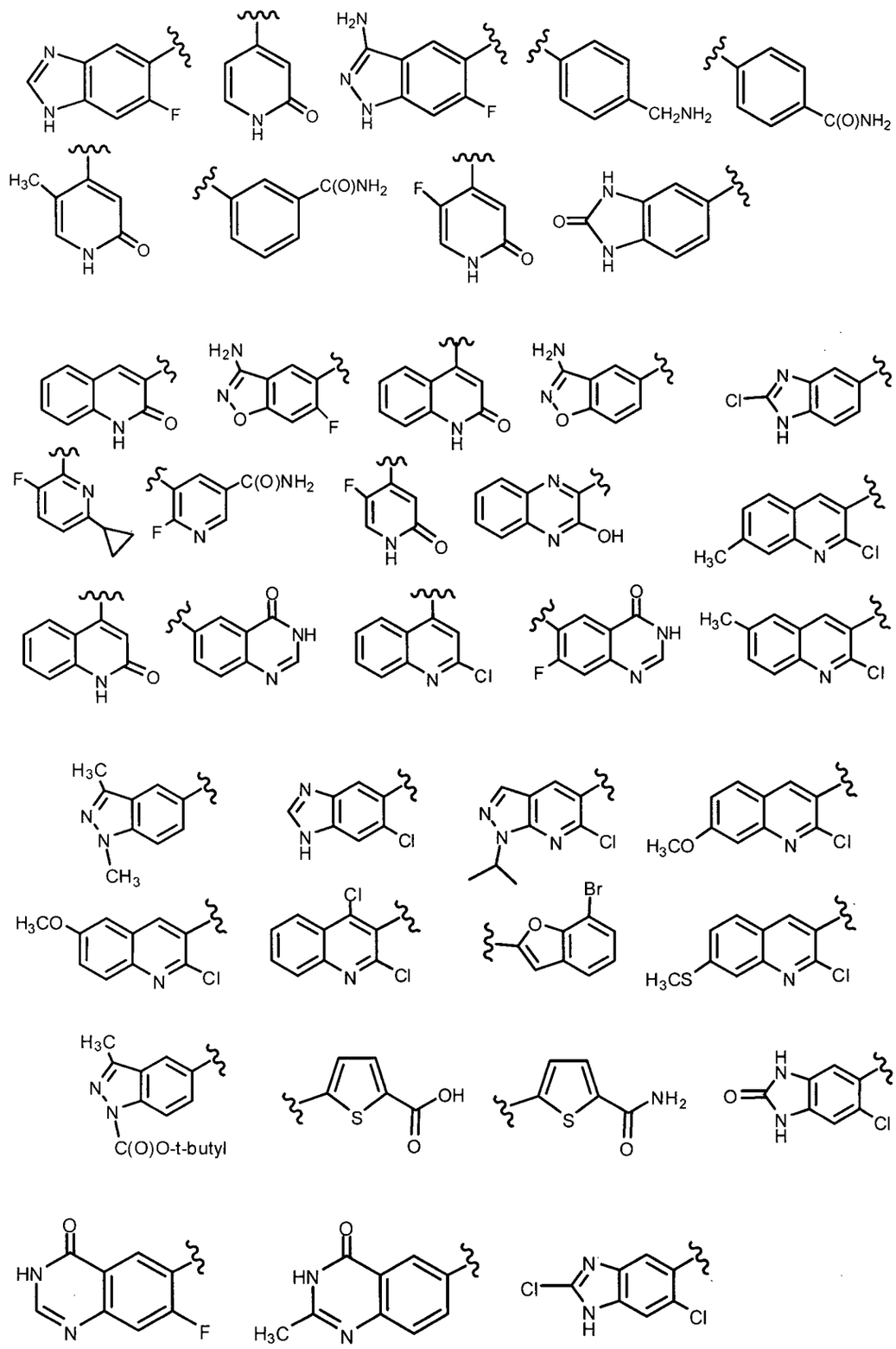
sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

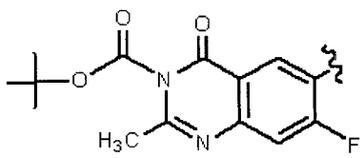
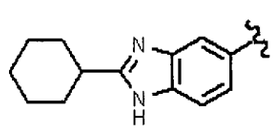
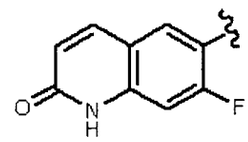
En una realización, R^{10} es quinolina o quinolinona, either of which puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

En una realización, R^{10} es:

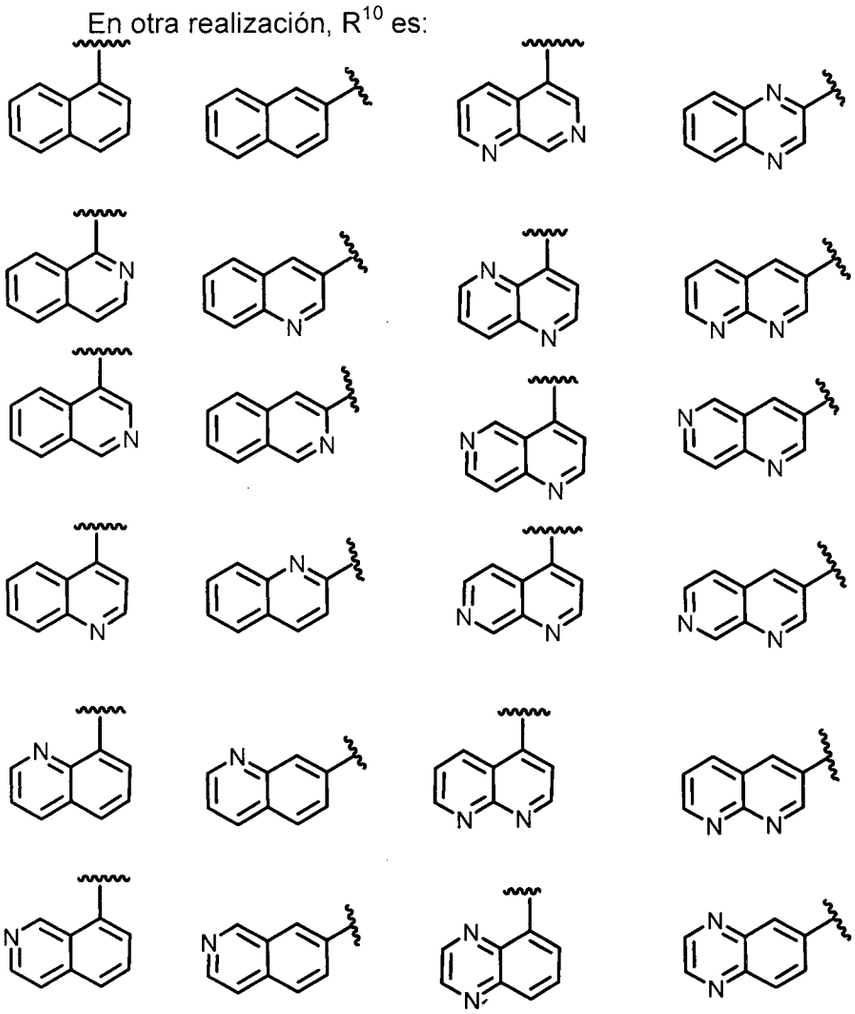


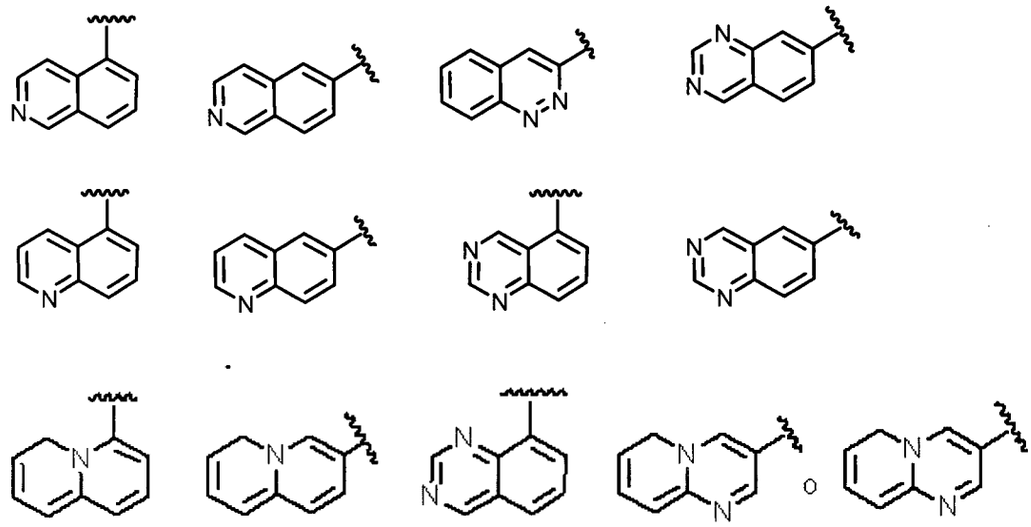
En otra realización, R^{10} es:


C(O)O-t-butyl

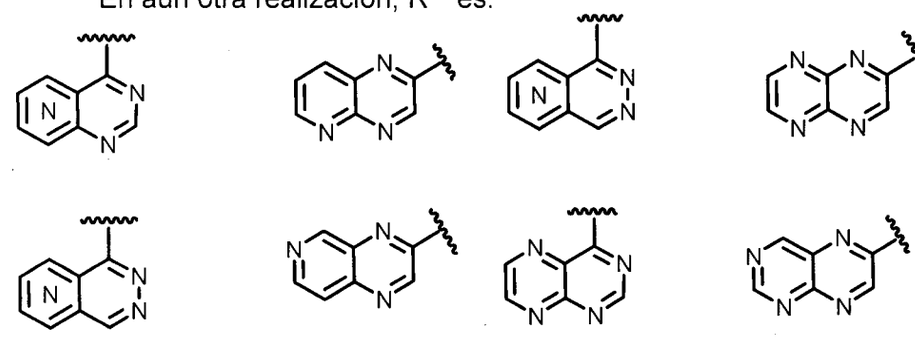
En otra realización, R^{10} es:

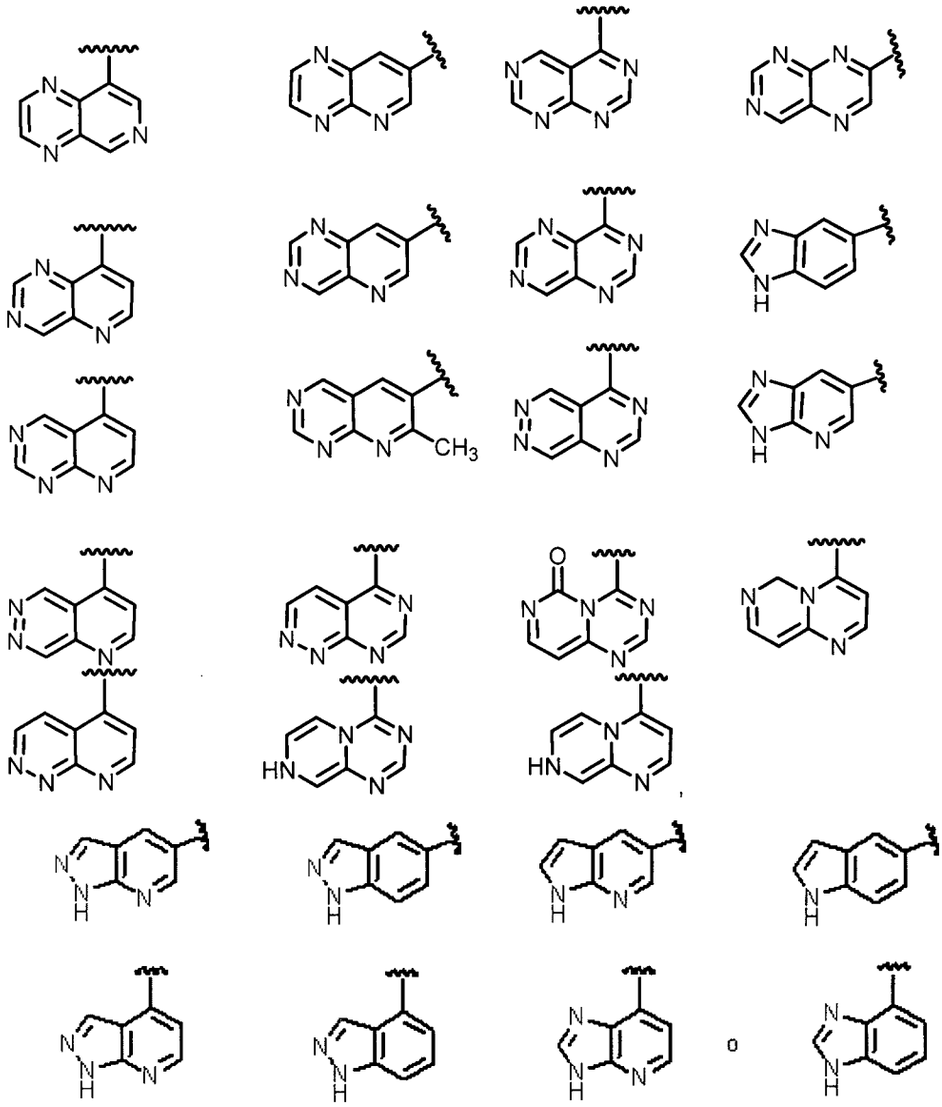




cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

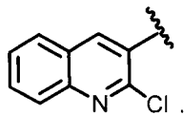
En aún otra realización, R^{10} es:





, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro del anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

En una realización, R^{10} es:



En una realización, R^2 es –C(O)OH; el enlace opcional está ausente; y R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

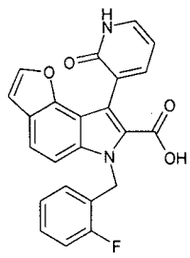
En otra realización, R^2 es –C(O)OH; el enlace opcional está ausente; y R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

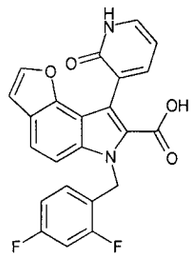
En otra realización, R^2 es –C(O)OH; el enlace opcional está ausente; y R^{10} es quinolina, quinolinona, pteridina o pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $–NHSO_2$-alquilo.

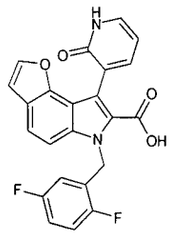
En una realización, para los compuestos de fórmula (I), R^1, R^2, R^3, R^6, R^7, R^{10} y Z se seleccionan independientemente entre sí.

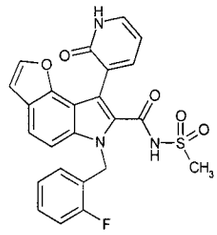
En otra realización, un Compuesto de fórmula (I) está en forma purificada.

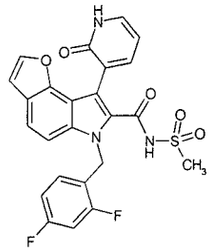
Los ejemplos no limitantes de los compuestos de fórmula (I) incluyen, pero sin limitación, los siguientes compuestos:

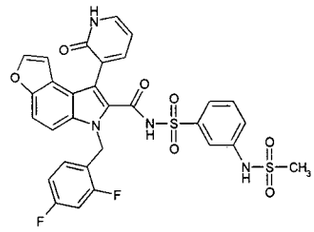
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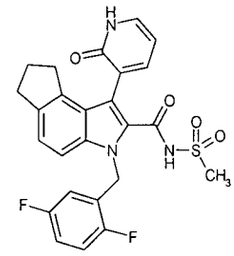
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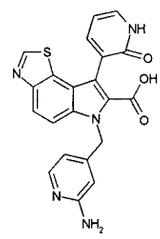
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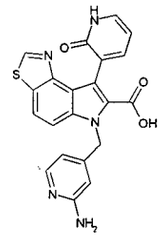
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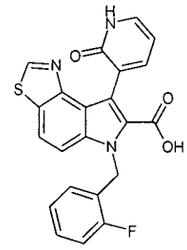
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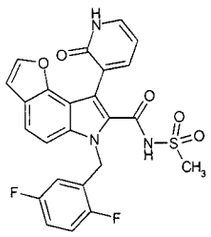
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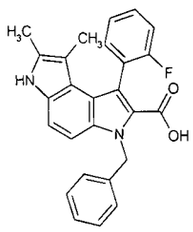
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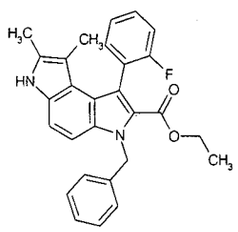
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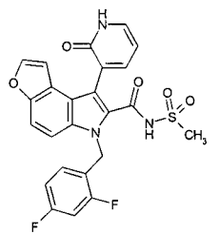
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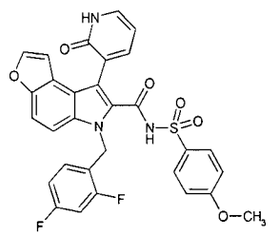
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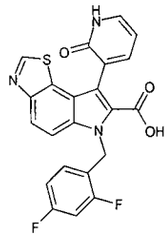
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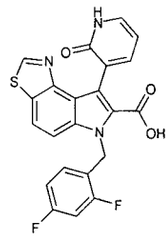
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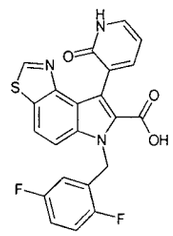
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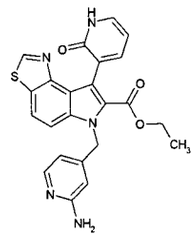
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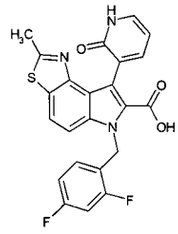
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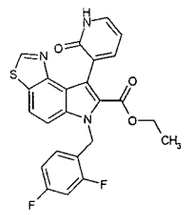


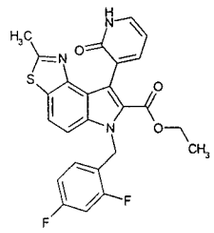
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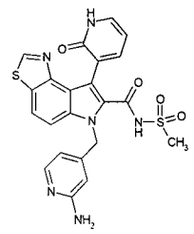


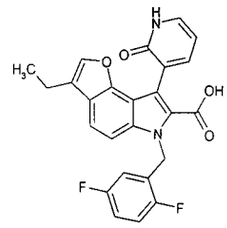
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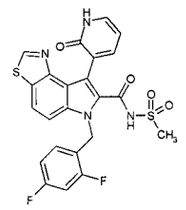


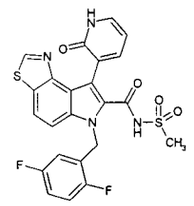
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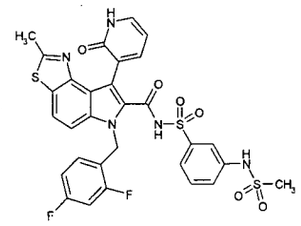
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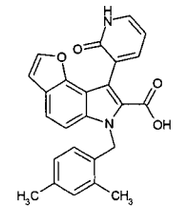
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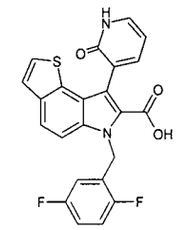
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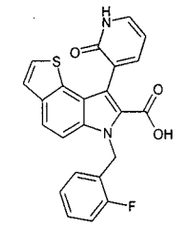
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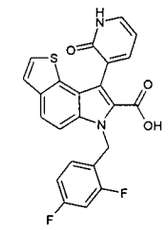
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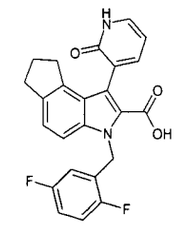
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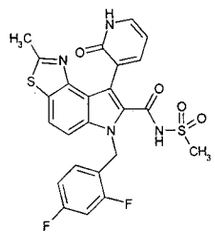
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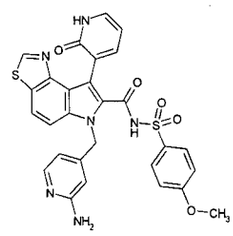
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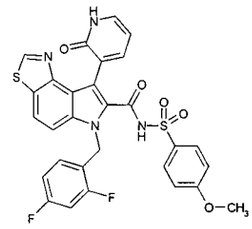
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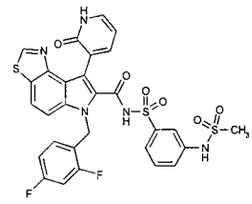
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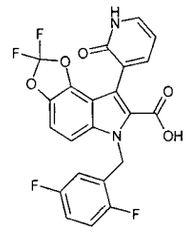
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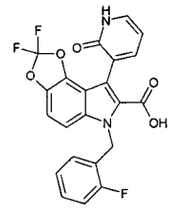
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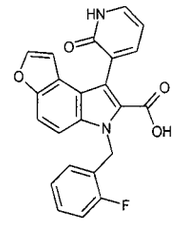
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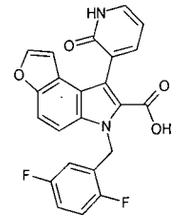
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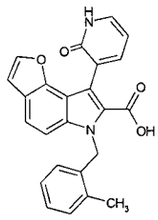
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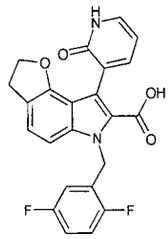
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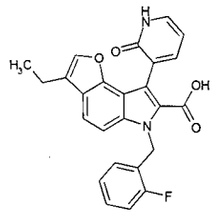
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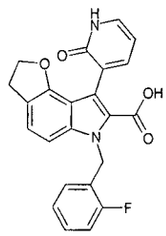
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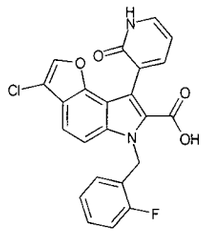
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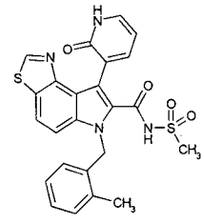
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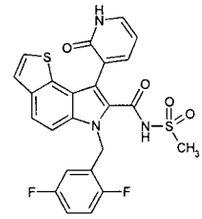
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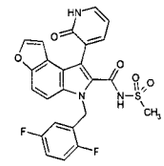
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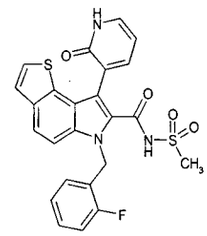
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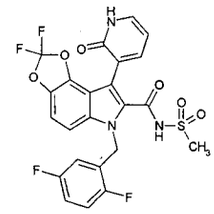
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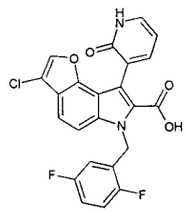
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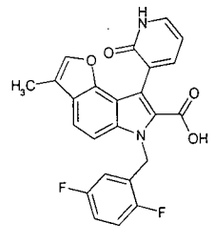
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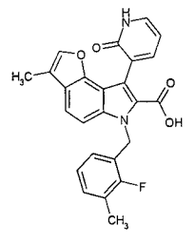
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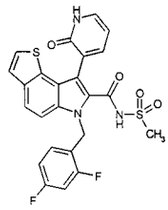
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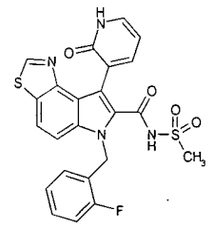
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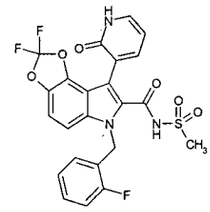
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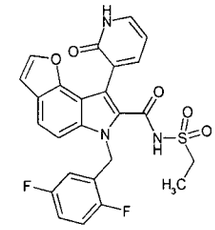
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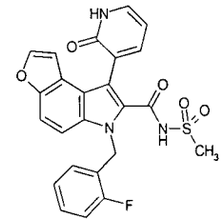
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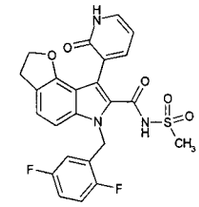
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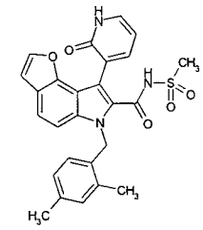
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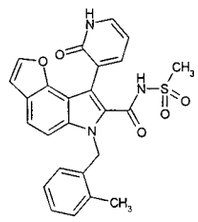
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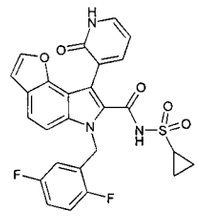
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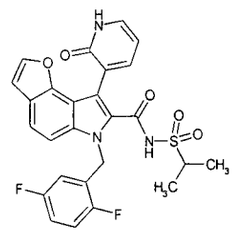
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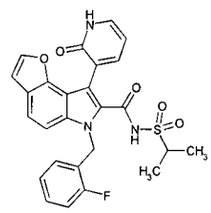
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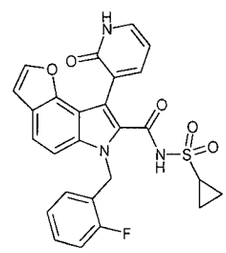
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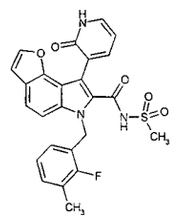
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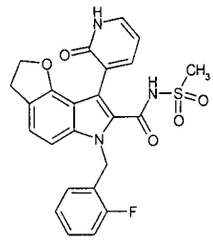
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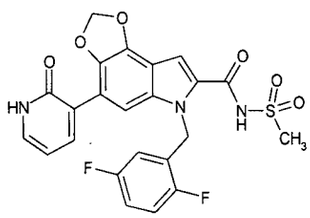
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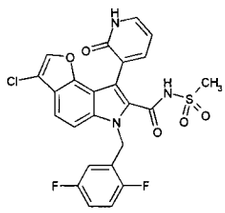
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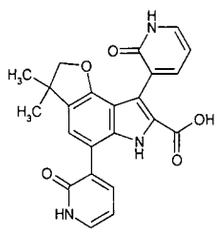
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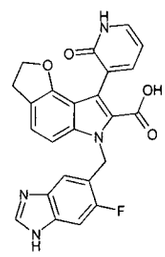
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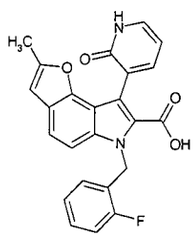
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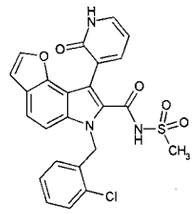
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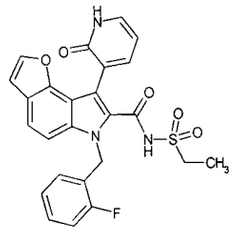
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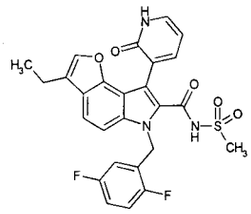
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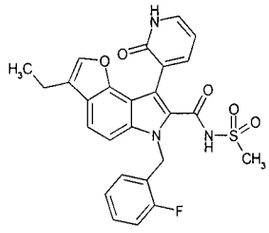
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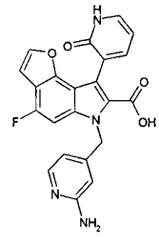
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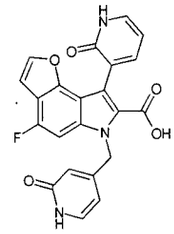
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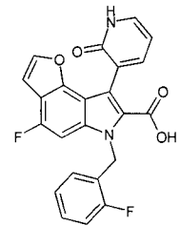
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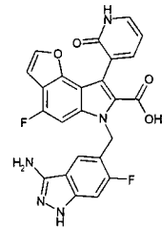
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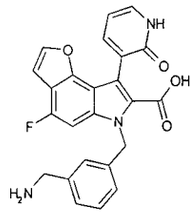
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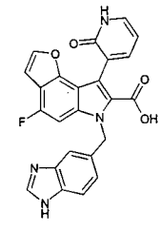
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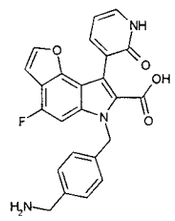
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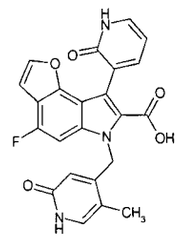
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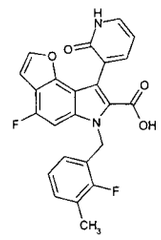
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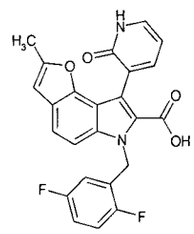
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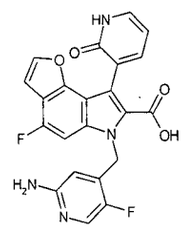
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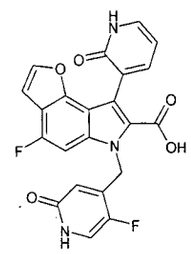
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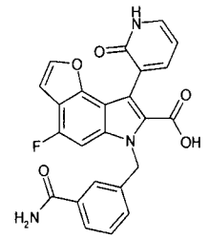
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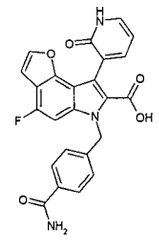
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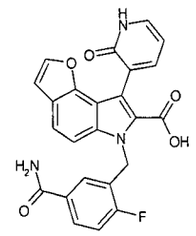
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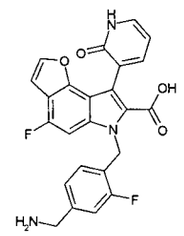
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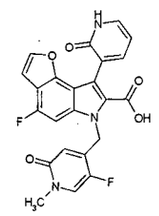
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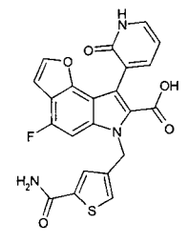
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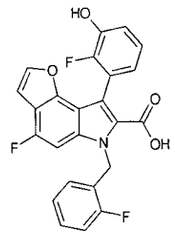
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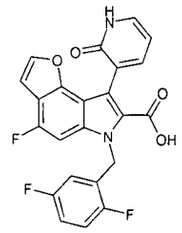
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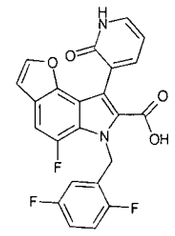
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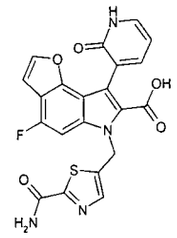
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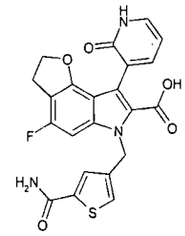
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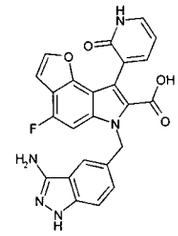
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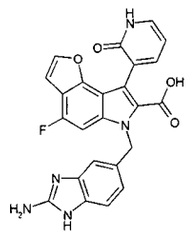
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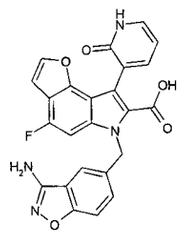
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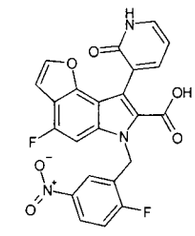
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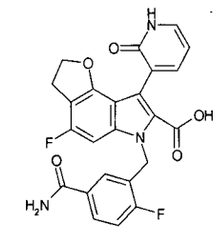
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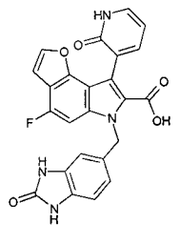
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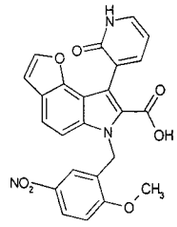


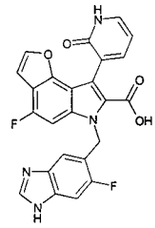
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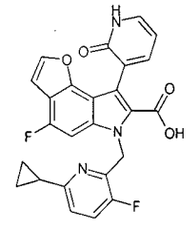


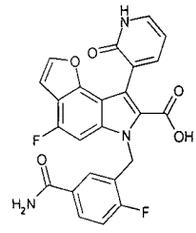
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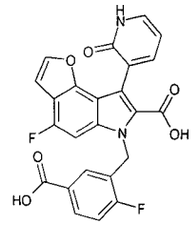
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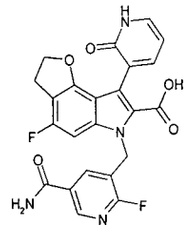
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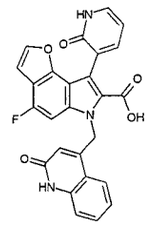
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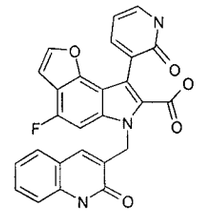
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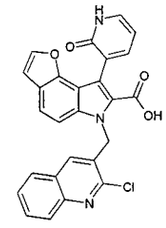
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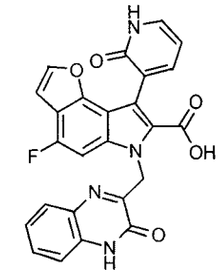
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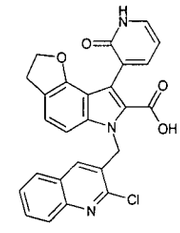
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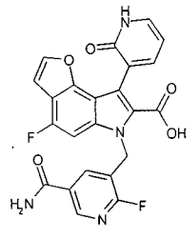
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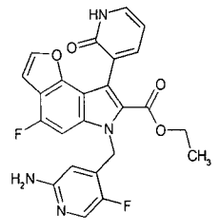
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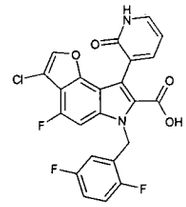
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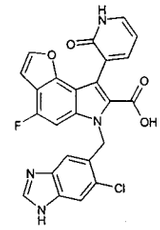
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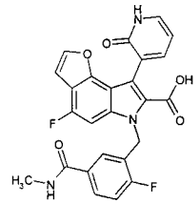
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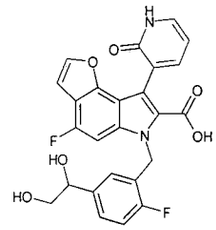
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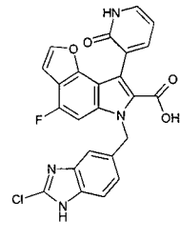
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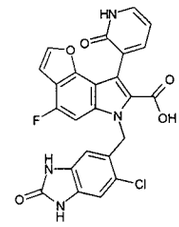
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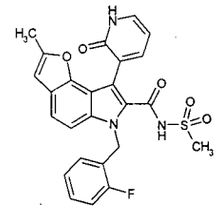
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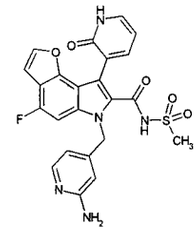
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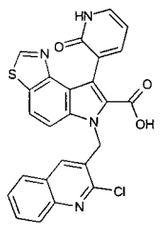


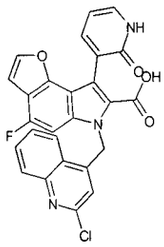
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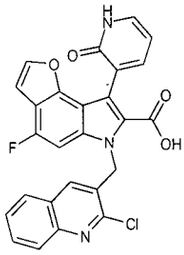


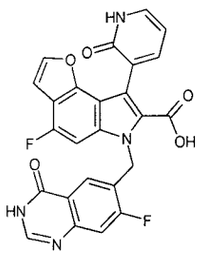
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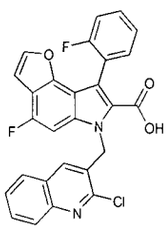


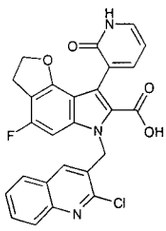
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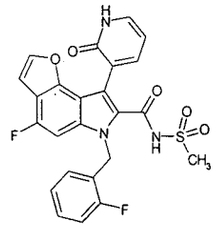
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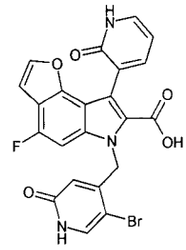
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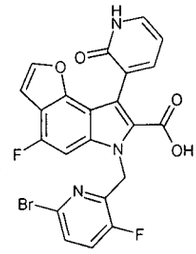
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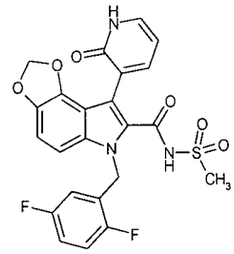
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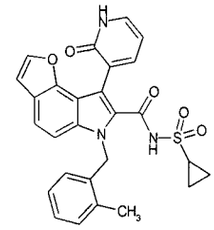
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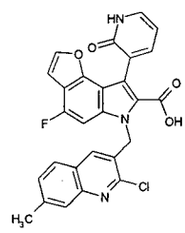
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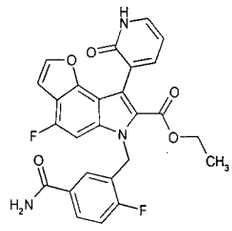
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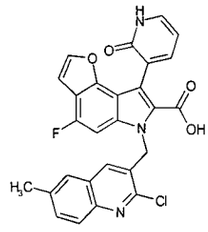
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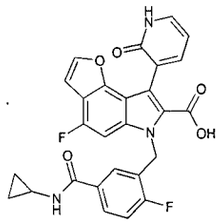
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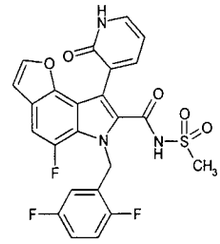
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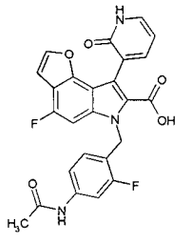
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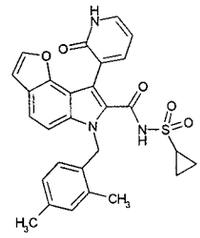
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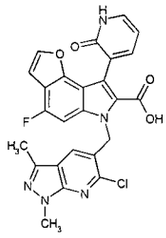
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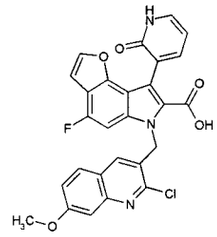
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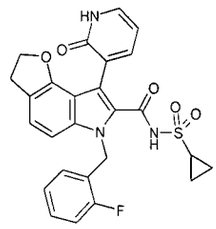
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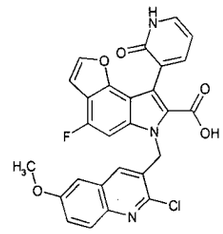
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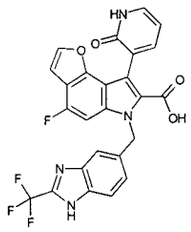
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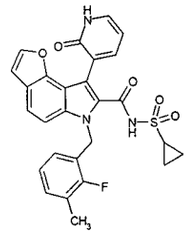
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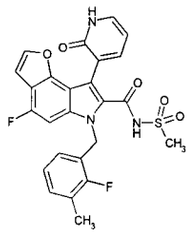
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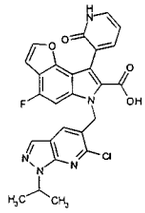
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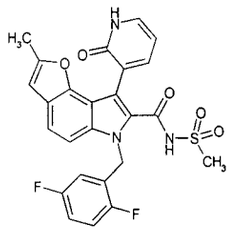
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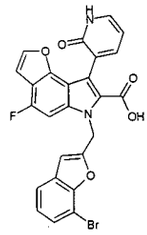
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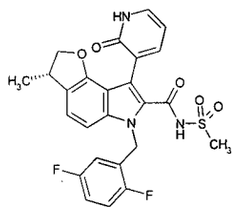
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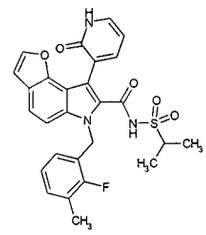
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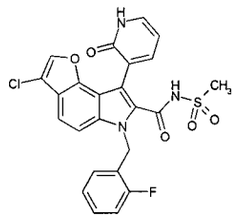
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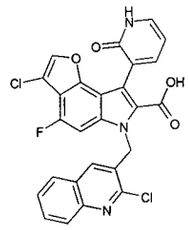
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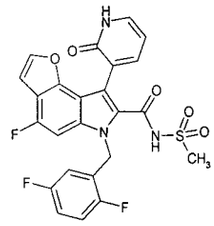
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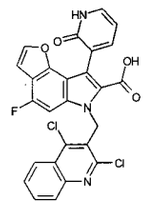
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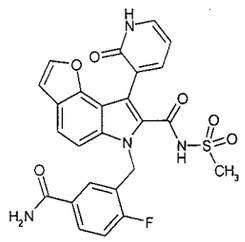
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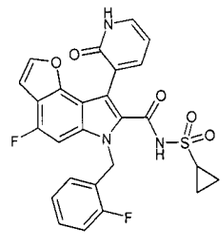
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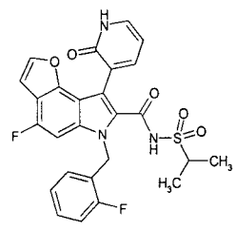
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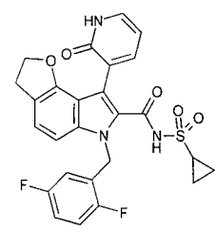
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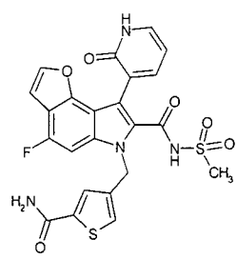
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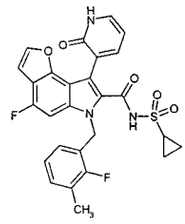
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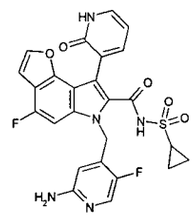
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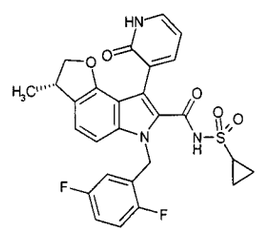
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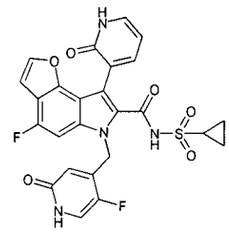
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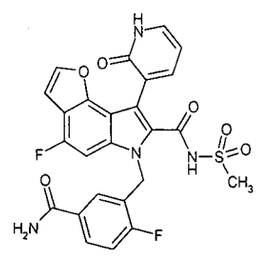
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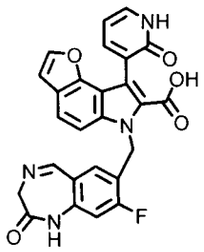
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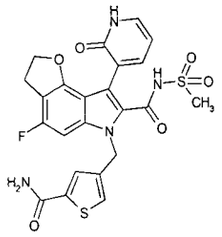
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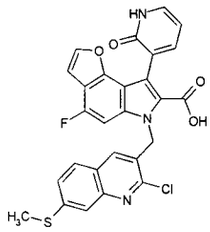
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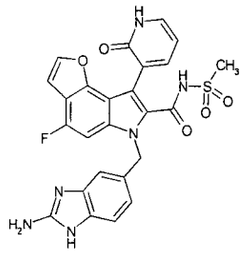
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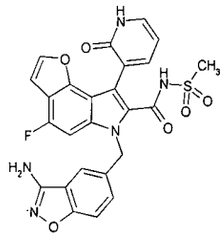
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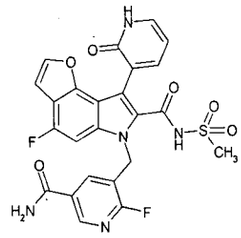
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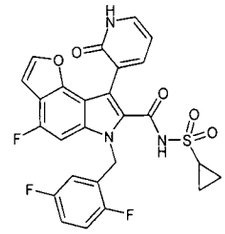
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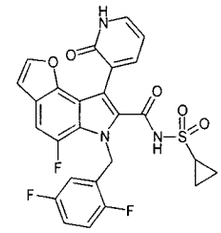
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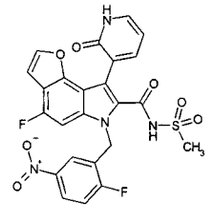
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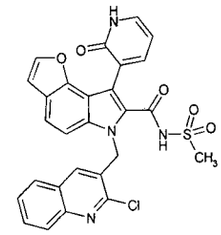
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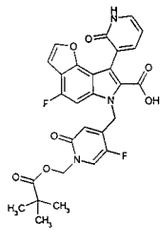
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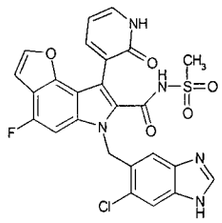
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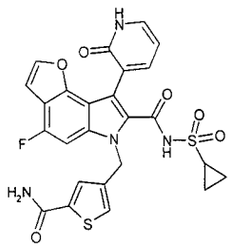
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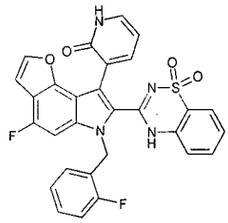
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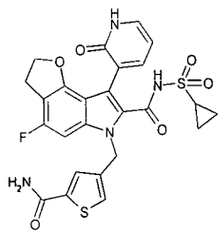
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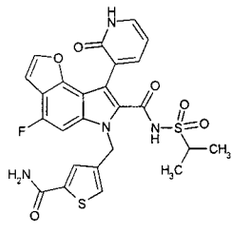
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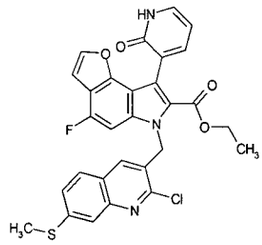
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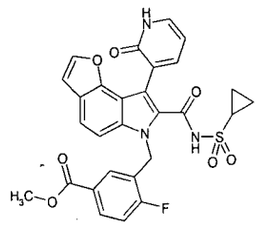
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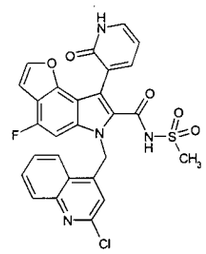
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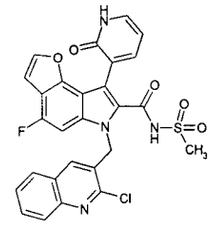
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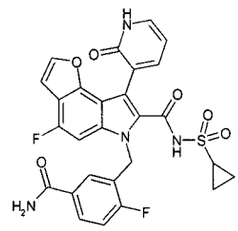
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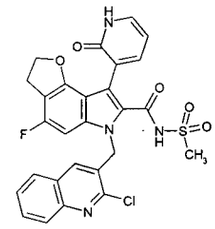
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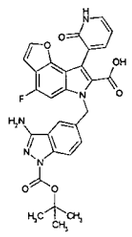


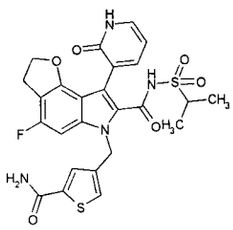
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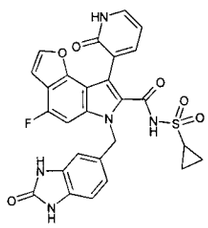


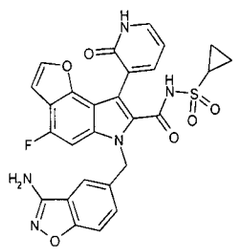
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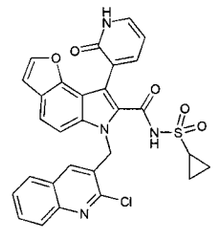


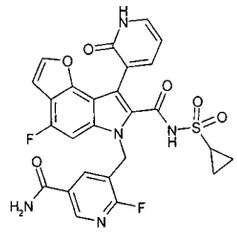
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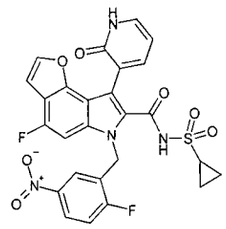
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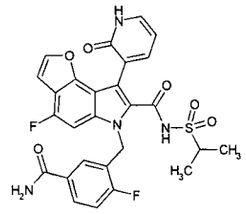
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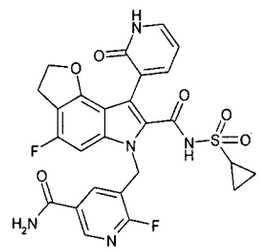
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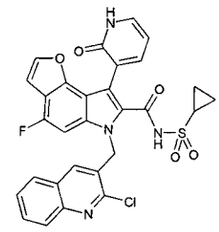
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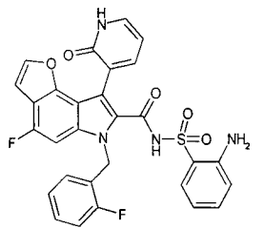
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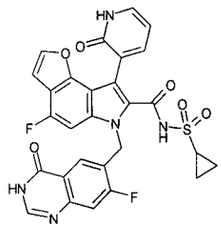
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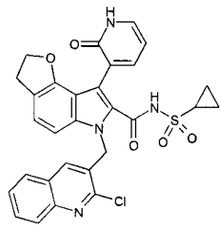
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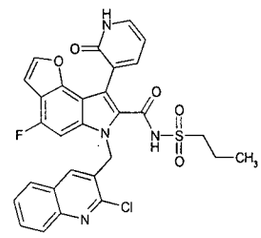
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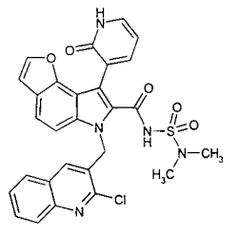
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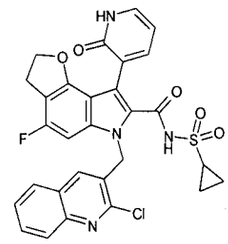
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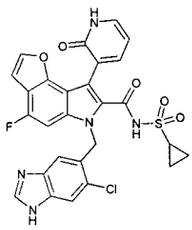
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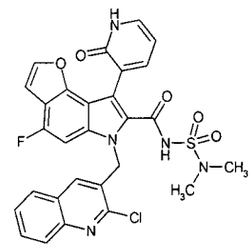
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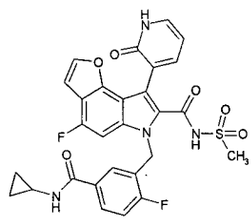
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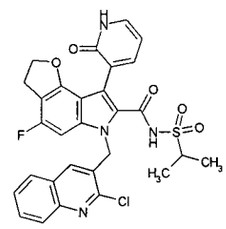
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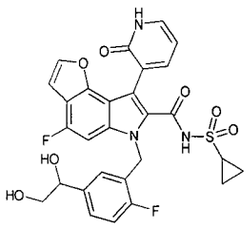
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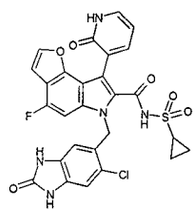
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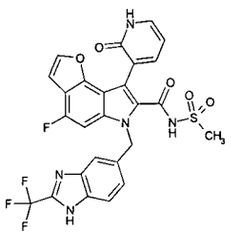
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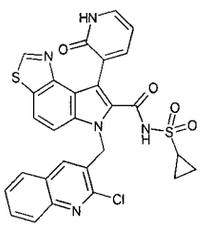
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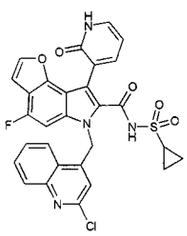
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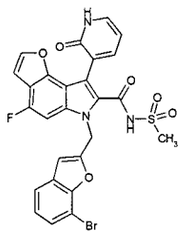
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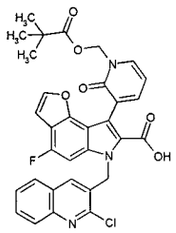
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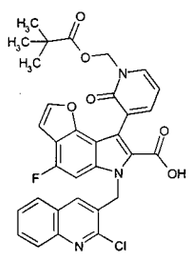
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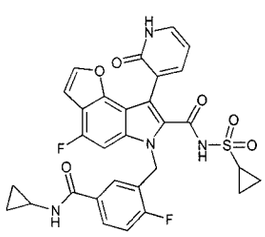
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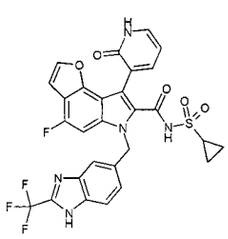
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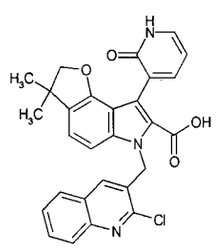
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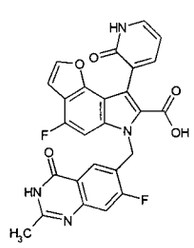
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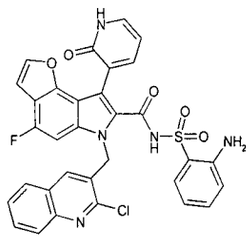


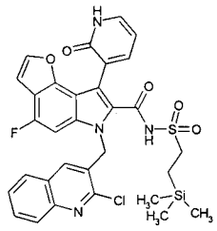
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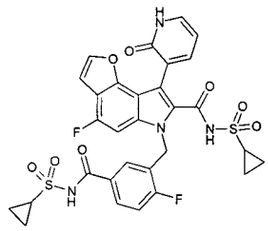


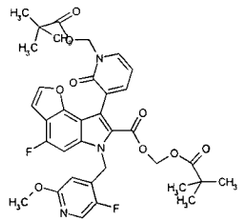
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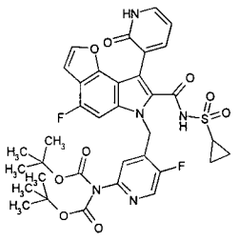


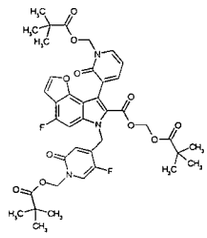
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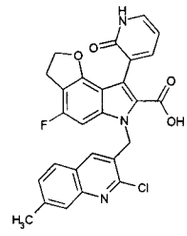
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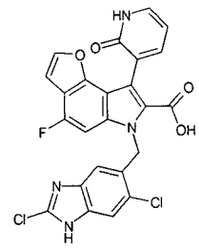
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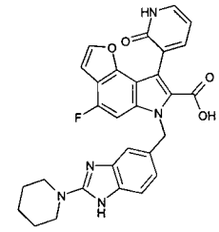
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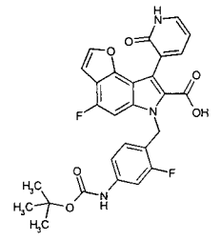
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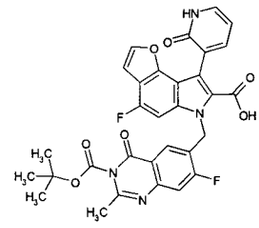
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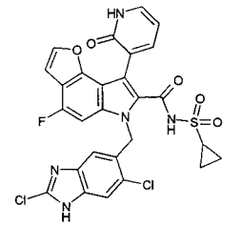
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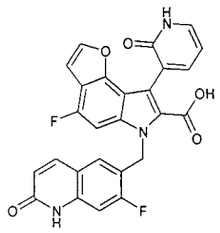
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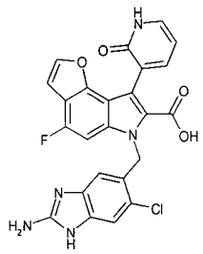
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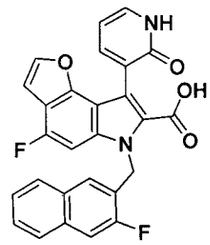
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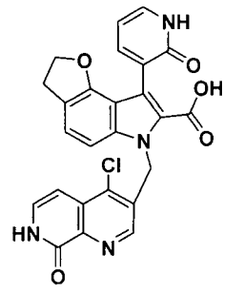
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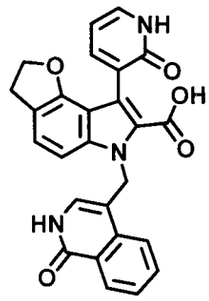
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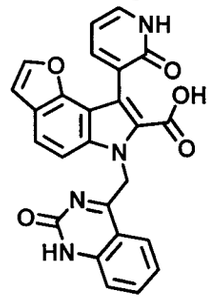
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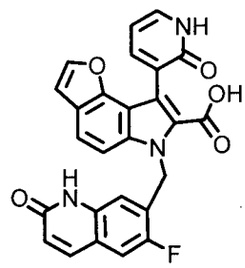
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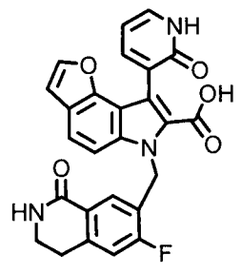
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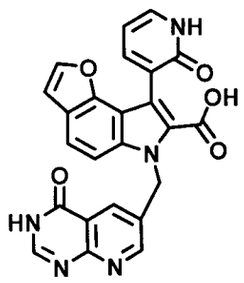


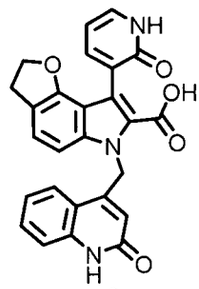
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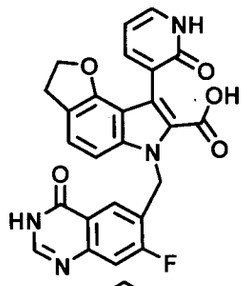


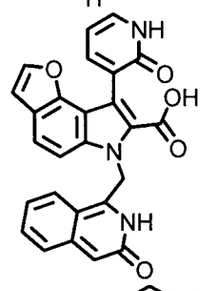
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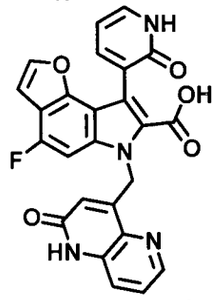


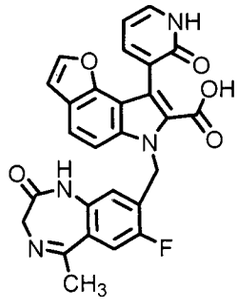
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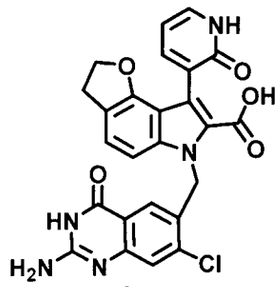
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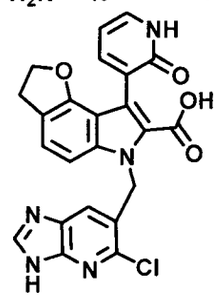
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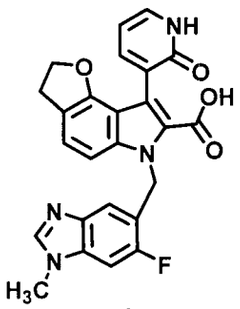
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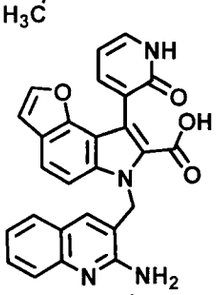
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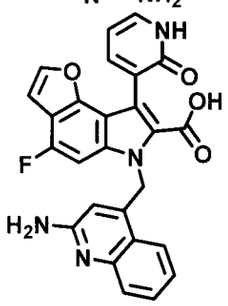
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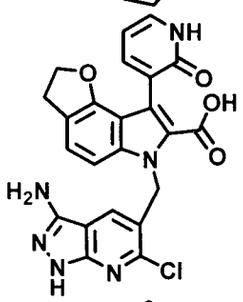
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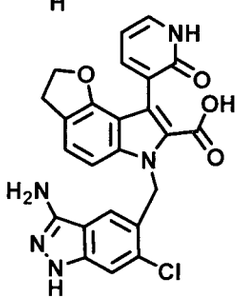
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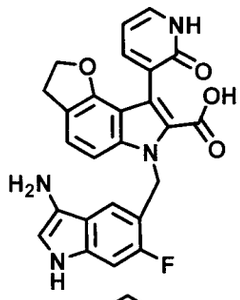


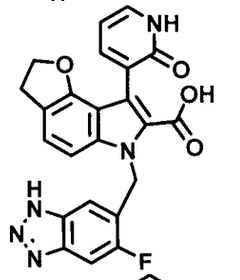
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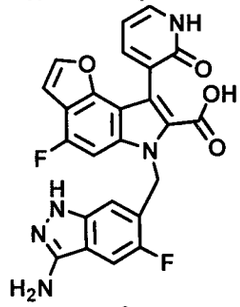


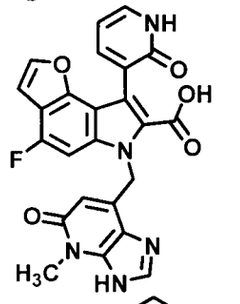
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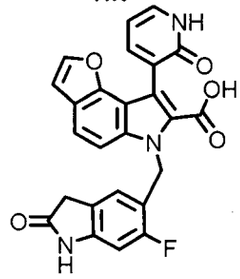


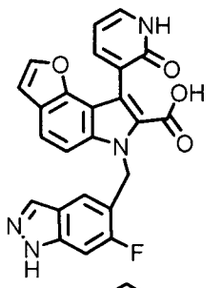
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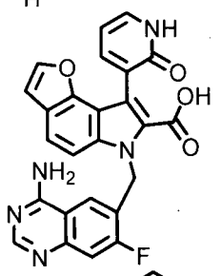
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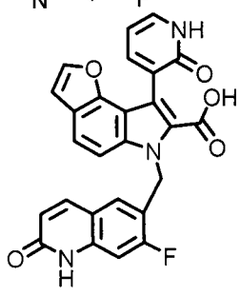
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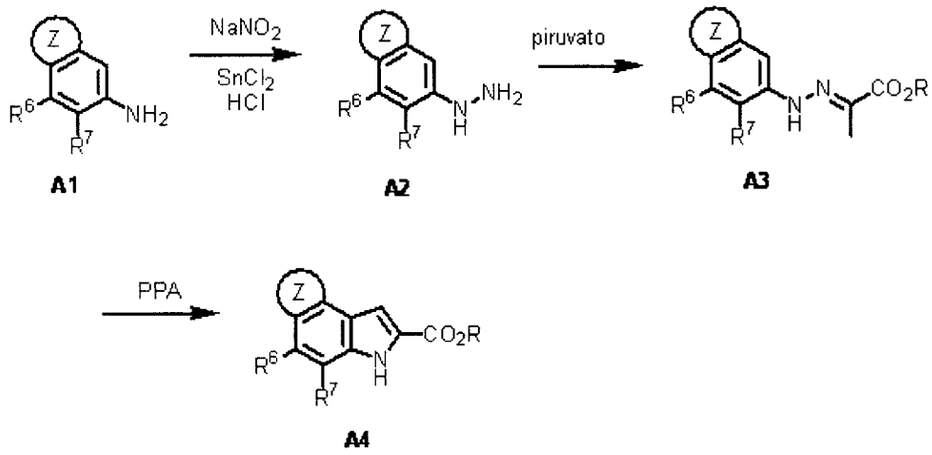
y sales, solvatos, ésteres o profármacos aceptables para uso farmacéutico de los mismos .

Métodos para preparar los compuestos de fórmula (I)

Los métodos útiles para preparar los compuestos de fórmula (I) se exponen en los siguientes Ejemplos y se generalizan en los Esquemas 1-9.

El Esquema 1 muestra un método para preparar Compuestos de fórmula **A4**, que son intermediarios útiles para la preparación de los compuestos de fórmula (I).

Esquema 1

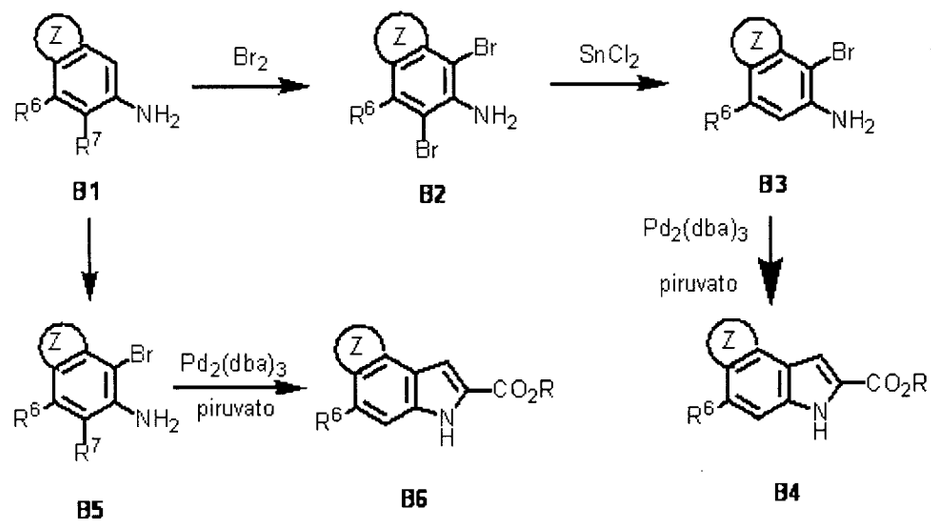


donde R^6, R^7 y Z se definieron anteriormente para los compuestos de fórmula (I), y R es cualquier sustituyente carbonilo que está comprendidito por R^2, como se definió anteriormente para los compuestos de fórmula (I).

Una anilina fusionada al anillo en 3,4 del compuesto de fórmula **A1** se puede convertir en un indol compuesto de fórmula **A4** mediante varias síntesis de indol que bien conocidos por los expertos en el arte de la síntesis orgánica, que incluye, pero sin limitación, una síntesis de indol de Fischer a través de los intermediarios de tipo **A2** y **A3**, el método se expone en Nazare *et al.*, *Angew. Chem.*, 116:4626-4629 (2004).

El Esquema 2 muestra métodos útiles para preparar compuestos **B4** y **B6**, que son intermediarios útiles para la preparación de los compuestos de fórmula (I).

Esquema 2

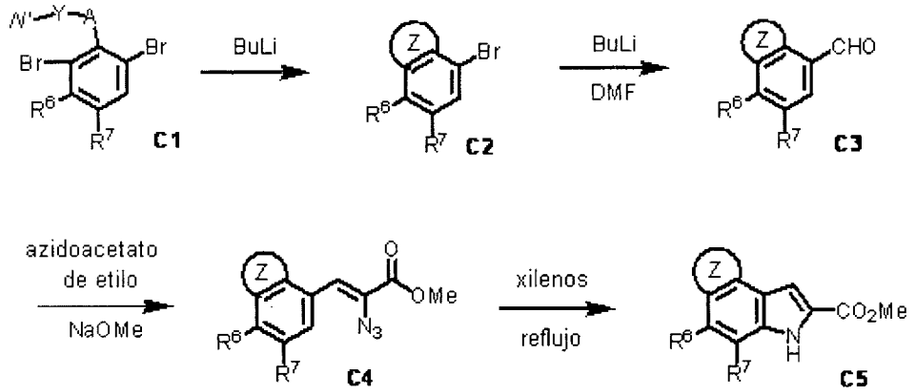


donde R^6, R^7 y Z se definieron anteriormente para los compuestos de fórmula (I), y R es cualquier sustituyente carbonilo que está comprendido por R^2, como se definió anteriormente para los compuestos de fórmula (I).

Un derivado bencénico bicíclico de fórmula **B1**, donde R^7 es H, se puede di-bromar para dar el compuesto **B2**. La des-bromación selectiva del correspondiente análogo monobromo **B3**, que en condiciones de ciclización catalizada por paladio proporciona el intermediario deseado **B4**, donde R^7 es H. Alternativamente un compuesto de fórmula **B1**, donde R^7 es diferente de H, se puede monobromar para dar el compuesto **B5**. El compuesto **B5** luego puede experimentar la ciclización catalizada por paladio que proporciona el intermediario deseado **B6**, donde R^7 es diferente de H.

El Esquema 3 muestra un método alternativo para preparar Compuestos de fórmula **C5**, que son análogos a los **B4** y **B6** y también son intermediarios útiles para la preparación de los compuestos de fórmula (I).

Esquema 3

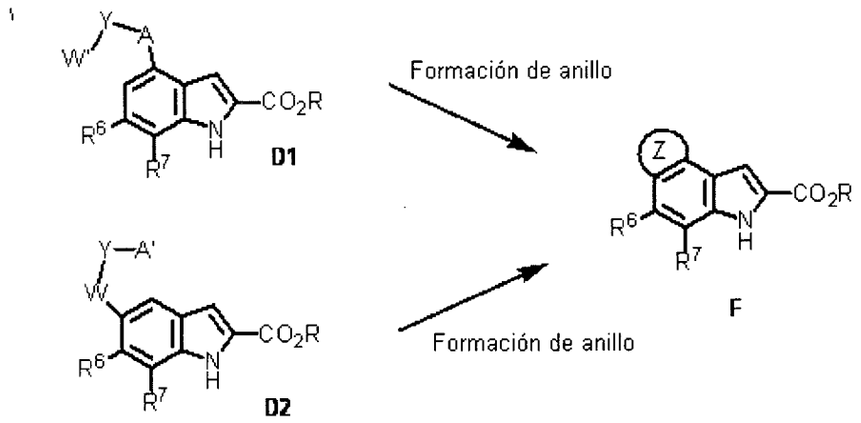


donde R^6, R^7 y Z se definieron anteriormente para los compuestos de fórmula (I), y W', Y y A se definen a continuación.

Un 2,6-dibromofenol compuesto de fórmula **C1**, que tiene un grupo –A-Y-W', donde A y Y son átomos del anillo Z y W' es un grupo capaz de experimentar una reacción de formación de anillo con el grupo bromuro de arilo en presencia de n-butillitio, se puede cerrar el anillo usando las reacciones de formación que son bien conocidos por los expertos en el arte de la síntesis orgánica para proporcionar los Compuestos de fórmula **C2**. El bromuro bicíclico **C2** a su vez puede convertir en un aldehído aromático de fórmula **C3**. El aldehído aromático **C3** puede experimentar una reacción de condensación reacción en presencia de un azidoacetato de alquilo para proporcionar los compuestos azido de fórmula **C4** que se puede convertir en indoles tricíclicos de fórmula **C5** usando métodos bien conocidos por los expertos en el arte de la química orgánica de síntesis.

El Esquema 4 muestra métodos útiles para preparar los compuestos de fórmula **F**, que son intermediarios útiles para la preparación de los compuestos de fórmula (I).

Esquema 4



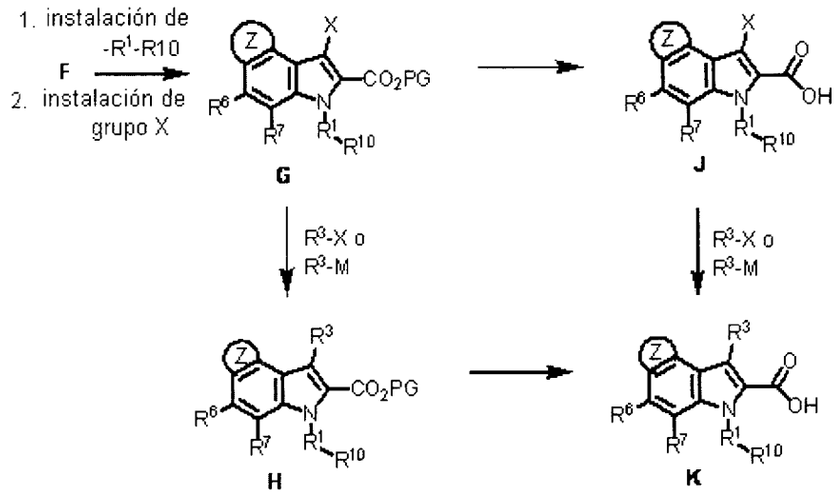
donde R^6, R^7 y Z se definieron anteriormente para los compuestos de fórmula (I); R es cualquier sustituyente carbonilo que está comprendido por R^2, como se definió anteriormente para los compuestos de fórmula (I); y W, W', Y, A y A' se definen a continuación.

Un compuesto de fórmula **D1**, que tiene un grupo –A-Y-W', donde A y Y son átomos del anillo Z y W' es un grupo capaz de experimentar una reacción de formación de anillo con el anillo benceno al que se une –A-Y-W', puede experimentar numerosas reacciones de formación de anillo que son bien conocidas por los expertos en el arte de la síntesis orgánica para formar compuestos tricíclicos de fórmula **F**. De modo similar, un compuesto de fórmula **D2**, que tiene un grupo –W-Y-A', donde W y Y son átomo del anillo Z y A' es capaz de experimentar una reacción de formación de anillo con el anillo benceno al que se une –A-Y-W', puede experimentar numerosas reacciones de formación de anillo que son bien conocidas por los expertos en el arte de la síntesis orgánica para formar compuestos tricíclicos de fórmula **F**. Los ejemplos de estos métodos de formación de anillo incluyen, pero sin limitación, los descriptos en *Comprehensive Heterocyclic Synthesis* (Pergamon Press); John *et al.*, *J. Org. Chem*, 47:2196 (1982); Maria *et al., Synthesis*, 1814 (2000); Martin *et al.*, *J. Med.*

Chem., 44:1561 (2001); Morsy et al., *Pak. J. Sci. Ind. Res*, 43:208 (2000); Koguro *et al.*, *Synthesis*, 911 (1998); Cowden *et al.*, *Tet. Lett.*, 8661 (2000); Norton *et al.*, *Synthesis*, 1406 (1994); Carl *et al.*, *Tet. Lett.*, 2935 (1996); Gunter *et al.*, *J. Org. Chem*, 46:2824 (1981).

El Esquema 5 ilustra los métodos por el cual los intermediarios de los compuestos de fórmula **F** se pueden derivatizar adicionalmente para proporcionar los compuestos de fórmula (I), donde R^2 es –C(O)OH.

Esquema 5



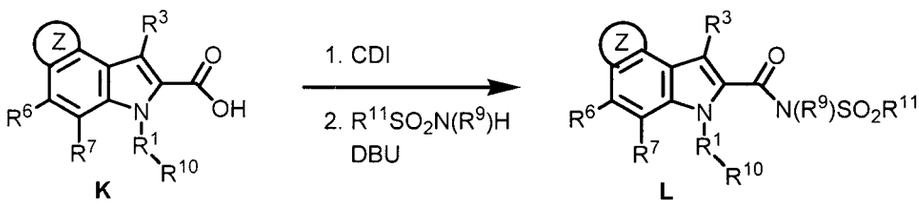
donde R^1, R^3 R^6 R^7, R^{10} y Z se definieron anteriormente para los compuestos de fórmula (I); PG es un grupo protector de carboxi y X es halo, -O-triflato, $-B(OH)_2$, $-Sn(alquilo)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, o cualquier metal que pueda participar en una reacción de acoplamiento cruzado con un organometálico.

Un compuesto de fórmula intermediario **F** se puede convertir en un indol 3 sustituido de fórmula **G** mediante métodos bien conocidos por los expertos en el arte de la síntesis orgánica. Un compuesto de fórmula **G**, donde X es halo o –O-triflato luego se puede acoplar con un compuesto de fórmula R^3-M apropiado (donde M es $-B(OH)_2$, $-Sn(alquilo)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, o cualquier metal que pueda participar en una reacción de acoplamiento cruzado con un organometálico usando un método acoplamiento cruzado con un organometálico. Alternativamente, un compuesto de fórmula **G**, donde X es $-B(OH)_2$, $-Sn(alquilo)_3$, -MgBr, -MgCl, -ZnBr, -ZnCl, o cualquier metal que pueda participar en una reacción de acoplamiento cruzado con un organometálico, luego se puede acoplar con un compuesto de fórmula R^3-M apropiado (donde M es halo o -O-triflato) usando un método acoplamiento cruzado con un organometálico. Los métodos de

acoplamiento cruzado adecuados incluyen, pero sin limitación, un acoplamiento Stille (ver Choshi *et al.*, *J. Org. Chem.*, 62:2535-2543 (1997), y Scott *et al.*, *J. Am. Chem. Soc.*, 106:4630 (1984)), un acoplamiento Suzuki (ver Miyaura *et al.*, *Chem. Rev.*, 95:2457 (1995)), un acoplamiento Negishi (ver Zhou *et al.*, *J. Am. Chem. Soc.*, 127:12537-12530 (2003)), y un acoplamiento Kumada (ver Kumada, *Pure Appl. Chem.*, 52:669 (1980) y Fu *et al.*, *Angew. Chem.* 114:4363 (2002)) para proporcionar un compuesto de fórmula **H**. El grupo protector de carboxi, PG, luego se puede eliminar del compuesto de fórmula **H** y el ácido carboxílico resultante se puede derivatizar mediante los métodos que se describen a continuación en los Esquemas 6-8 par hacer los grupos R^2 apropiados y preparar los compuestos de fórmula **K**, que corresponden a los compuesto de fórmula (I), donde R^2 es –C(O)OH. Alternativamente, un compuesto de fórmula **F** se puede desproteger primero y el grupo R^2 unido mediante los métodos anteriores para proporcionar a compuesto de fórmula **J**. Un compuesto de fórmula **J** luego se puede acoplar en forma cruzada con un compuesto de R^3-X o R^3-M descripto anteriormente para proporcionar la preparación de los compuestos de fórmula **K**.

El Esquema 6 muestra un método útil para preparar los compuestos de fórmula (I), donde R^2 es $-C(O)N(R^9)SO_2R^{11}$.

Esquema 6



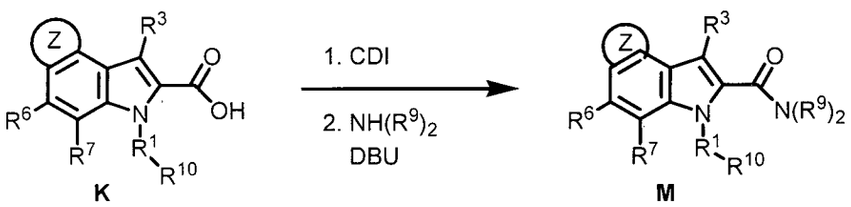
donde R^1, R^3, R^6, R^7, R^9, R^{10}, R^{11} y Z son como se definieron para los compuestos de fórmula (I).

Un compuesto 2-carboxi indol de fórmula **K** se puede acoplar con un compuesto de fórmula $R^{11}SO_2NH_2$ en presencia de carbonildiimidazol (CDI) y 1,8-

diazabiciclo[5.4,0]undec-7-eno (DBU) para proporcionar los compuestos de fórmula **L**, que corresponden a los compuestos de fórmula (I) donde R^2 es $-C(O)NHSO_2R^{11}$.

El Esquema 7 muestra un método útil para preparar los compuestos de fórmula (I), donde R^2 es $-C(O)N(R^9)_2$.

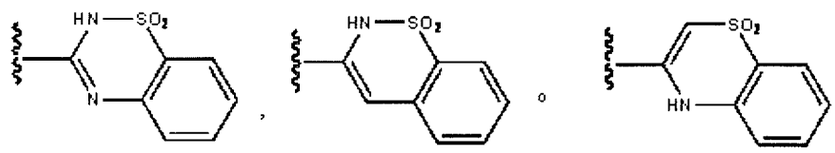
Esquema 7



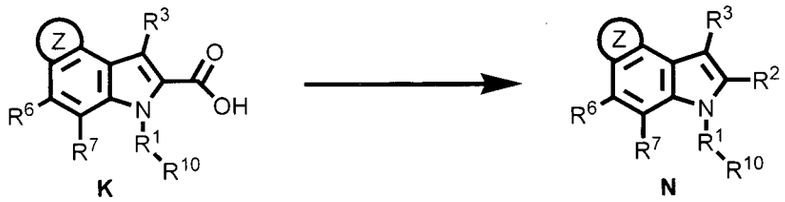
donde R^1, R^3, R^6, R^7, R^9, R^{10} y Z son como se definieron para los compuestos de fórmula (I).

Un compuesto 2-carboxiindol de fórmula **K** se puede acoplar con una amina de fórmula $NH(R^9)_2$ en presencia de carbonildiimidazol (CDI) y 1,8-diazabiciclo[5.4,0]undec-7-eno (DBU) para proporcionar los compuestos de fórmula **M**, que corresponden a los compuestos de fórmula (I) donde R^2 es $-C(O)N(R^9)_2$.

El Esquema 8 muestra un método útil para preparar los compuestos de fórmula (I), donde R^2 es:

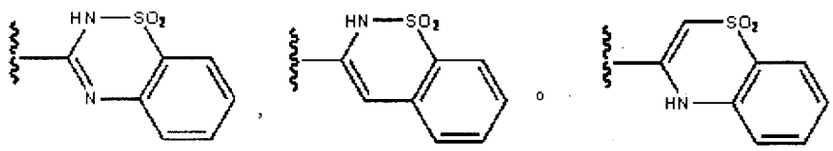


Esquema 8

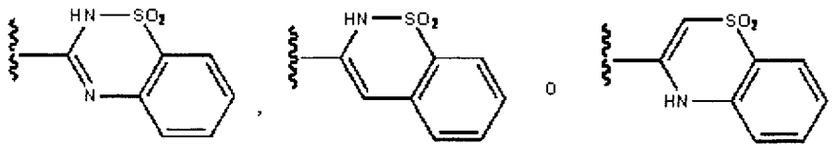


K **N**

donde R^1, R^3, R^6, R^7, R^{10} y Z son como se definieron para los compuestos de fórmula (I) y R^2 es:



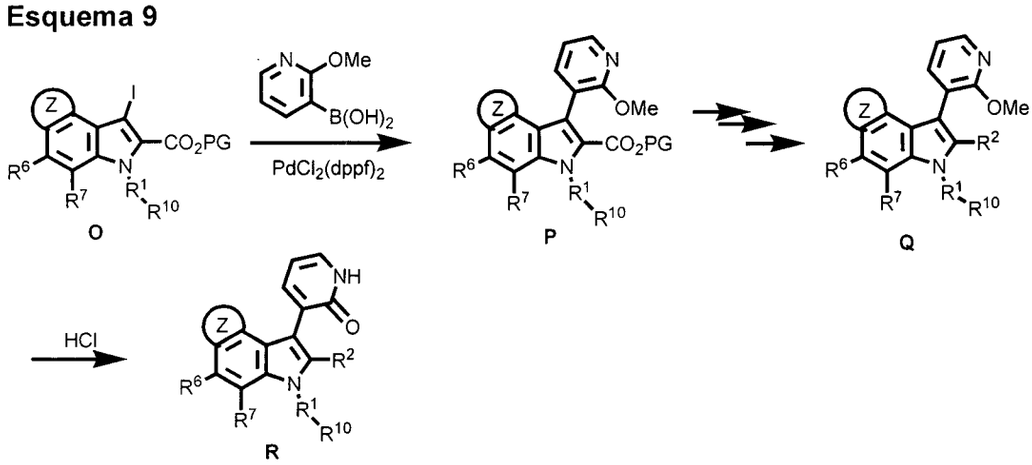
Un 2-carboxiindol compuesto de fórmula **K** se puede convertir con los compuestos de fórmula **N**, que corresponden con los compuestos de fórmula (I) donde R^2 es:



mediante los métodos expuestos en la Solicitud de Patente Estadounidense No. US2005/0075331.

El Esquema 9 muestra un método útil para preparar los compuestos de fórmula (I), donde R^3 es 1*H*-piridin-2-on-3-ilo.

Esquema 9



donde R^1, R^2, R^6, R^7, R^{10} y Z son cono se definieron para los compuestos de fórmula (I), y PG es un grupo protector de carboxi.

Un compuesto 3-yodoindol de fórmula **O** se puede acoplar con ácido 2-hidroxipiridin-3-borónico mediante una reacción de acoplamiento Suzuki para proporcionar los compuestos indólicos sustituidos en R^3 de fórmula **P**. Un compuesto de fórmula **P** se puede elaborar adicionalmente mediante los métodos expuestos anteriormente para proporcionar los compuestos de fórmula **Q**. El residuo 2-hidroxipiridilo de un compuesto de fórmula **Q** luego se puede hacer reaccionar con ácido clorhídrico para proporcionar un compuesto de fórmula **R**, que corresponde a los compuestos de fórmula (I), donde R^3 es 1*H*-piridin-2-on-3-ilo.

El material de partida y reactivos representados en los Esquemas 1-9 están disponibles de los proveedores comerciales tales como Sigma-Aldrich (St. Louis, MO) y Acros Organics Co. (Fair Lawn, NJ), o se pueden preparar mediante los métodos bien conocidos por los expertos en el arte de la síntesis orgánica.

Un experto en el arte reconocerá que la síntesis de los compuestos de fórmula (I) pueden requerir la necesidad de protección de ciertos grupos funcionales (es decir, la derivatización con el propósito de compatibilidad química con una condición de reacción particular). Los grupos protectores adecuados para

los diversos grupos funcionales de los compuestos de fórmula (I) y métodos para su instalación y eliminación se pueden hallar en Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

Un experto en el arte reconocerá que será óptima una ruta de acuerdon con la elección de sustituyentes del apéndice. Adicionalmente, un experto en el arte reconocerá que en algunos casos el orden de los pasos puede diferir del presentado en la presente memoria para evitar las incompatibilidades de grupos funcionales y en consecuencia, corregir la ruta de síntesis.

Un experto en el arte reconocerá que la síntesis de ciertos compuestos de fórmula **1** requiere la construcción de un enlace amida. Los métodos útiles para preparar tales enlaces amida, incluyen pero sin limitación, el uso de un derivado carboxi reactivo (por ej., haluro ácido, o éster a temperaturas elevadas) o el uso de un ácido con un reactivo de acoplamiento (por ej., DECI, DCC) con una amina.

Los materiales de partida usados y los intermediarios preparados mediante los métodos expuestos en los Esquemas 1-9 se pueden aislar y purificar si se desea mediante técnicas convencionales, que incluye, pero sin limitación filtración, destilación, cristalización, cromatografía y similares. Tales materiales se pueden caracterizar usando medios convencionales, que incluyen constantes físicas y datos de espectro.

EJEMPLOS

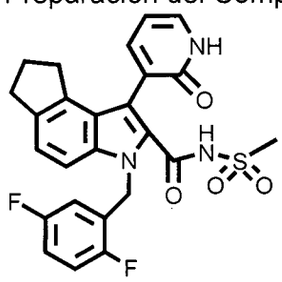
Métodos generales

Los solventes, reactivos e intermediarios que están disponibles en el mercado se usaron como se recibieron. Los reactivos e intermediarios que no están disponibles en el mercado se prepararon de la siguiente manera. Los datos de especto ^{1}H RMN se obtuvieron en un Bruker Avance 500 (500 MHz) y se informan como ppm a campos más bajos que Me_4Si con número de protones,

multiplicidades y constantes de acoplamiento en Hertz indicadas entre paréntesis. Cuando se presentan los datos de LC/MS, los análisis se realizaron en un espectrómetro de masa Applied Biosystems API-100 y una columna Shimadzu SCL-10A LC: Altech de platino C18, 3 micrones, 33 mm x 7mm ID; flujo del gradiente: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 5-7 min – 95% CH_3CN, 7 min – detención. Se brindan los datos de tiempo de retención y el ion progenitor observado. La cromatografía en columna flash se realizó mediante una fase de sílice preempacada de Biotage, Inc. o sílice a granel de Fisher Scientific. A menos oque se indique de otro modo, se realizó una cromatografía en columna usando un gradiente de elución de hexanos/acetato de etilo, de 100% de hexanos a 100% de acetato de etilo.

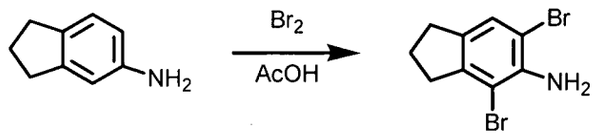
Ejemplo 1

Preparación del Compuesto **12**



12

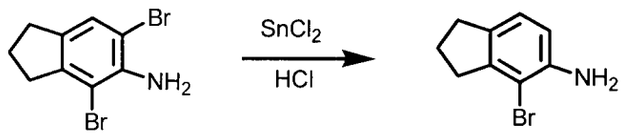
Paso A – Síntesis del Compuesto 12A



12A

A una solución de 5-aminoindano (5,00 g, 37.55 mmol) en ácido acético (200 ml) se agregó bromo (15 ml). La mezcla resultante se dejó agitar durante 1 hora y luego se concentró a ~ 100 ml. Se agregó cloroformo para dar un precipitado. El sólido se aisló por filtración, y se lavó con cloroformo para proporcionar el compuesto **12A** como un sólido ligeramente coloreado (12.63 g). mp 220-221°C; ^{1}H RMN (400 MHz, d_6-DMSO) δ 2,07 (m, 2H), 2,90 (m, 4H), 7,33 (s, 1H).

Paso B – Síntesis del Compuesto 12B

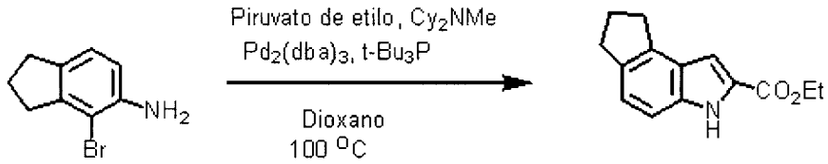


12A **12B**

Se agregó cloruro estañoso (0,89 g) a un solución del Compuesto **12A** (1,0g, 3,5 mmol) en ácido acético (5 ml) y HCl acuoso concentrado (4 ml). La

mezcla resultante se calentó a reflujo durante 30 minutos, luego se enfrió a temperatura ambiente. Luego se eliminaron los solventes *in vacuo* y el residuo resultante se dividió entre NaOH y CH_2Cl_2. La fase orgánica se separó y la fase acuosa se extrajo con CH_2Cl_2. La fases orgánicas combinadas se secaron con $MgSO_4$ y concentraron para proporcionar un residuo bruto que se purificó cromatografía en gel de sílice (EtOAc:Hexano=1:20) para proporcionar el compuesto **12B** (0,501 g) como un sólido blanco. ^{1}H RMN (400MHz, CDCl3) δ6,95 & 6,93 (d, J = 8,05 Hz, 1H), 6,59 & 6,57 (d, J = 7,32 Hz, 1H), 3,96 (s, 2H), 2,91 (q, J = 7,32 & 15,38 Hz, 4H), 2,07 (quinteto, J = 7,32 Hz, 2H).

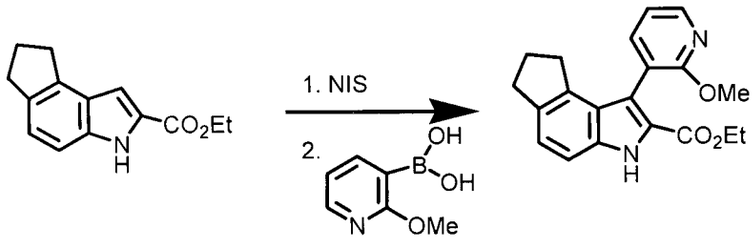
Paso C – Síntesis del Compuesto 12C



12B **12C**

Se agregó $Pd_2(dba)_3$ (185 mg) a una solución de dioxano (20 ml) del Compuesto **12B** (0,455 g, 2,1 mmol), tri-ter-butilfosfina (0,81 ml of a 1,0 M solución en tolueno), diciclohexilmetilamina (2,92 ml) y piruvato de etilo (0,9 ml). La mezcla se calentó a 100°C bajo una atmósfera de nitrógeno toda la noche. Después de enfriar, la mezcla de reacción se dividió entre CH_2Cl_2 y diluyó con HCl acuoso (1N). La fase orgánica se separó y se extrajo con CH_2Cl_2 (2X). Las fases orgánicas combinadas se secaron ($MgSO_4$) y se concentraron *in vacuo*. El producto de reacción bruto se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexano=1:10) para proporcionar el compuesto **12C** (0,263 g). MS experimental para $C_{14}H_{15}NO_2$ = 230,07 (M+H).

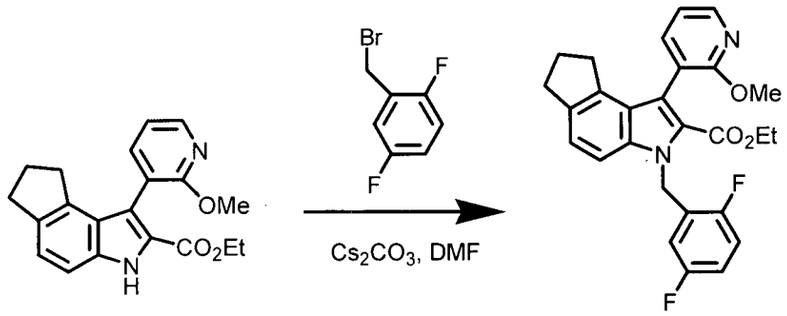
Paso D – Síntesis del Compuesto 12D



12C **12D**

Se agregó N-yodosuccinimida (0,402 g, 2,05 mmol) a una solución agitada del Compuesto **12C** (0,47 g, 2,05 mmol) en CH_2Cl_2 (15 ml) a 4°C. La reacción se controló por TLC hasta que no quedaron materiales de partida (aproximadamente 1 hora). La reacción se dividió entre EtOAc y se diluyó con tiosulfato de sodio acuoso (5%). La fase orgánica se separó, se lavó con bicarbonato de sodio acuoso saturado y agua. El producto bruto se usó directamente en el próximo paso sin purificación. La solución SME (30 ml) del indol bruto anterior y $PdCl_2(DPPF)_2$ (0,141 g, 0,1 eq) se calentó a 90°C (temperatura del baño de aceite) durante un período de 0,5 horas y se agregó gota a gota una solución del ácido borónico (0,318 g, 1,2 eq) y carbonato de potasio (1,197 g, 5 eq) in H_2O/DME (6 ml/6ml). Cuando finalizó la adición la mezcla de reacción se calentó a 150°C (baño de aceite) durante 2 horas. Después de enfriar, se agregó 3% de sulfato de sodio acuoso seguido por EtOAc y se filtró a través de celite. El filtrado se dividió entre agua y CH_2Cl_2. La fase orgánica se separó y la fase acuosa se extrajo adicionalmente con CH_2Cl_2. La fase orgánica combinada se secó ($MgSO_4$) y se concentró. El residuo se purificó mediante cromatografía en gel de sílice (EtOAc:Hexano=1:10) para proporcionar el compuesto **12D**. MS experimental $C_{20}H_{20}N_2O_3$ = 337,18 (M+H).

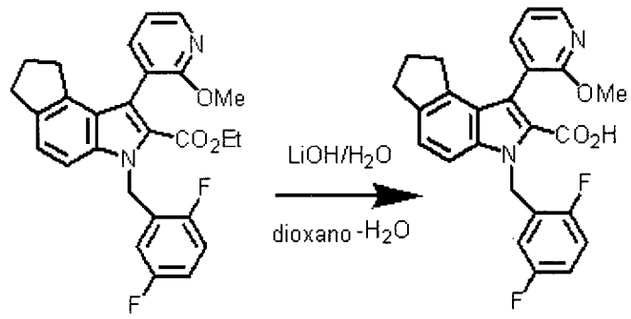
Paso E – Síntesis del Compuesto 12E



12D **12E**

Se agregó gota a gota bromuro de 2,4-difluorobencilo (0,187 g, 1,5 eq) a una solución dejada a agitar del Compuesto **12D** (202 mg, 0,6 mmol) y Cs_2CO_3 in DMF a temperatura ambiente bajo una atmósfera de nitrógeno. Después de 16 horas, la mezcla de reacción se dividió entre EtOAc y water. La fase acuosa se separó, se lavó con agua tres veces, se secó ($MgSO_4$) y se concentró. El residuo se purificó mediante cromatografía flash en gel de sílice (EtOAc:Hexano=1:20) para proporcionar el compuesto **12E** (0,263 g) como un sólido blanco. MS experimental $C_{27}H_{24}N_2O_3$ = 463,18 (M+H).

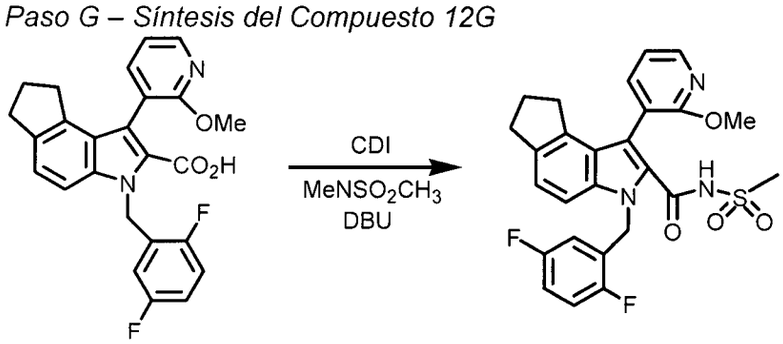
Paso F – Síntesis del Compuesto 12F



12E **12F**

Se agregó hidróxido de litio (53 mg, 3 eq) a una solución dejada a agitar del etiléster **12E** (196 mg, 0,42 mmol) en THF/H_2O acuoso (3 ml /1 ml) bajo una atmósfera de nitrógeno. La mezcla de reacción resultante se calentó a 100°C durante 4 horas (baño de aceite). Después de enfriar, la reacción se dividió entre CH_2Cl_2 y se diluyó con HCl acuoso (1N). Las fases orgánicas se separaron y se extrajeron con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$) y concentraron *in vacuo* para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexano=1:10) seguido por EtOAc como eluyente para proporcionar el compuesto **12F** como un sólido blanco (95,2 mg). MS experimental $C_{25}H_{20}F_2N_2O_3$ = 435,11 (M+H).

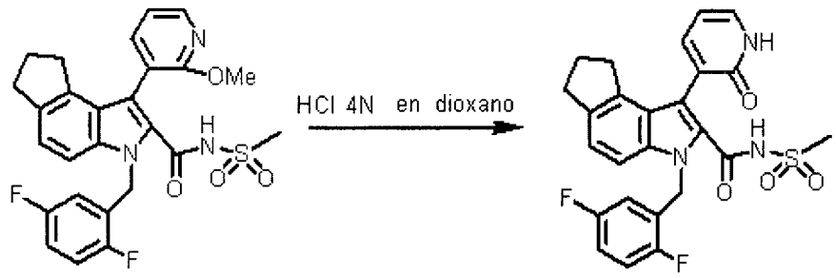
Paso G – Síntesis del Compuesto 12G



12F **12G**

Se agregó CDI (35 mg, 1 eq) a una solución dejada a agitar del ácido **12F** (95 mg) en THF y la mezcla de reacción se calentó a reflujo bajo una atmósfera de nitrógeno durante un período de 2 horas. Después de enfriar, se agregaron metansulfonamida (31 mg, 1,5 eq) seguida por DBU (0,26 mmol). Después de 6 horas la mezcla se dividió entre EtOAc y se diluyó con HCl acuoso(1N), la fase orgánica se separó y la fase acuosa se extrajo adicionalmente con EtOAc. Las fases orgánicas combinadas se secaron ($MgSO_4$) y concentraron *in vacuo* para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice (CH_2Cl_2:MeOH=20:1) para proporcionar el compuesto **12G** (20,6 mg). MS experimental $C_{26}H_{23}F_2N_3O_4S$ = 517,12

*Paso H – Síntesis del Compuesto **12***



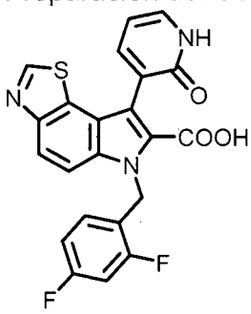
12G **12**

Se agregó HCl (4N en dioxano, 10 ml) al compuesto **12G** (50 mg) en un tubo sellado y la suspensión resultante se calentó a 80°C (baño de aceite) y se dejó agitar a esta temperatura toda la noche. La mezcla de reacción luego se dejó enfriar a temperatura ambiente y el solvente se eliminó *in vacuo* para proporcionar un residuo bruto que se trituró con éter y se recogió el sólido resultante para proporcionar el compuesto **12** (35,2 mg). MS experimental $C_{25}H_{21}F_2N_3O_4S$: 498,03 $(M+H)^+$. ^1H RMN (500 MHz, d_6-DMSO) δ 12,68 (bs, 1H), 12,50 (bs, 1H), 7,74 (d, J = 6.59 Hz, 1H), 7,67 (m, 1H), 7,37 (d, J = 8,79 Hz, 1H), 7,32-7,26 (m, 1H), 7,24 (d, J = 8,79 Hz, 1H), 7,17-7,12 (m, 1H), 6,59-6,54 (m, 2H), 5,69 (s, 2H), 3,23 (s, 3H), 2,86-2,83 (m, 2H), 2,8-2,0 (bs, 2H), 1,95 (s, 2H).bs, 2H), 1.95 (s, 2H). ^{13}C RMN

(125 MHz, DMSO-d_6) δ 162,864, 161,097, 158,974, 157,059, 156,602, 154,687, 144,974, 136,933, 136,884, 135,826, 135,781, 128,571, 127,140, 127.083, 127,004, 126,944, 123,307, 123,155, 122,083, 117,030, 116,962, 116,837, 116,769, 115,700, 115,628, 115,511, 114,911, 114,726, 108,947, 106,806, 106,194, 72,068, 66,255, 41,665, 41,102, 32,178, 31,747, 24,874.

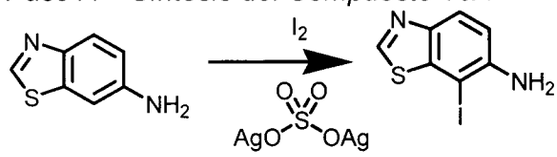
Ejemplo 2

Preparación del Compuesto **16**



16

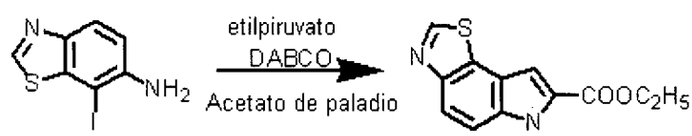
Paso A – Síntesis del Compuesto 16A



16A

A una solución de benzotiazol-6-ilamina(5,00 g, 33,25 mmol) en etanol 50 ml) se agregó sulfato de plata (10,5 g, 33,25 mmol) y yodo (8,45 g, 33,25 mmol) y la reacción se dejó agitar a temperatura ambiente durante 48 horas. A la mezcla de reacción se agregó tiosulfato de sodio y se dejó agitar durante 1 h y se filtró. La mezcla de reacción se extrajo con EtOAc (350 ml), se lavó con salmuera, se secó ($MgSO_4$), se filtró, y concentró *in vacuo*. El residuo resultante se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexanos, 0-100%) para proporcionar el compuesto **16A** como un sólido incoloro (1,7 g).

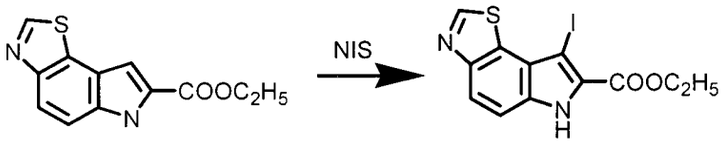
Paso B– Síntesis del Compuesto 16B



16A **16B**

Una solución del Compuesto **16A** (1,7 g, 6,16 mmol) en DMF (15 ml) se desgasificó extensamente y trató con piruvato de etilo (0,965 g, 8,4 mmol), DABCO y acetato de paladio (139 mg, 0,616 mmol) y luego se calentó a 105°C durante 12 horas. La mezcla de reacción se vertió en agua y se extrajo con acetato de etilo y la fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo y se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexanos 0-70%) para proporcionar el compuesto **16B** (500 mg).

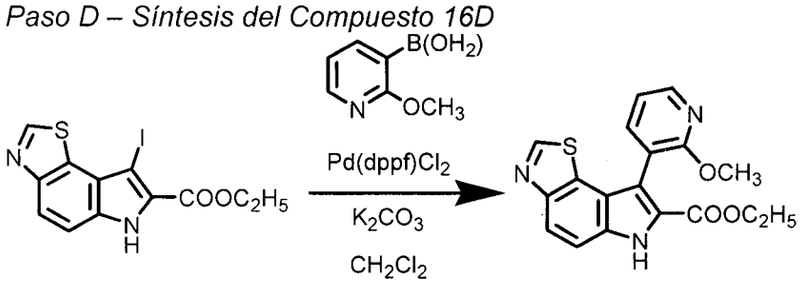
Paso C – Síntesis del Compuesto 16C



16B **16C**

A una solución del Compuesto **16B** (430 mg, 1,75 mmol) en cloroformo (30 ml) se agregó N-yodosuccinimida y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con agua, y se extrajo con acetato de etilo (500 ml). Las fases orgánicas combinadas se extrajeron con salmuera, secaron ($MgSO_4$), se filtraron, concentraron al vacío, se pre-absorbieron en sílice y se purificaron mediante cromatografía flash (1:1 EtOAc/Hexanos) para proporcionar el compuesto **16C** como un sólido incoloro.

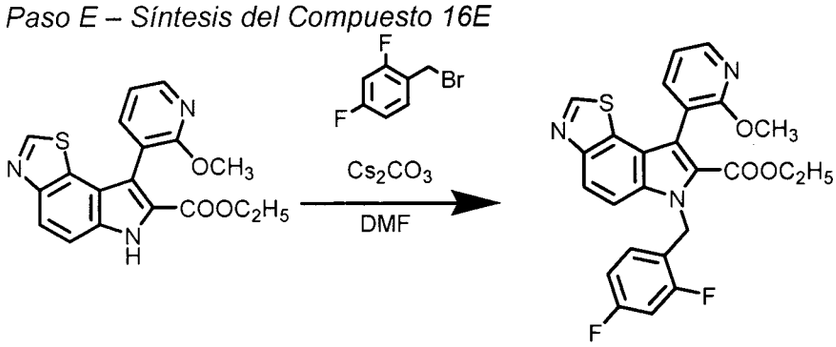
Paso D – Síntesis del Compuesto 16D



16C **16D**

A una solución del Compuesto **16C** (500 mg, 1,35 mmol) en DME (15 ml) se agregó ácido 2-metoxi-3-piridilborónico (413 mg, 2,7 mmol) y $Pd(dppf)Cl_2$ (130 mg) y la reacción se dejó agitar a temperatura ambiente bajo nitrógeno durante 0,5 horas. La mezcla de reacción luego se trató con una solución de carbonato de potasio (932 mg, 6,75 mmol) en 10 ml de agua y se calentó a 90°C durante 3 horas. La mezcla de reacción se diluyó con EtOAc (250 ml), concentró in vacuo y se purificó mediante cromatografía flash en gel de sílice mediante EtOAc/Hexanos (0 a 100% EtOAc) para proporcionar el compuesto **16D**.

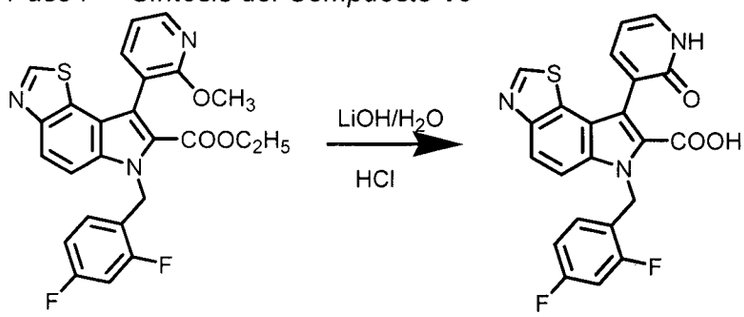
Paso E – Síntesis del Compuesto 16E



16D **16E**

A una solución del Compuesto **16D** (100 mg, 0,29 mmol) en DMF (3 ml) se agregó carbonato de cesio (189 mg, 0,58 mmol) y bromuro de 2,4-difluorobencilo y la reacción resultante se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de reacción se diluyó con EtOAc (300 ml) y se lavó con salmuera (2x100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo. El residuo resultante se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexano, 0 to 100% EtOAc) para proporcionar el compuesto **16E** como un sólido incoloro.

*Paso F – Síntesis del Compuesto **16***



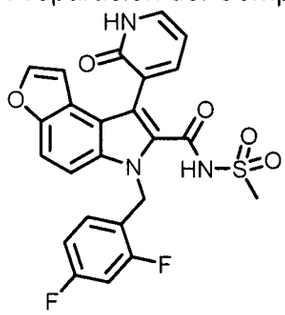
16E **16**

A una solución del Compuesto **16E** (200 mg, 0,041 mmol) en metanol/agua/THF (cada uno 5 ml) se agregó hidróxido de litio y la reacción resultante se dejó agitar a reflujo toda la noche. La mezcla de reacción se diluyó con HCl acuoso y se extrajo en acetato de etilo (100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, concentraron in vacuo y se usaron

como tales en el próximo paso. El residuo se tomó en metanol (1 ml) y se trató con HCl acuoso (4M) y calentó durante 1 h a 80°C. Se separó una gran cantidad de sólido blanco que se filtró y secó para proporcionar el compuesto **16**. MS experimental $C_{22}H_{13}F_2N_3O_3S$: 438,00 $(M+H)^+$. ^1H RMN (400 MHz, d_6-DMSO) δ 9,15 (s, 1H), 8,01 + 7,98 (d, J = 9,52 Hz, 1H), 7,79 & 7,77 (d, J = 8,79 Hz, 1H), 7,59 & 7,57 (d, J = 6,59 Hz, 1H), 7,497 & 7,48 (d, J = 5,86 Hz, 1H), 7,29 (t, J = 9,52 Hz, 1H), 6,96 (t, J = 9,50 Hz, 1H), 6,70 (q, J = 8,79 & 15,38 Hz, 1H), 6,34 (t, J = 7,32 Hz, 1H), 5,98 (q, J = 16,11 & 46,87 Hz, 2H).

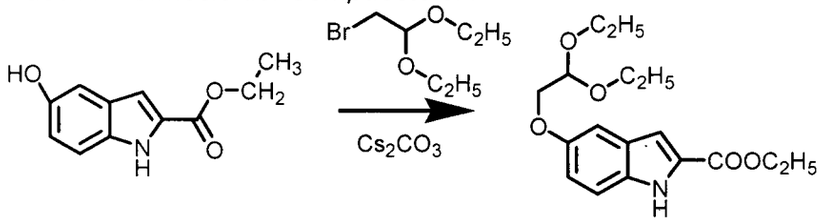
Ejemplo 3

Preparación del Compuesto **9**



9

Paso A – Síntesis del Compuesto 9A

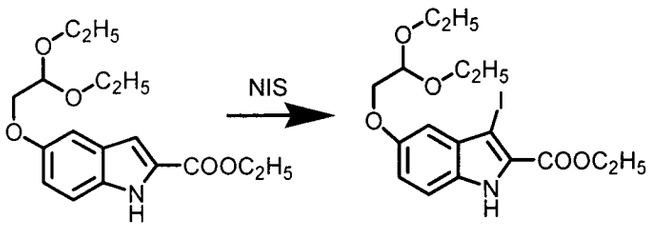


9A

A una solución de etil éster del ácido 5-hidroxi-1*H*-indol-2-carboxílico (5,00 g, 25,00 mmol) en DMF (30 ml) se agregó Cs_2CO_3 (9,00 g, 1,1 mmol) y bromoacetaldehído-dietilacetal (20 g, 5,00 mmol) y la reacción resultante se dejó agitar a reflujo durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente, se trató con NaOH acuoso (1M, 500 ml) y se extrajo en EtOAc (500 ml).

Las fases orgánicas se secaron ($MgSO_4$), se filtraron, concentraron in vacuo (alto vacío para destilar DMF y bromoacetaldehído) y se purificaron mediante cromatografía flash (Hexanos/EtOAc, 0 a 100%) para proporcionar el compuesto **9A** como un sólido incoloro.

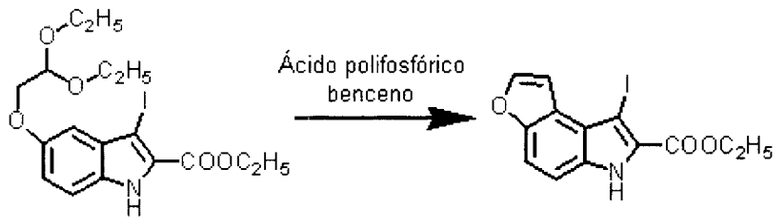
Paso B – Síntesis del Compuesto 9B



9A **9B**

A una solución del Compuesto **9A** (2,3 g, 7,1 mmol) en cloroformo (20 ml) se agregó N-yodosuccinimida (1,77 g, 7,8 mmol) y la reacción se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con EtOAc (200 ml) y se lavó tres veces con agua. La fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo y se purificó mediante cromatografía flash (eluyente: EtOAc/Hexanos, 0 a 50% EtOAc) para proporcionar el compuesto **9B** como un sólido incoloro (2,7 g).

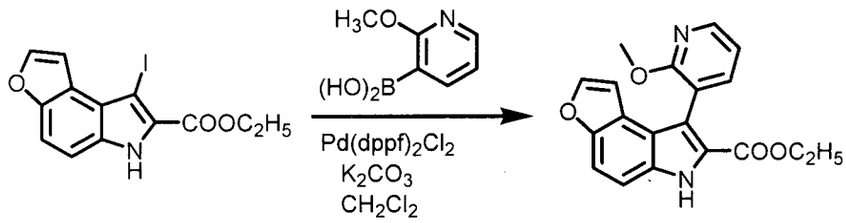
Paso C – Síntesis del Compuesto 9C



9B **9C**

A una solución del Compuesto **9B** (2,7 g, 6,00 mmol) en benceno (30 ml) se agregó ácido polifosfórico (3 g) y la reacción resultante se dejó agitar a reflujo durante aproximadamente 1 hora. Luego la reacción se inactivó mediante agua fría y la solución resultante se extrajo en EtOAc. La fase orgánica se secaron ($MgSO_4$), se filtró, concentró in vacuo y se purificó mediante cromatografía flash (Hexano:EtOAc, 1:1) para proporcionar el compuesto **9C**.

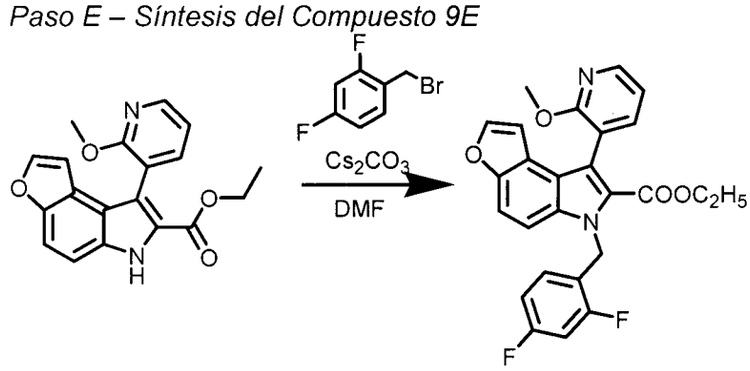
Paso D – Síntesis del Compuesto 9D



9C **9D**

A una solución del Compuesto **9C** (1,5 g, 4,33 mmol) en DME (20 ml) se agregó ácido 2-metoxi-3-piridilborónico (795 mg, 5,2 mmol) y $Pd(dppf)_2Cl_2$ (408 mg) y la reacción se dejó agitar a temperatura ambiente bajo nitrógeno durante 30 minutos. La mezcla de reacción se agregó a una solución de carbonato de potasio (2,4 g, 17,3 mmol) en 10 ml de agua y se calentó a 90°C durante 1 hora. La mezcla de reacción se diluyó con EtOAc (250 ml), concentró in vacuo, y se purificó mediante cromatografía flash (EtOAc/Hexanos, 1:1) para proporcionar el compuesto **9D** como un sólido incoloro (620 mg).

Paso E – Síntesis del Compuesto 9E

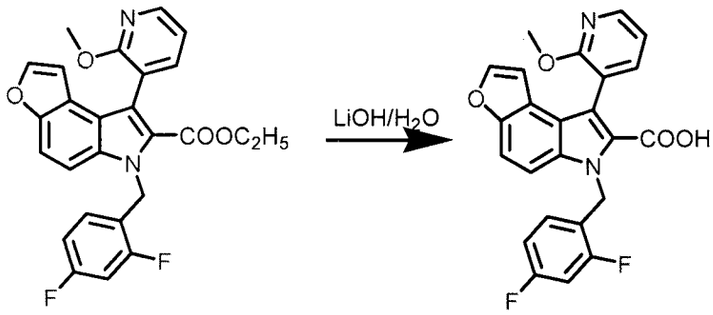


9D **9E**

A una solución del Compuesto **9D** (620 mg, 1,86 mmol) en DMF (5,00 ml) se agregó Cs_2CO_3 (1,21 g, 3,72 mmol) y bromuro de 2,4-difluorobencilo (577, 2,79 mmol) y la reacción resultante se dejó agitar toda la noche. La mezcla de reacción luego se diluyó con agua (250 ml) y se extrajo en EtOAc (300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, concentraron in vacuo y

se purificaron mediante cromatografía flash (EtOAc/Hexanos, 1:1) para proporcionar el compuesto **9E** (900 mg).

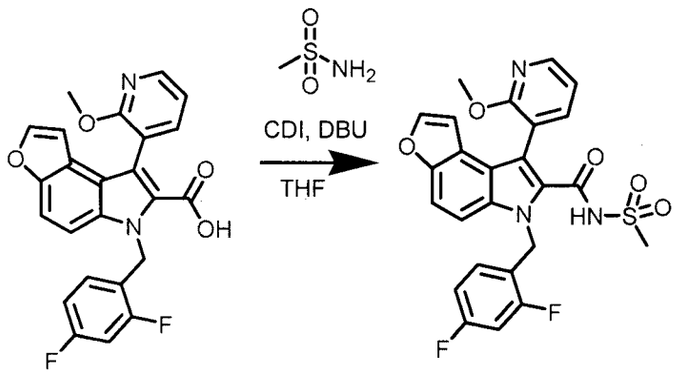
Paso F – Síntesis del Compuesto 9F



9E **9F**

A una solución del Compuesto **9E** (1,95 mmol) en metanol/agua/THF (15 ml, 1:1:1) se agregó hidróxido de litio (10 mmol) y la reacción resultante se dejó agitar durante 4 horas reflujo. La mezcla de reacción se acidificó con HCl acuoso (1N, 20 ml) y se extrajo en EtOAc (250 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar el compuesto **9F**, que se usó sin purificación adicional.

Paso G – Síntesis del Compuesto 9G

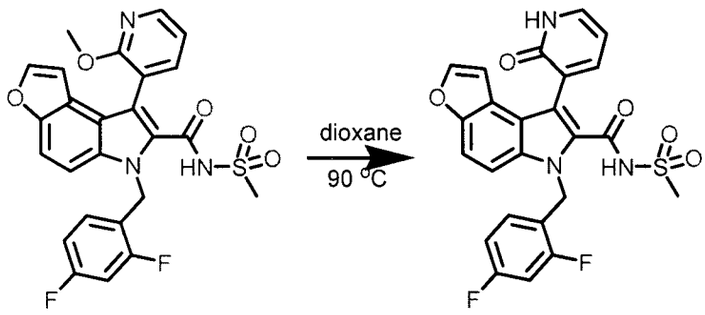


9F **9G**

A una solución del Compuesto **9F** (0,34 mmol) en 3 ml de THF se agregó CDI (0,5 mmol) y la reacción resultante se calentó a reflujo y se dejó agitar a esta temperatura guante 3 horas. La mezcla de reacción luego se dejó enfriar a 0°C y se trató con metansulfonamida y DBU. La mezcla de reacción resultante se dejó

agitar a temperatura ambiente durante 48 horas, luego se diluyó con EtOAc (100 ml) y la solución resultante se lavó con agua y HCl acuoso(1N). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y su residuo resultante se purificó mediante cromatografía flash en gel de sílice (acetone/CH_2Cl_2, 0 a 70% acetona) para proporcionar el compuesto **9G** (100 mg).

Paso H – Síntesis del Compuesto ***9***

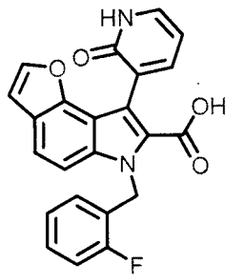


9G **9**

Una solución del Compuesto **9G** (100 mg, 0,2 mmol) en una solución 4M de dioxano (5ml) se calentó a 90°C y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción luego se concentró in vacuo y el residuo resultante se diluyó con EtOAc. El producto sólido se filtró y se lavó con EtOAc, luego éster dietílico, para proporcionar el compuesto **9**. MS experimental $C_{24}H_{17}F_2N_3O_5S$: 498,05 $(M+H)^+$. ^1H RMN (400 MHz, d_6-DMSO) □12.77 (s, 1H), 12.70 (s, 1H), 7.97&Õ□□□d, J = 2,14 Hz, 1H), 7,87 (q, J = 2,14 & 7,26 Hz, 1H), 7,76-7,72 (m, 1H), 7,66 & 7,63 (d, J = 8,97 Hz, 1H), 7,56 & 7,54 (d, J = 9,40 Hz, 1H), 7,30-7,25 (m, 1H), 6,99-6,86 (m, 2H), 6,65 (t, J = 6,41 Hz, 1H), 6,468 & 6,464 (d, J = 1,71 Hz, 1H), 5,78 (s, 2H), 3,26 (s, 3H).

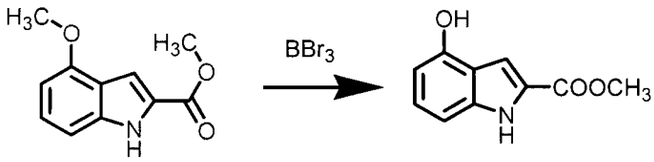
Ejemplo 4

Preparación del Compuesto **1**



1

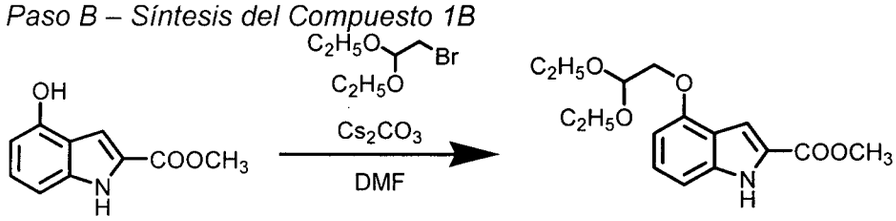
Paso A – Síntesis del Compuesto 1A



1A

Una solución de metil éster del ácido 4-metoxi-1*H*-indol-2-carboxílico (410 mg, 2,00 mmol) en CH_2Cl_2 (5 ml) enfriada a -78°C y se agregó BBr_3 (6 ml de solución, 1M). La reacción resultante luego se dejó agitar a 0°C durante 3 horas. La mezcla de reacción luego se inactivó usando agua y la solución resultante se extrajo con EtOAc (200 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, concentraron in vacuo y se purificaron mediante cromatografía flash para proporcionar el compuesto **1A**.

Paso B – Síntesis del Compuesto 1B

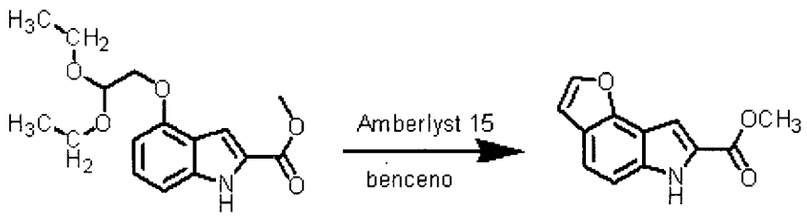


1A **1B**

A una solución del Compuesto **1A** (2,5 g, 13,10 mmol) en DMF (50 ml) se agregó Cs_2CO_3 (5,12 g, 15,72 mmol), luego bromoacetaldehído-dietilacetal (12,90 g, 65,6 mmol), y la reacción resultante se dejó agitar a reflujo durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente, se trató con NaOH acuoso

(1M, 50 ml) y se extrajo en EtOAc (250 ml). Las fases orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash (Hexanos/EtOAc 0 a 100%) para proporcionar el compuesto **1B** como un sólido incoloro.

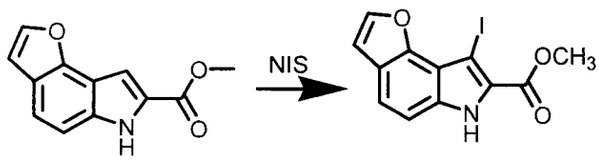
Paso C – Síntesis del Compuesto 1C



1B **1C**

A una solución del Compuesto **1B** en benceno (60 ml) se agregó una resina fuertemente ácida Amberlyst-15 (4,5 g) y la reacción resultante se calentó a 70°C y se dejó agitar a esta temperatura durante 4 horas. La mezcla de reacción luego se dejó enfriar temperatura ambiente, se diluyó con EtOAc (300 ml) y se lavó con $NaHCO_3$ acuoso. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, concentraron in vacuo y se purificaron mediante cromatografía flash en gel de sílice (EtOAc/Hexanos, 0-30% EtOAc) para proporcionar el compuesto **1C** (1,2 g).

Paso D – Síntesis del Compuesto 1D

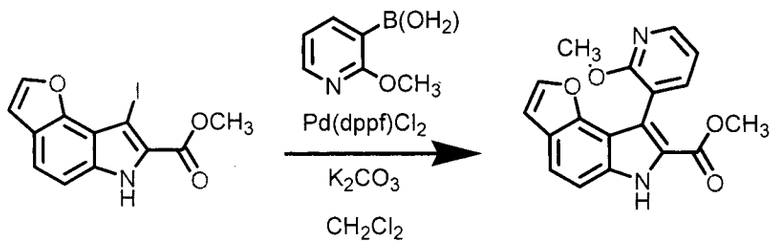


1C **1D**

A una solución del Compuesto **1C** (2,00 g, 9,3 mmol) en DMF (20 ml) se agregó N-yodosuccinimida (2,29 g, 10,2 mmol) y la reacción resultante se dejó

agitar a temperatura ambiente durante 12 horas. La mezcla de reacción luego se concentró in vacuo, se diluyó con agua y se extrajo en EtOAc (300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo. El residuo marrón resultante se diluyó con una cantidad mínima de CH_2Cl_2 y se trituró usando hexanos. El compuesto **1D** separado como un sólido marrón, se filtró, luego se secó *in vacuo*. (Rendimiento 2,6 g, 84%).

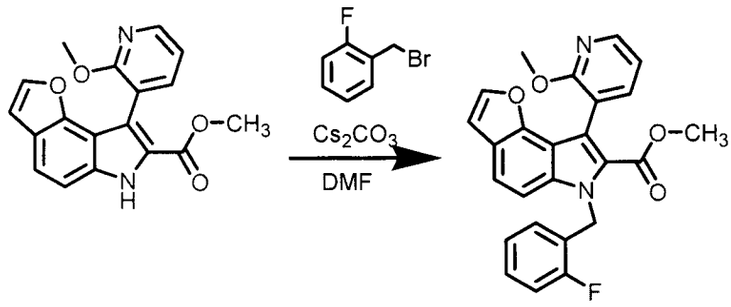
Paso E – Síntesis del Compuesto 1E



1D **1E**

A una solución del Compuesto **1D** (2,6 g, 7,6 mmol) en DME (40 ml) bajo atmósfera de nitrógeno se agregaron ácido 2-metoxi-3-piridilborónico (3,5 g, 22,8 mmol) y Pd $(dppf)_2Cl_2$ (616 mg) y la reacción resultante se dejó agitar a temperatura ambiente bajo nitrógeno durante 0,5 horas. La mezcla de reacción luego se trató con una solución de carbonato de potasio (6,3 g, 45,6 mmol) en agua (40 ml) y la solución resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción luego se diluyó con EtOAc (300 ml) y la solución resultante se concentró in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash (EtOAc/Hexanos, 0 a 50% EtOAc) para proporcionar el compuesto **1E** como un sólido (2,0 g).

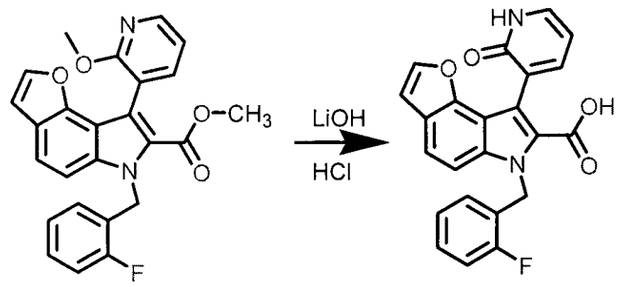
Paso F – Síntesis del Compuesto 1F



1E **1F**

A una solución de indol **1E** (300 mg, 0,93 mmol) en DMF (10 ml) se agregó carbonato de cesio (604 mg, 1,86 mmol) y bromuro de 2-fluorobencilo (351 mg, 1,86 mmol) y se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con EtOAc (250 ml) y se lavó con salmuera (2x100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y se purificaron mediante cromatografía flash en gel de sílice para proporcionar el compuesto **1F** como un sólido incoloro.

*Paso G – Síntesis del Compuesto **1***



1F **1**

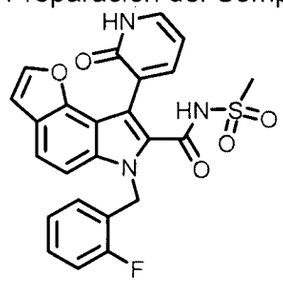
A una solución del Compuesto **1F** (100 mg, 0,23 mmol) en THF/agua/metanol (4 ml de cada uno) se agregó hidróxido de litio (40 mg, 1 mmol) y la reacción resultante se dejó agitar a reflujo durante 4 horas. La mezcla de reacción se diluyó con ácido y se extrajo con EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$), concentró in vacuo y se usó como tal en el próximo paso. Una solución de ácido bruto (80 mg) en HCl 4 M en dioxano (5 ml) y metanol (1 ml) se

calentó a 80°C durante horas. La mezcla de reacción se concentró in vacuo y el producto bruto se purificó mediante HPLC en fase reversa usando las siguientes condiciones, para proporcionar el compuesto **1**: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15 mM, 300 A, 343K16006 (W): caudal de flujo: 30 ml/min; fase móvil: 30-70% aumento de acetonitrilo, agua; 0--> 40 minutos.

Para el compuesto **1**: MS experimental $C_{23}H_{15}FN_2O_4$: 403,08 $(M+H)^+$. ^1H RMN (300 MHz, d_6-DMSO) δ 11,72 (bs, 1H), 7,84 & 7,83 (d, J = 2,20 Hz, 1H), 7,68 & 7.66 (dd, J = 6,59 & 2,20 Hz, 1H), 7,55 & 7,53 (d, J = 8,79 Hz, 1H), 7,45 & 7,43 (d, J = 8,79 Hz, 1H), 7,41-7,39 (m, 1H), 7,30-7,19 (m, 2H), 7,02 (t, J = 7,32 Hz, 1H), 6,963 & 6,957 (d, J = 2,20 Hz, 1H), 6,60 (t, J = 7,32 Hz, 1H), 6,33 (t, J = 7,32 Hz, 1H), 5,95 (s, 2H).

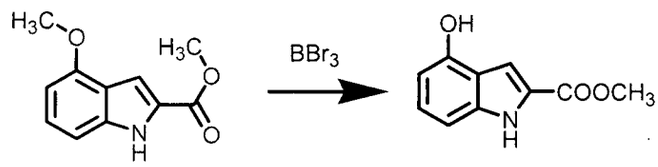
Ejemplo 5

Preparación del Compuesto **4**



4

Paso A –Síntesis del Compuesto 4A

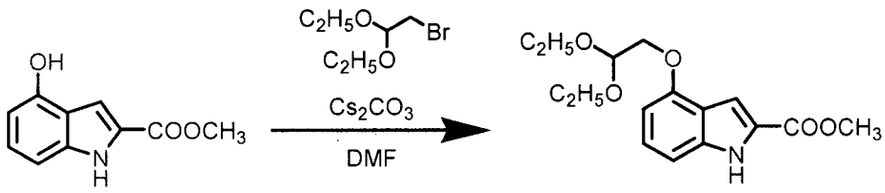


4A

A una solución de metiléster del ácido 3-metoxi-1*H*-indol-2-carboxílico (410 mg, 2,00 mmol) en CH_2Cl_2 (5 ml) se agregó BBr_3 (6 ml de solución, 1M) a -78°C y

la reacción se dejó agitar a 0°C durante 3 horas. La mezcla de reacción se inactivó con agua y se extrajo con EtOAc (200 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y se purificaron mediante cromatografía flash para proporcionar el compuesto **4A**.

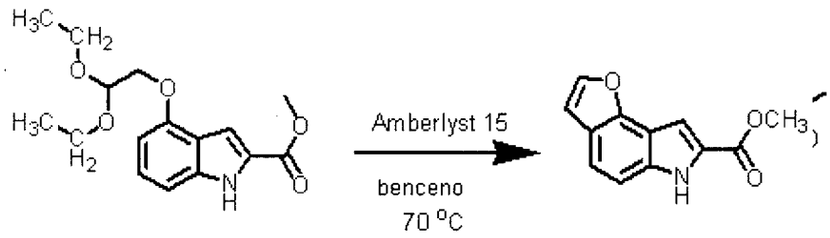
Paso B - Síntesis del Compuesto 4B



4A **4B**

A una solución del Compuesto **4A** (2,5 g, 13,10 mmol) en DMF (50 ml) se agregó Cs_2CO_3 (5,12 g, 15,72 mmol) y bromoacetaldehído-dietilacetal (12,90 g, 65,6 mmol) y la reacción resultante se dejó agitar a reflujo durante 2 horas.. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó, se trató con NaOH acuoso (1M, 50 ml) y se extrajo en EtOAc (250 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash (Hexano/EtOAc 0 a 100%) para proporcionar el compuesto **4B** como un sólido incoloro.

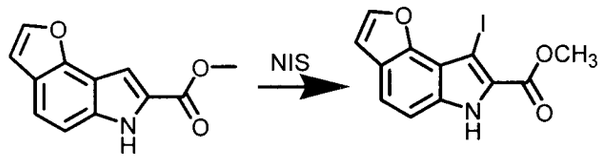
Paso C – Síntesis del Compuesto 4C



4B **4C**

A una solución del Compuesto **4B** en benceno (60 ml) se agregó Resina fuertemente ácida Amberlyst (4,5 g) y la reacción se calentó a 70°C y se dejó agitar a esta temperatura durante 4 horas. La mezcla de reacción enfriada se diluyó con EtOAc (300 ml) y se lavó con HCO_3 acuoso. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron, y concentraron in vacuo y se purificaron mediante cromatografía flash (SiO_2) EtOAc/Hexanos (0-30%) para proporcionar el compuesto **4C** (1,2 g).

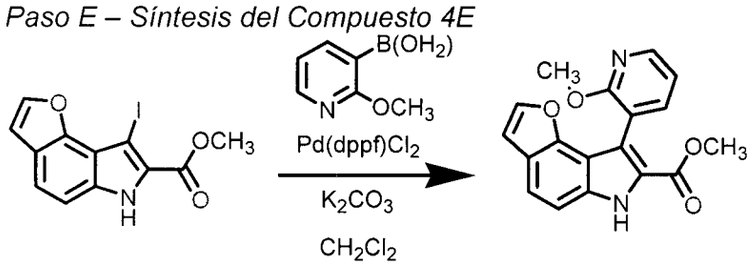
Paso D – Síntesis del Compuesto 4D



4C **4D**

A una solución del Compuesto **4C** (2,00 g, 9,3 mmol) en DMF (20 ml) se agregó N-yodosuccinimida (2,29 g, 10,2 mmol) y la reacción se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró in vacuo y se diluyó con agua y extrajo en EtOAc (300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo. El residuo marrón se tomó en una cantidad mínima de CH_2Cl_2 y se trituró con hexanos. El compuesto **4D** se separó como un sólido marrón que se filtró, y secó *in vacuo.* (Rendimiento 2,6 g, 84%)

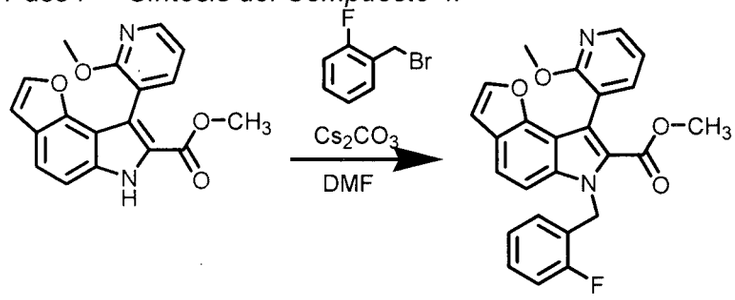
Paso E – Síntesis del Compuesto 4E



4D **4E**

A una solución del Compuesto **4D** (2,6 g, 7,6 mmol) en DME (40 ml) se agregaron ácido 2-metoxipiridilborónico (3,5 g, 22,8 mmol) y $Pd(dppf)_2Cl_2$ (616 mg), se dejó agitar a temperatura ambiente bajo nitrógeno durante 0,5 horas. La mezcla de reacción luego se trató con una solución de carbonato de potasio (6,3 g, 45,6 mmol) en 40 ml de agua y la solución resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción se diluyó con EtOAc (300 ml), se concentró in vacuo y se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexanos, 0 a 50%) para proporcionar el compuesto **4E** (2,00 g).

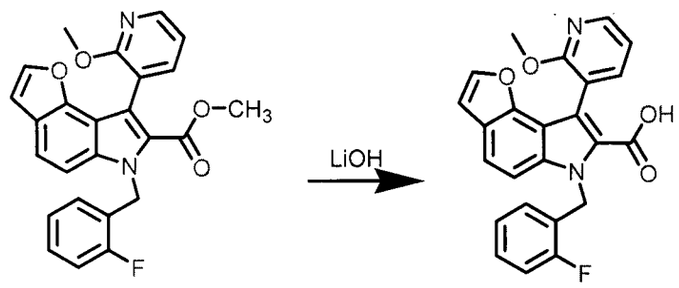
Paso F – Síntesis del Compuesto 4F



4E **4F**

A una solución del Compuesto **4E** (300 mg, 0,93 mmol) en DMF (10 ml) se agregó carbonato de cesio (604 mg, 1,86 mmol) y bromuro de 2-fluorobencilo (351 mg, 1,86 mmol) y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con EtOAc (250 ml) y se lavó con salmuera (2x100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice para proporcionar el compuesto **4F** como un sólido incoloro.

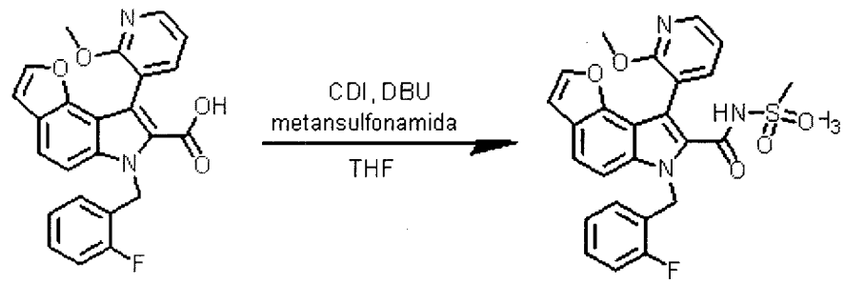
Paso G – Síntesis del Compuesto 4G



4F **4G**

A una solución del Compuesto **4F** (100 mg, 0. 23 mmol) en THF/agua/metanol (4 ml de cada uno) se agregó hidróxido de litio (40 mg, 1 mmol) y la reacción resultante se calentó a reflujo y se dejó agitar a esta temperatura durante 4 horas. La mezcla de reacción se diluyó con HCl acuoso (1N) y se extrajo con EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$) y se concentró in vacuo para proporcionar el compuesto **4G** que se usó sin purificación adicional.

Paso H – Síntesis del Compuesto 4H



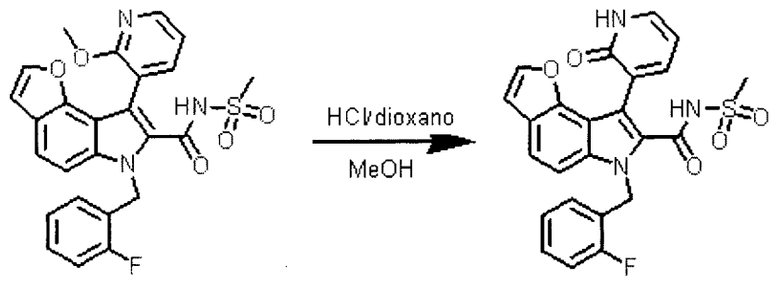
v

4G **4H**

A una solución del Compuesto **4G** (150 mg, 0,36 mmol) en 5 ml de THF se agregó CDI (70 mg, 0,43 mmol) y la reacción resultante se calentó a reflujo durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se agregaron metansulfonamida (40 mg, 0,43 mmol) y DBU (100 mg, 0,65 mmol). La mezcla de reacción resultante se dejó agitar a 65°C durante 48 horas, se diluyó

con EtOAc (150 ml) y se lavó con agua y HCl acuoso(1N). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice (acetona/CH_2Cl_2, 0 a 70% acetona) para proporcionar el compuesto **4H** como un sólido incoloro.

*Paso I – Síntesis del Compuesto **4***

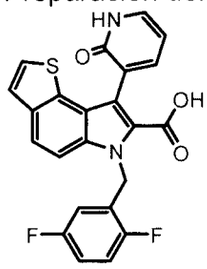


4H **4**

A una solución del Compuesto **4H** (80 mg, 0,16 mmol) en 4 M HCl en dioxano (5ml) y metanol (1,5 ml) se calentó a 80°C y se dejó agitar a esta temperatura durante 4 horas. La mezcla de reacción se concentró in vacuo y el producto bruto resultante se purificó mediante HPLC (fase reversa) mediante las siguientes condiciones: Columna: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15mM, 300 A, 343K16006 (W): flujo 30 ml/min; 30-70% aumento de acetonitrilo, agua; 0--> 40 minutos, para proporcionar el compuesto **4** como un sólido incoloro (60 mg). MS experimental $C_{24}H_{18}FN_3O_5S$: 480,05 $(M+H)^+$. H RMN (300 MHz, d_6-DMSO) □ı□□□bs ı□ı□□ı(bs ı□□□□□□d, J = 6.04 Hz, 1H), 7.86-7.83 (m, 1H), 7.67 (s, 1H), 7,60 & 7,58 (d, J = 7,69 Hz, 1H), 7,51 & 7,49 (d, J = 8,24 Hz, 1H), 7,32-7,27 (m, 1H), 7,21 (t, J = 8,79 Hz, 1H), 7,05 (t, J = 7,69 Hz, 1H), 6,82 (t, J = 7,69 Hz, 1H), 6,67-6,60 (m, 1H), 5,81 (s, 2H), 3,22 (s, 3H).

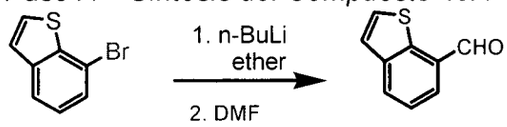
Ejemplo 6

Preparación del Compuesto **49**



49

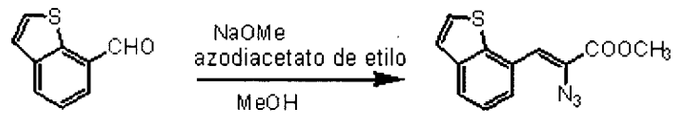
Paso A – Síntesis del Compuesto 49A



49A

Una solución de 7-bromotiofeno (8,0 g, 37,5 mmol) en éter (50 ml) se enfrió a -78°C y se trató gota a gota con n-BuLi (1,6 M solución en hexanos, 1,0 eq.) y la reacción resultante se dejó agitar a -78°C durante 20 minutos. La mezcla de reacción luego se diluyó con DMF (5,4 g seco, 67,4 mmol) y se dejó agitar -78°C durante 1 hora. La mezcla de reacción luego se diluyó con agua y se extrajo en éter. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y se purificaron mediante cromatografía flash en gel de sílice para proporcionar el compuesto **49A** como un sólido incoloro.

Paso B – Síntesis del Compuesto 49B



49A **49B**

A una solución de metóxido de sodio recién preparado (preparado por disolución (1,42 g, 62,0 mmol) en metanol (30 ml)) se agregó gota a gota a una solución de azidoacetato de etilo (7,99 g, 62 mmol) y el compuesto **49A** (5,1 g, 31

mmol) en metanol (30 ml) que fue preenfriada a -20°C. La mezcla de reacción se dejó agitar a temperatura ambiente durante 3 horas, luego se diluyó con EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice para proporcionar un residuo bruto amarillo que se recristalizó en éter y hexanos para proporcionar el compuesto **49B** (1,95 g).

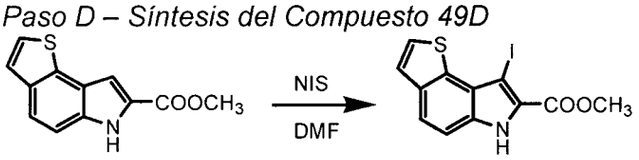
Paso C – Síntesis del Compuesto 49C



49B **49C**

Una solución del Compuesto **49B** (1,95 g) en xilenos (20 ml) se calentó a reflujo durante 30 minutos, luego se enfrió a temperatura ambiente. La mezcla de reacción luego se concentró in vacuo hasta que apareció un precipitado sólido y se recogió para proporcionar el compuesto **49C** como un sólido incoloro (1,1 g).

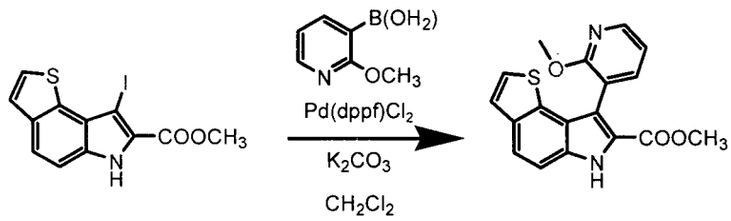
Paso D – Síntesis del Compuesto 49D



49C **49D**

A una solución del Compuesto **49C** (1,00 g, 4,33 mmol) en DMF (20 ml) se agregó *N*-yodosuccinimida y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró in vacuo y el residuo resultante se diluyó con agua y se extrajo en EtOAc (300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, concentró in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice para proporcionar el compuesto **49D** como un sólido incoloro.

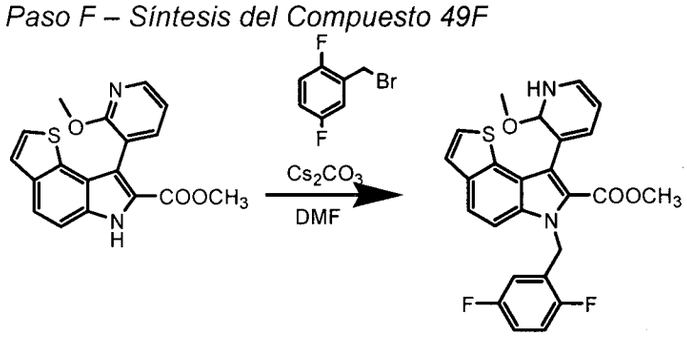
Paso E – Síntesis del Compuesto 49E



49D **49E**

A una solución del Compuesto **49D** (1,2 g, 3,35 mmol) rn DME (25 ml) se agregó ácido 2-metoxi-3-piridilborónico (1,52 g, 10 mmol) y $Pd(pddf)_2Cl_2$ (324 mg) se dejó agitar a temperatura ambiente bajo nitrógeno durante 15 minutos. La mezcla de reacción luego se trató con una solución of carbonato de potasio (2,77 g, 20,1 mmol) in 25 ml of agua y la reacción resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción se diluyó con EtOAc (300 ml), concentró in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexanos, 0 a 70% EtOAc) para proporcionar el compuesto **49E**.

Paso F – Síntesis del Compuesto 49F

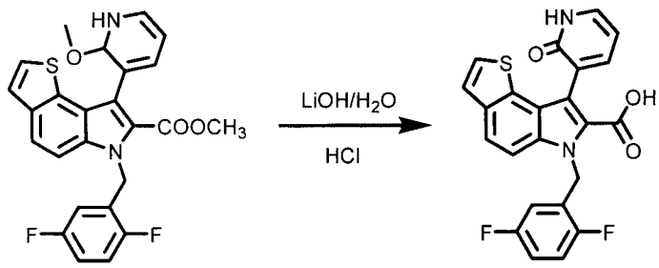


49E **49F**

A una solución del Compuesto **49E** (300 mg, 0,90 mmol) en DMF (10 ml) se agregó carbonato de cesio (585 mg, 1,80 mmol) y 2,4-difluorobenzil bromide (372 mg, 1,80 mmol) y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción luego se diluyó con EtOAc (250 ml) y la fase orgánica se lavó con salmuera (2x100 ml), luego se secó ($MgSO_4$), se filtró, y concentró in vacuo. El residuo resultante se purificó una primera vez usando cromatografía en columna flash en gel de sílice

(EtOAc/Hexanos, 0 a 70% EtOAc) y una segunda vez mediante acetona/CH_2Cl_2 (0 a 50% acetona) como eluyente para proporcionar el compuesto **49F** como un sólido incoloro.

*Paso G – Síntesis del Compuesto **49***

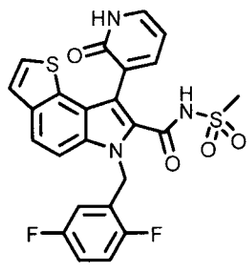


49F **49**

A una solución del Compuesto **49F** (100 mg, 0,23 mmol) en THF/agua/metanol (4 ml de cada uno) se agregó hidróxido de litio (40 mg, 1 mmol) y la reacción resultante se dejó agitar a reflujo durante 4 horas. La mezcla de reacción se diluyó con HCl acuoso(1N) y se extrajo con EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$) luego se concentró in vacuo, y el residuo bruto se diluyó con ácido clorhídrico (solución 4M en dioxano). A la solución ácida resultante se agregó 1 ml de metanol y la mezcla resultante se dejó agitar a 90°C durante 3 horas. La mezcla de reacción se concentró in vacuo y el residuo resultante se disolvió en EtOAc. A la solución resultante se agregaron hexanos, hasta que el compuesto **49** se separó y se filtró y se usó como tal (45 mg). MS experimental $C_{23}H_{14}F_2N_2O_3S$: 437,10 $(M+H)^+$. ^1H RMN (300 MHz, d_6-DMSO) δ 11.76 (bs, 1H), 7.81 + 7.87 (d, J = 8.79Hz, 1H), 7.62 (s, 1H), 7,61-7,58 (m, 1H), 7,50-7,46 (m, 1H), 7,33-7,28 (m, 1H), 7,16-7,10 (m, 1H), 6,35-6,31 (m, 2H), 5,98 (q, J = 16,84 & 40,27 Hz, 2H).

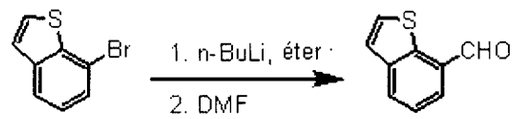
Ejemplo 7

Preparación del Compuesto **52**



52

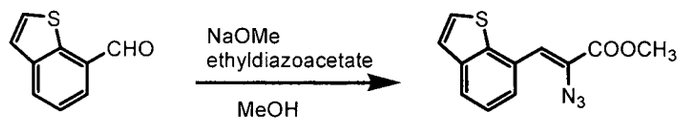
Paso A – Síntesis del Compuesto 52A



52A

Una solución de 7-bromotiofeno (8,0 g, 37,5 mmol) en éter (50 ml) se enfrió a -78°C, luego se agregó gota a gota n-BuLi (1,6 M solución en hexanos, 1,0 eq.) y la reacción resultante se dejó agitar a -78°C durante 20 minutos. La mezcla de reacción se diluyó con DMF (5,4 g seco, 67,4 mmol) y se dejó agitar a -78°C durante 1 hora. La mezcla de reacción luego se inactivó con agua y la solución resultante se extrajo en éter. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice para proporcionar el compuesto **52A** como un sólido incoloro.

Paso B – Síntesis del Compuesto 52B



52A **52B**

A solución de metóxido de sodio recién preparado (preparado por disolución (1,42 g, 62,0 mmol) en metanol (30 ml)) se agregó gota a gota a una

solución de azidoacetato de etilo (7,99 g, 62 mmol) y 5,1 g (31 mmol) del Compuesto **52A** en metanol (30 ml) que fue preenfriada a -20°C. La reacción resultante se dejó agitar a temperatura ambiente durante 3 horas y luego se diluyó con EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$), se filtró, y concentró in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice para proporcionar un sólido amarillo que se recristalizó en éter y hexanos para proporcionar el compuesto **52B** (1,95 g).

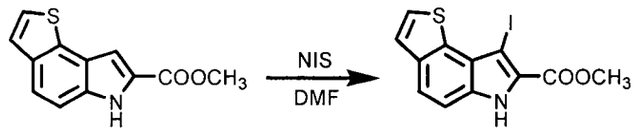
Paso C – Síntesis del Compuesto 52C



52B **52C**

Una solución del Compuesto **52B** en xileno se calentó a reflujo durante 30 minutos, luego se enfrió a temperatura ambiente y concentró in vacuo hasta que apareció un precipitado sólido. El sólido se recolectó para proporcionar el compuesto **52C** (1,1 g) como un sólido incoloro que se usó sin purificación adicional.

Paso D – Síntesis del Compuesto 52D

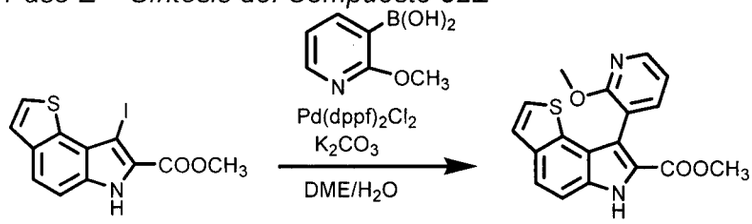


52C **52D**

A una solución del Compuesto **52C** (1,00 g, 4,33 mmol) en DMF (20 ml) se agregó *N*-yodosuccinimida y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción luego se concentró in vacuo y

el residuo resultante se diluyó con agua y se extrajo en EtOAc (300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice (EtOAc/Hexanos, 0 a 50% EtOAc) para proporcionar el compuesto **52D** como un sólido incoloro.

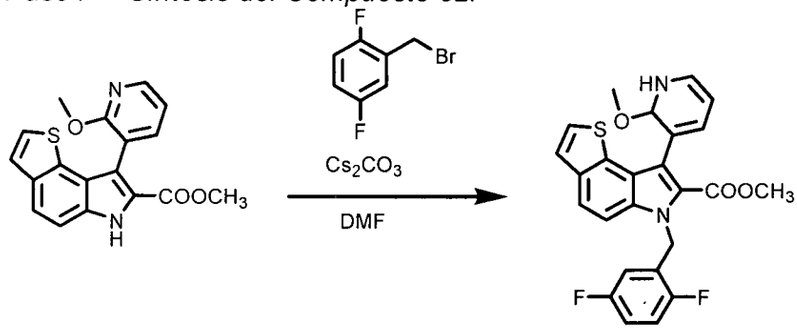
Paso E – Síntesis del Compuesto 52E



52D **52E**

A una solución del Compuesto **52D** (1,2 g, 3,35 mmol) en DME (25 ml) se agregó ácido 2-metoxi-3-piridilborónico (1,52 g, 10 mmol) y $Pd(dppf)_2Cl_2$ (324 mg) y la reacción resultante se dejó agitar bajo una atmósfera de nitrógeno a temperatura ambiente durante 15 minutos. La mezcla de reacción luego se trató con una solución de carbonato de potasio (2,77 g, 20,1 mmol) in 25 ml de agua y la reacción resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción luego se diluyó con EtOAc (300 ml), concentró in vacuo y el residuo resultante se purificó mediante cromatografía flash en gel de sílice mediante EtOAc/Hexanos (0-70% EtOAc) para proporcionar el compuesto **52E**.

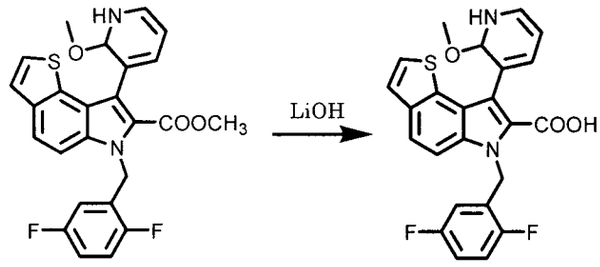
Paso F – Síntesis del Compuesto 52F



52E **52F**

A una solución del Compuesto **52E** (300 mg, 0,90 mmol) en DMF (10 ml) se agregó carbonato de cesio (585 mg, 1,80 mmol) y bromeuro de 2,4-difluorobencilo (372 mg, 1,80 mmol) y la reacción resultante se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción luego se diluyó con EtOAc (250 ml) y se lavó con salmuera (2x100 ml). La fase orgánica se secó ($MgSO_4$), se filtró, y concentró in vacuo para proporcionar un residuo bruto que se purificó primero por cromatografía en columna flash en gel de sílice (EtOAc/Hexanos, 0 a 70% EtOAc) y otra vez usando (acetona/CH_2Cl_2, 0 a 50% acetona) para proporcionar el compuesto **52F** como un sólido incoloro.

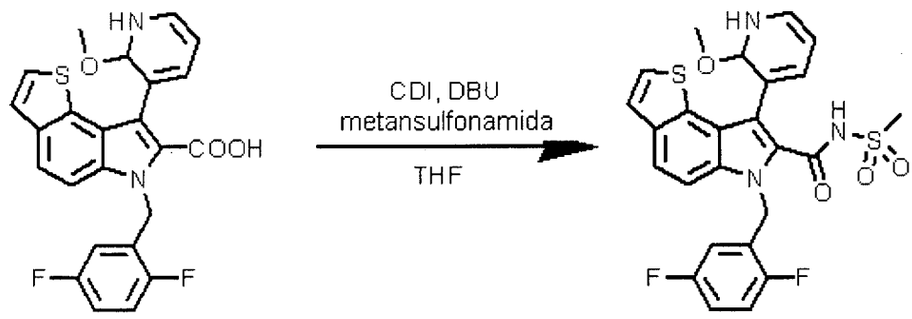
Paso G – Síntesis del Compuesto 52G



52F **52G**

A una solución del Compuesto **52F** (100 mg, 0,23 mmol) en THF/agua/metanol (4 ml de cada uno) se agregó hidróxido de litio (40 mg, 1 mmol) y la reacción resultante se calentó a reflujo y se dejó agitar a esta temperatura durante 4 horas. La mezcla de reacción se diluyó con HCl acuoso (1N) y se extrajo en EtOAc (200 ml). La fase orgánica se secó ($MgSO_4$), se filtró y concentró in vacuo para proporcionar el compuesto **52G** que se usó sin purificación adicional.

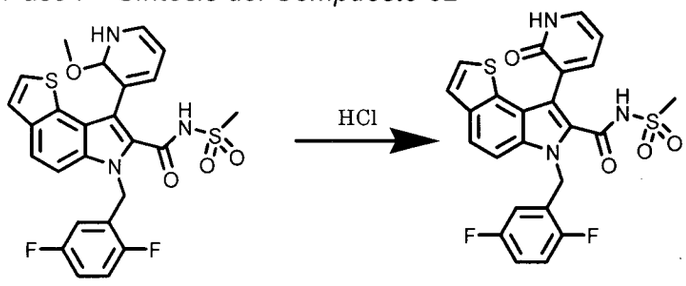
Paso H – Síntesis del Compuesto 52H



52G **52H**

A una solución del Compuesto **52G** (170 mg, 0,37 mmol) en 5 ml de THF se agregó CDI (74 mg, 0,45 mmol) y la reacción resultante se calentó a reflujo y se dejó agitar a esta temperatura durante 2 horas. La mezcla de reacción luego se dejó enfriar temperatura ambiente y se trató con metansulfonamida (43 mg, 0,45 mmol) y DBU (100 mg, 0,65 mmol). La reacción resultante se calentó a 65°C y se dejó agitar a esta temperatura durante 12 horas, después de este tiempo se diluyó con EtOAc (150 ml) y se lavó con agua y HCl acuoso(1N). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice (acetona/CH_2Cl_2, 0 a 50% acetona) para proporcionar el compuesto **52H**.

*Paso I – Síntesis del Compuesto **52***



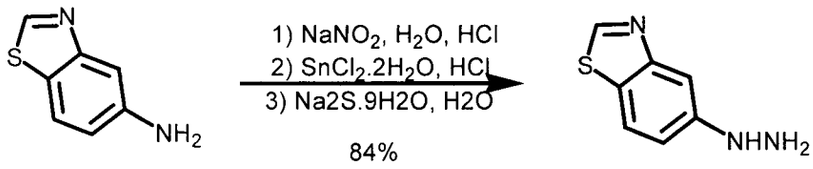
52H **52**

A una solución del Compuesto **52H** (110 mg, 0,21 mmol) in HCl (4M en dioxano) se agregó 1 ml de metanol y la reacción resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción se concentró in vacuo y el residuo resultante se disolvió en EtOAc, luego se purificó mediante HPLC (fase reversa) usando las siguientes condiciones para proporcionar el compuesto **52**:Columna: Waters Delta Pk, P/No 11805, Watman 011805, 300x30 mm (L/ID) C18, 15mM, 300 A, 343K16006 (W); caudal de flujo: 30 ml/min; fase móvil: 30-70% aumento de acetonitrilo/agua durante 40 minutos. Para el compuesto **52**: MS experimental $C_{24}H_{17}F_2N_3O_4S_2$: 513,97 $(M+H)^+$. ^1H RMN (300 MHz, d_6-DMSO) δ 12.77 (bs, 1H), 12.50 (bs, 1H), 7.97 & 7.95 (d, J = 6,59 Hz, 1H), 7,84 & 7,82 (d, J = 8,79 Hz,1H), 7,76 (s, 1H), 7,65 & 7,63 (d, J = 8,79 Hz, 1H), 7,52-7,47 (m, 2H), 7,34-7,28 (m, 1H), 7,19-7,13 (m, 1H), 6,66-6,59 (m, 2H), 5,82 (s, 2H), 3,25 (s, 3H).

Ejemplo 8

Preparación del Compuesto **51**

Paso A – Síntesis del Compuesto 51A

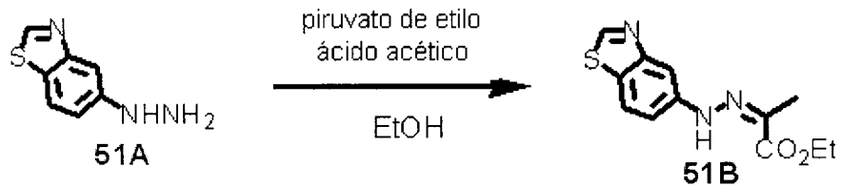


51A

A una suspensión de 1,3-benzotiazol-5-amina (16 g, 107 mmol) en HCl concentrado (180 ml) a -10 °C se agregó muy lentamente una solución de nitrito de sodio (7,66 g, 111 mmol) in agua (35 ml). Después de la adición, la mezcla se dejó agitar vigorosamente a -5°C a 0°C durante 0,5 horas. A la mezcla de reacción luego se agregó gota a gota una solución de cloruro de estaño (II) (81,0 g, 359 mmol) en HCl concentrado (60 ml). La temperatura interna se mantuvo por debajo de O o debajo de -5°C durante la adición y la suspensión resultante se

dejó agitar a -10°C a 20°C durante aproximadamente 1,5 horas. El precipitado se filtró y el matraz se lavó con una pequeña cantidad de agua. Los sólidos recogidos se disolvieron en agua (100 ml), y a la solución resultante se agregó $Na_2S,9H_2O$ (39 g). La fase acuosa se ajustó a pH 11 usando solución de hidróxido solución acuosa 50% (4 ml). Los sólidos se eliminaron por filtración y se lavaron con agua. La fase acuosa se extrajo con THF/acetato de etilo (1:2) (2 X 200 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró, y concentró in vacuo para proporcionar el compuesto **51A** (14,8 g, 84%), que se usó sin purificación adicional.

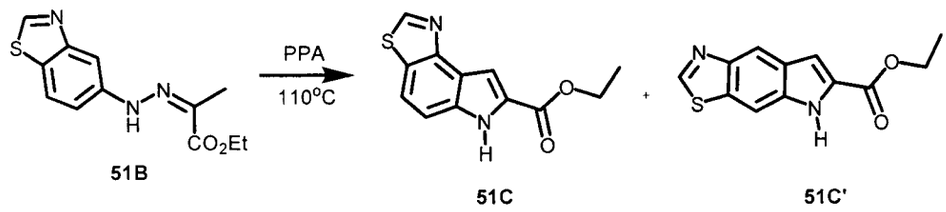
Paso B – Síntesis del Compuesto 51B



51A **51B**

A una solución del Compuesto **51A** (14,8 g, 89,6 mmol) en etanol (300 ml) a temperatura ambiente, se agregó piruvato de etilo (15 ml, 137 mmol) y ácido acético (1,35 ml). La reacción se calentó a reflujo y se dejó agitar a esta temperatura durante 2,5 horas. Después de enfriarse a temperatura ambiente, la mezcla de reacción se concentró in vacuo y el residuo resultante se diluyó con acetato de etilo (300 ml) y una solución de carbonato de socio acuoso 0,1 N (300 ml). La fase orgánica separada se secó (sulfato de magnesio), se filtró y concentró in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash en gel de sílice (EtOAc:Hexanos, 0 a 50% EtOAc) para proporcionar el compuesto **51B** (22,7 g, 96%).

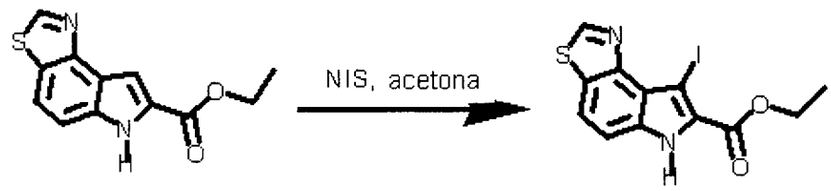
Paso C – Síntesis del Compuesto 51C



51B **51C** **51C'**

El compuesto **51B** (22 g, 83,6 mmol) se molió en un polvo, luego se mezcló con ácido polifosfórico (180 g). La mezcla bifásica se dejó agitar vigorosamente a 110 °C durante 1,5 h, luego se enfrió a temperatura ambiente y se vertió en agua helada. La fase acuosa de la mezcla se alcalinizó a pH 11 mediante hidróxido de amonio acuoso (37 N). La mezcla resultante se extrajo con 300 ml de acetato de etilo/THF (2:1) cuatro veces. Las fases orgánicas combinadas se secaron (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que contenía los compuestos **51C** y **51C'**. El residuo bruto se purificó mediante cromatografía flash en gel de sílice (EtOAc:Hexanos, 0 a 50% EtOAc) para proporcionar el compuesto **51C** (2,55 g, 12%). ^{1}H RMN (500 MHz, d_6-DMSO):δ 12,28 (s, 1H), 7,86 (d, J= 8,8 Hz, 1H), 7,52 & 7,50 (dd, J=0,6 Hz & 8,5 Hz, 1H), 7,40 & 7,39 (dd, J= 0,9 Hz & 2,2 Hz, 1H), 4,37 (q, J= 6,9 Hz & 7,3 Hz, 2H), 2,85 (s, 3H), 1,36 (t, J= 6,9 Hz, 3H). ^{13}C RMN (125 MHz, d_6-DMSO): δ166,4, 161,0, 136,3, 126,9, 126,7, 120,5, 117,8, 110,8, 109,1, 105,1, 60,4, 19,6, 14,2. HRMS calculado para $C_{13}H_{12}N_2O_2S$: 261,0698 $(M+H)^+$. Experimental: 261,0701.

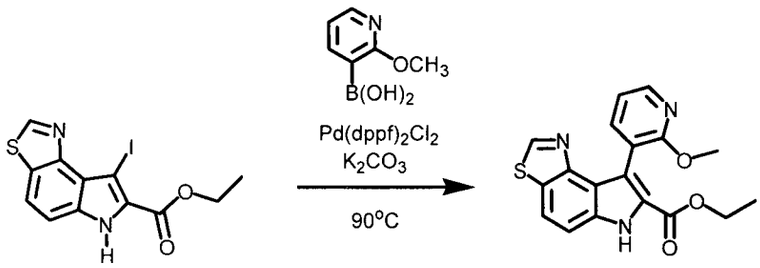
Paso D – Síntesis del Compuesto 51D



51C **51D**

A una solución del Compuesto **51C** (2,55 g, 10,4 mmol) en acetona (400 ml) a temperatura ambiente, se agregó *N*-yodosuccinimida (15,8 mmol). La reacción resultante se dejó agitar a temperatura ambiente durante 18 horas, luego concentró in vacuo, y el residuo resultante se disolvió con acetato de etilo (150 ml). La fase orgánica se recogió y se lavó con una solución de tiosulfato de sodio acuoso saturado (80 ml). La fase acuosa luego se extrajo con acetato de etilo (2 X 100 ml) y las fases orgánicas combinadas se secaron (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **51D** (cuant.), que se usó sin purificación adicional. ^{1}H RMN (500 MHz, d_6-DMSO) δ12,66 (s, 1H), 9,49 (s, 1H), 8,06 & 8,04 (dd, J= 3,47 Hz & 8,83 Hz, 1H), 7,66 & 7,65 (dd, J= 3,15 Hz & 8,51 Hz, 1H), 4,40 (q, J= 4,42 Hz & 4,39 Hz, 2H), 1,40 (dt, J= 3,47 Hz & 7,09 Hz, 3H); ^{13}C RMN (125 MHz, d_6-DMSO): δ160,25, 154,74, 146,47, 146,25, 135,83, 127,14, 126,49, 125,64, 119,00, 111,86, 60,71, 14,19. M.S. experimental $C_{12}H_9IN_2O_2S$: 373,17 $(M+H)^+$.

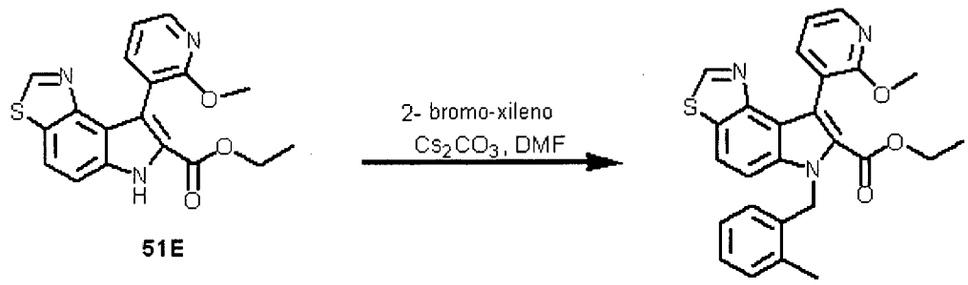
Paso E – Síntesis del Compuesto 51E



51D **51E**

A una solución del Compuesto **51D** (10,4 mmol) en 1,2-dimetoxietano (225 ml) se agregó $Pd(dppf)_2Cl_2$ (1,05 mmol) y la solución resultante se desgasificó mediante burbujeo de argón durante 5 minutos. La solución desgasificada luego se calentó a 90°C y se dejó agitar durante 0,5 horas. En un segundo matraz, se disolvieron ácido 2-metoxi-3-piridinborónico (14,6 mmol) y carbonato de potasio (52,1 mmol) en dimetoxietano (75 ml) y agua (75 ml) y la solución resultante se desgasificó mediante burbujeo de argón durante 5 minutos, luego los contenidos del segundo matraz se agregaron a la solución que contiene el compuesto **51D**. La mezcla bifásica resultante se calentó a 90 °C y se dejó agitar vigorosamente a esta temperatura. Después de 4 horas la reacción se enfrió a temperatura ambiente y se inactivó por la adición de una solución de sulfito de sodio (3,6 g) in agua (80 ml) a temperatura ambiente. Se agregaron acetato de etilo (200 ml) y agua (100 ml) a la reacción inactivada y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 200 ml) y las fases orgánicas combinadas se secó (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **51E** (100%). ^{1}H RMN (500 MHz, d_6-DMSO): δ12,41 (s, 1H), 9,21 (s, 1H), 8,19 & 8,18 (ddd, J= 0,63 Hz, 1,89 Hz & 5,04 Hz, 1H), 7,99 (d, J= 8,83 Hz, 1H), 7,72 (s, 1H), 7,66 (d, J= 8,83 Hz, 1H), 7,04 (q, J= 5,04 Hz & 2,21 Hz, 1H), 4,17 (q, J= 7,25 Hz & 6,94 Hz, 2H), 3,69 (s, 3H), 1,09 (t, J= 7,09 Hz, 3H). ^{13}C RMN (125 MHz, d_6-DMSO): δ161,42, 160,80, 154,43, 152,61, 146,80, 145,17, 140,71, 135,05, 126,34, 123,64, 120,32, 118,25, 116,36, 116,02, 111,75, 60,10, 39,00, 13,78. M.S. experimental $C_{18}H_{15}N_3O_3S$: 354,04 $(M+H)^+$.

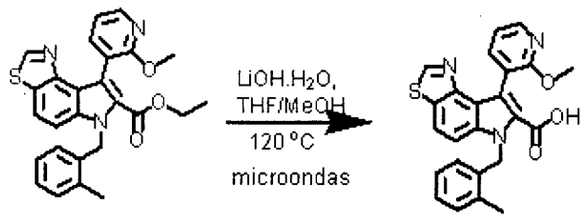
Paso F – Síntesis del Compuesto 51F



51E **51F**

A una solución del Compuesto **51E** (0,71 mmol) en DMF (25 ml) a temperatura ambiente, se agregó 2-bromo-xileno (1,00 mmol) y carbonato de cesio (1,23 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas, luego se agregaron acetato de etilo (200 ml) y agua (100 ml) a la mezcla de reacción, y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 X 100 ml). La fase orgánica combinada se lavó con agua (2 X 100 ml). La fase orgánica separada se secó (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía flash para proporcionar el compuesto **51F** (0,21 g, 65%). M.S. experimental $C_{26}H_{23}N_3O_3S$: 458,11 $(M+H)^+$.

Paso G – Síntesis del Compuesto 51G

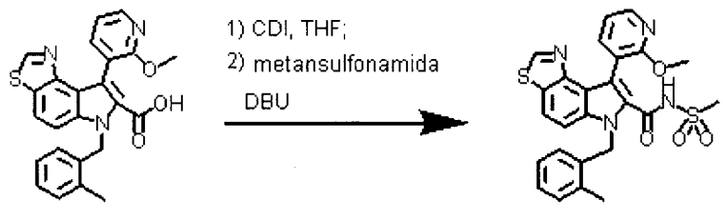


51F **51G**

A una solución del Compuesto **51F** (0,21 g, 0,45 mmol) en tetrahidrofurano (2 ml) y metanol (3 ml) se agregó hidróxido de litio monohidrato (60 mg, 1,43

mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 5 minutos antes de colocarse en el reactor de microondas durante 20 minutos (120°C, alta potencia). La reacción luego se concentró in vacuo y se agregaron acetato de etilo (50 ml) y tetrahidrofurano (50 ml) al residuo. La fase acuosa se acidificó a pH=1 por agregado de 5% de ácido fosfórico y las fases se separaron. La fase acuosa se extrajo adicionalmente con acetato de etilo (2 X 50 ml). La fase orgánica combinada se secó (sulfato de magnesio) y se filtraron y concentraron in vacuo para proporcionar el compuesto **51G** (100%). M.S. experimental $C_{24}H_{19}N_3O_3S$: 430,10 $(M+H)^+$.

Paso H – Síntesis del Compuesto 51H

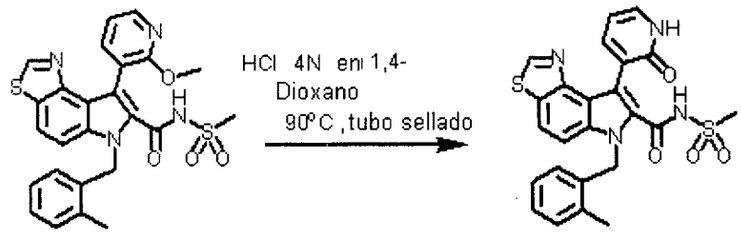


51G **51H**

A una solución del Compuesto **51G** (132 mg, 0,31 mmol) en tetrahidrofurano (5 ml) se agregó carbonildiimidazol (60 mg). La suspensión resultante se reflujó a 75 °C durante 1 hora, y luego se enfrió a temperatura ambiente antes de agregar metansulfonamida (70 mg, 0,74 mmol) y 1,8-diazabiciclo(5,4,0)undec-7-eno (0,11 ml). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 48 horas. Se agregaron acetato de etilo (80 ml), tetrahidrofurano (10 ml) y 1% de ácido fosfórico acuoso (50 ml) a la mezcla de reacción, y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 X 50 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtraron y concentraron in vacuo. El producto bruto se purificó

mediante cromatografía flash en gel de sílice para proporcionar el compuesto **51H** (106 mg, 68%).

*Paso I – Síntesis del Compuesto **51***



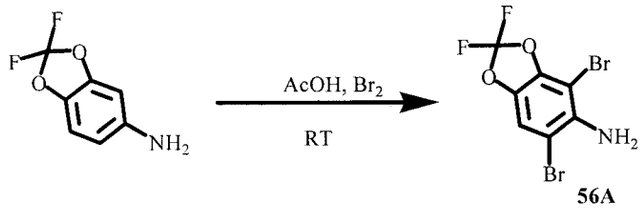
51H **51**

Una solución del Compuesto **51H** (103 mg, 0,20 mmol) in 4N HCl (4,5 ml en 1,4-dioxano) se colocó en un tubo sellado, se calentó a 90 °C, y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción luego se dejó enfriar temperatura ambiente y concentró in vacuo. El producto bruto se purificó mediante fase reversa HPLC para proporcionar el compuesto **51** (35 mg, 35%). ^{1}H RMN (500 MHz, d_6-DMSO): δ12,72 (s,1H), 12,57 (s, 1H), 9,32 (s, 1H), 8,04 (d, J= 8,83 Hz, 1H), 7,98 (d, J= 6,62 Hz, 1H), 7,68 – 7,64 (m, 2H), 7,21 (d, J= 7,57 Hz, 1H), 7,12 (t, J= 7,41 Hz, 1H), 6,98 (t, J= 7,57 Hz, 1H), 6,59 (t, J= 6,62 Hz, 1H), 6,23 (d, J= 7,88 Hz, 1H), 5,79 (s, 2H), 3,09 (s, 3H), 2,40 (s, 3H). ^{13}C RMN (125 MHz, d_6-DMSO): δ163,64, 162,74, 160,88, 155,03, 146,60, 142,59, 136,12, 135,32, 134,60, 132,27, 129,89, 129,01, 127,38, 127,07, 126,72, 125,92, 124,64, 119,03, 114,42, 110,27, 106,96, 73,69, 45,91, 18,71. M.S. experimental $C_{24}H_{20}N_4O_4S_2$: 493,06 $(M+H)^+$.

Ejemplo 9

Preparación del Compuesto **56**

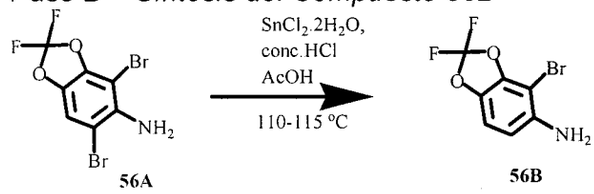
Paso A – Síntesis del Compuesto 56A



56A

Se agregó bromo (11,3 ml) en una solución de 5-amino-2,2-difluorobenzodioxol (Maybridge, 5,0 g, 28,9 mmol) en ácido acético (150 ml). La mezcla se dejó agitar a temperatura ambiente durante 1 hora, luego concentró in vacuo. El residuo resultante se diluyó con cloruro de metileno (50 ml) y el sólido se filtró, se lavó con cloruro de metileno (4 x 15 ml) y se secó al vacío para proporcionar el compuesto **56A** (8,2 g, 86%) como un sólido amarillo. M.S. experimental $C_7H_3Br_2F_2NO_2$: 331,93 $(M+H)^+$.

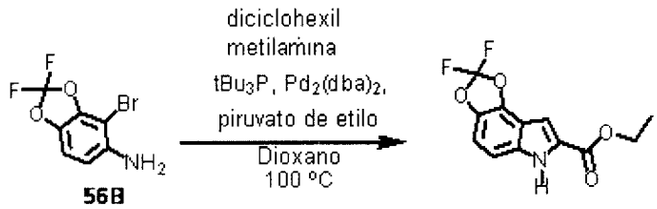
Paso B – Síntesis del Compuesto 56B



56A **56B**

A una suspensión del Compuesto **56A** (4,48 g,13,5 mmol) in ácido acético (glacial, 20 ml) y HCl concentrado (16,0 ml) se agregó cloruro estañoso (3,36 g, 14,9 mmol). La suspensión resultante se calentó a 110 - 115 °C y se dejó agitar a esta temperatura durante 30 minutos. La mezcla de reacción se enfrió a temperatura ambiente y concentró in vacuo. Al residuo se agregaron cloruro de metileno (80 ml) y hidróxido de sodio acuoso 1N (80 ml), y las fases se separaron. La fase acuosa se extrajo con cloruro de metileno (2 X 80 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró, y concentró in vacuo para proporcionar el compuesto **56B** (2,68 g, 79%) como un sólido blanco. ^{1}H RMN (500 MHz, d_6-DMSO): δ7,12 (d, J= 8,5 Hz, 1H), 6,54 (d, J= 8,8 Hz, 1H), 5,48 (s, 2H) ,1^3C RMN (125 MHz, d_6-DMSO): δ143,7, 141,6, 133,1, 130,7, 109,5, 108,4, 87,5. M.S. experimental $C_7H_4BrF_2NO_2$: 254,00 $(M+H)^+$.

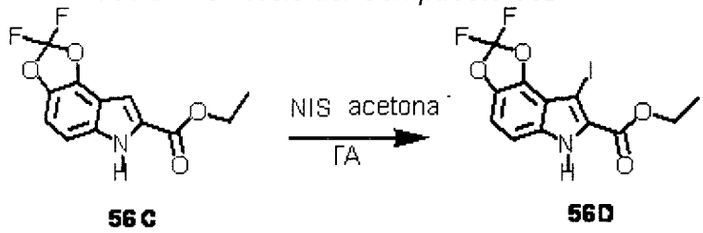
Paso C – Síntesis del Compuesto 56C



56B **56C**

El compuesto **56B** (2,66 g,10,6 mmol) se disolvió en dioxano anhidro (100 ml). A la solución se agregó diciclohexilmetilamina (14,8 ml, 69,1 mmol), tri-ter-butilfosfina (0,83 g, 4,10 mmol), $Pd_2(dba)_3$ (971 mg, 1,06 mmol) y piruvato de etilo (4,60 ml, 42,0 mmol). La mezcla se calentó a 100 °C y se dejó agitar durante 18 horas. La mezcla de reacción se enfrió a temperatura ambiente, y se diluyó con cloruro de metileno (300 ml) y solución de HCl acuoso 1N (300 ml). Las fases se separaron, y la fase acuosa se extrajo con cloruro de metileno (2 X 150 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtraron y concentraron in vacuo. El producto bruto se purificó mediante cromatografía flash en gel de sílice para proporcionar el compuesto **56C** (1,79 g, 62%),1H RMN (500 MHz, d_6-DMSO): δ12,40 (s, 1H), 7,38 (d, J=9,1 Hz, 1H), 7,31 & 7,30 (dd, J=0,9 Hz & 8,8 Hz, 1H), 7,17 (d, J= 2,2 Hz, 1H), 4,37 (q, J= 6,9 Hz & 7,3 Hz, 2H), 1,35 (t, J= 7,1 Hz, 3H). ^{13}C RMN (125 MHz, d_6-DMSO): δ160,5, 136,1, 135,8, 134,4, 133,6, 130,1, 111,6, 108,1, 107,4, 101,6, 60,9, 14,1.

Paso D – Síntesis del Compuesto 56D

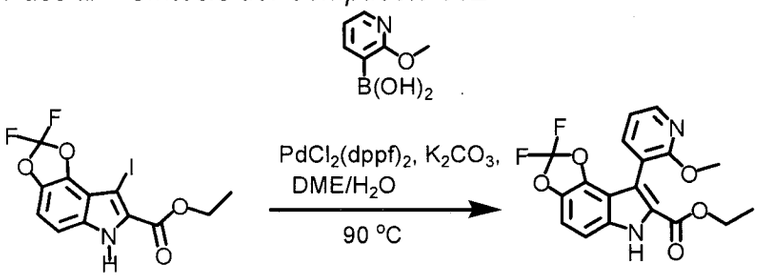


56C **56D**

El compuesto **56C** (1,79 g, 6,62 mmol) se disolvió en acetona (150 ml) a temperatura ambiente. A la mezcla se agregó N-yodosuccinimida (1,70 g, 7,18

mmol), y la suspensión resultante se dejó agitar a temperatura ambiente durante 3 horas. La mezcla se concentró in vacuo. El residuo se disolvió en acetato de etilo (100 ml) y se lavó con solución de tiosulfato de sodio acuoso saturado (50 ml). Las fases se separaron, y la fase acuosa se extrajo con acetato de etilo (2 x 100 ml). Las fases orgánicas combinadas se secaron (sulfato de magnesio), se filtró, y concentró in vacuo para proporcionar el compuesto **56D** (2,47 g, 94%).

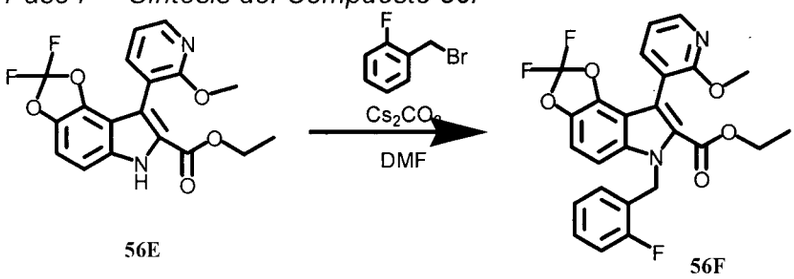
Paso E – Síntesis del Compuesto 56E



56D **56E**

El compuesto **56D** (2,46 g, 6,21 mmol) se disolvió en 1,2-dimetoxietano (75 ml). A la mezcla se agregó $PdCl_2(dppf)_2$ (510 mg, 0,63 mmol). La suspensión resultante se calentó a 90 °C y se desgasificó con burbujeo de nitrógeno durante 15 minutos. En un segundo matraz, se disolvieron ácido 2-metoxi-3-piridinborónico (1,15 g, 7,52 mmol) y carbonato de potasio (4,30 g, 31,1 mmol) en dimetoxietano (25 ml) y agua (25 ml). La mezcla se desgasificó con burbujeo de nitrógeno durante 5 minutos antes de transferirse al primer matraz. La mezcla resultante se dejó agitar vigorosamente a 90 °C durante 3,5 h, luego se enfrió a temperatura ambiente. Una solución de sulfito de sodio (4,3 g) in agua (57 ml) luego se agregó a la mezcla, seguido por acetato de etilo (150 ml), y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 100 ml) y las fases orgánicas combinadas se secaron (sulfato de magnesio), se filtró, y concentró in vacuo. El residuo resultante se purificó mediante cromatografía flash en gel de sílice para proporcionar el compuesto **56E** (0,96 g, 41%). M.S. experimental $C_{18}H_{14}F_2N_2O_5$: 377,02 $(M+H)^+$.

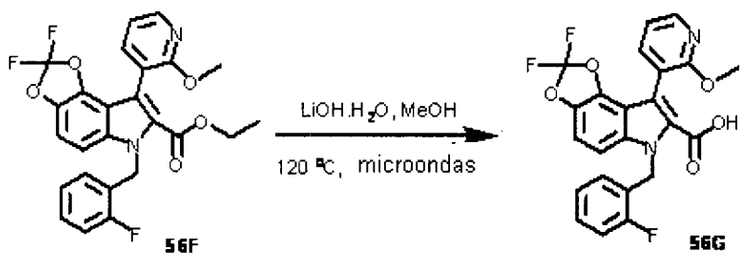
Paso F – Síntesis del Compuesto 56F



56E 56F

El compuesto **56E** (250 mg, 0,66 mmol) se disolvió en N,N-dimetilformamida (20 ml) a temperatura ambiente. A la mezcla se agregaron bromuro de 2-fluorobencilo (175 mg, 0,92 mmol) y carbonato de cesio (325 mg, 1,00 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas. Se agregaron acetato de etilo (200 ml) y agua (100 ml) a la mezcla de reacción, y luego las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 X 50 ml). La fase orgánica combinada se lavó con agua (2 X 50 ml), y luego se secó (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **56F** (0,27 g, 84%). M.S. experimental $C_{25}H_{19}F_3N_2O_5$: 485,10 $(M+H)^+$.

Paso G – Síntesis del Compuesto 56G

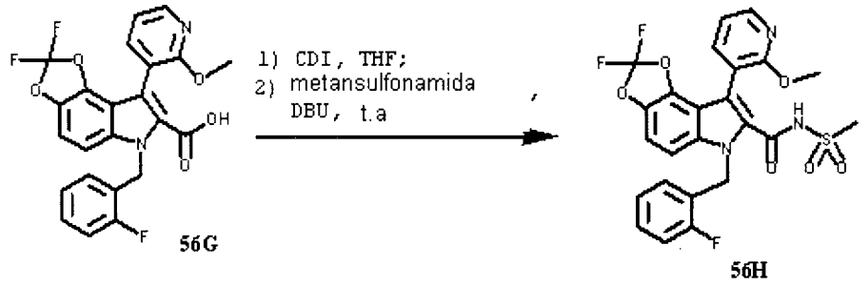


56F **56G**

A una solución del Compuesto **56F** (0,55 mmol) en metanol (5 ml) se agregó hidróxido de litio monohidrato (2,19 mmol) y la suspensión resultante se dejó agitar a temperatura ambiente durante 5 minutos antes de colocarse en un reactor de microonda durante 20 min (120 °C, alta potencia). La mezcla luego se

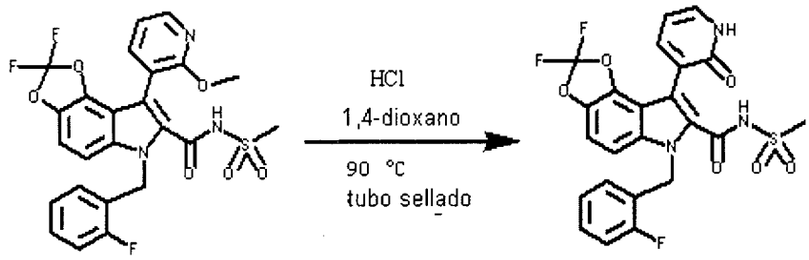
concentró in vacuo y el residuo resultante se diluyó con acetato de etilo (50 ml) y tetrahidrofurano (50 ml). La fase acuosa se acidificó a pH 1 mediante una solución de HCl 1N, y las fases se separaron. La fase acuosa se extrajo adicionalmente con acetato de etilo (2 x 50 ml), y la fase orgánica combinada se secó (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **56G** (100%). M.S. experimental $C_{23}H_{15}F_3N_2O_5$: 457,09 $(M+H)^+$.

Paso H – Síntesis del Compuesto 56H



El compuesto **56G** (143 mg, 0,31 mmol) se disolvió en tetrahidrofurano (5,0 ml) a temperatura ambiente. A la mezcla se agregó carbonildiimidazol (65 mg, 0,40 mmol). La suspensión se reflujó a 75°C durante 1 h, y luego se enfrió a temperatura ambiente antes de agregar metansulfonamida (60 mg, 0,63 mmol) y 1,8-diazabiciclo(5,4,0)undec-7-eno (1,00 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente for 68 horas. Acetato de etilo (80 ml), tetrahidrofurano (10 ml) y 1% de ácido fosfórico acuoso (50 ml) se agregaron to la mezcla de reacción, y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 X 50 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **56H** (113 mg, 68%). M.S. experimental $C_{24}H_{18}F_3N_3O_6S$: 534,04 $(M+H)^+$.

*Paso I – Síntesis del Compuesto **56***



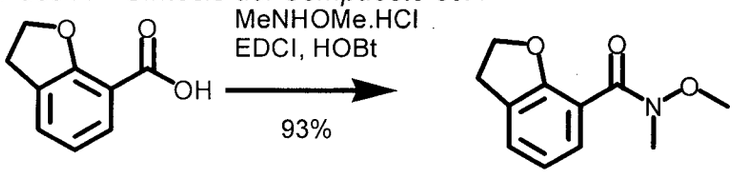
56H **56**

Una solución del Compuesto **56H** (65 mg, 0,12 mmol) in HCl (4N en dioxano, 5,0 ml) en un tubo sellado se calentó a 90 °C y se dejó agitar a esta temperatura durante 2 horas. La mezcla de reacción luego se dejó enfriar temperatura ambiente, luego concentró in vacuo para proporcionar un residuo bruto que se purificó mediante fase reversa HPLC para proporcionar el compuesto **56** (44 mg, 69%). ^{1}H RMN (500 MHz, d_6-DMSO): δ 12,77 (s, 1H), 12,49 (s, 1H), 7,82 & 7,81 (dd, J= 1,58 Hz & 6,94 Hz, 1H), 7,61 (t, J= 5,20 Hz, 1H), 7,50 (d, J= 8,83 Hz, 1H), 7,45 (d, J= 9,14 Hz, 1H), 7,33 (q, J= 6,31 Hz & 7,57 Hz, 1H), 7,22 (t, J= 9,46 Hz, 1H), 7,09 (t, J= 7,57 Hz, 1H), 6,89 (t, J= 7,72 Hz, 1H), 6,56 (t, J= 6,62 Hz, 1H), 5,76 (s, 2H), 3,23 (s, 3H). ^{13}C RMN (125 MHz, d_6-DMSO): δ161,81, 160,59, 158,65, 157,27, 145,62, 143,33, 137,17, 135,62, 135,24, 134,57, 129,54, 128,67, 127,17, 124,10, 123,99, 123,79, 115,23, 111,32, 107,34, 106,68, 106,45, 42,10, 40,95. M.S. experimental $C_{23}H_{16}F_3N_3O_6S$: 520,04 $(M+H)^+$.

Ejemplo 10

Preparación del Compuesto **59**

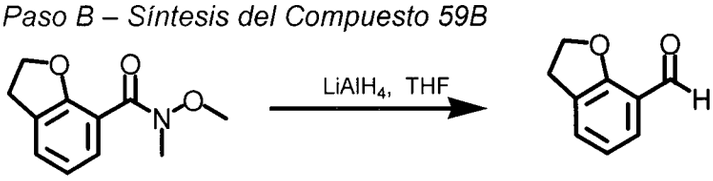
Paso A – Síntesis del Compuesto 59A



59A

Una suspensión de ácido 2,3-dihidro-benzofuran-7-carboxílico, (TCI, 20,0 g, 121,8 mmol) en 600 ml de acetonitrilo seco se enfrió a 0°C y se trató con clorhidrato de N,O-dimetilhidroxilamina (14,25 g, 146,1 mmol). La reacción se dejó agitar durante 10 minutos y se agregó EDCI (24,6 g, 158,3 mmol), seguido por HOBT (3,2 g, 24,2 mmol) y la mezcla resultante se dejó agitar durante 5 minutos. Luego se agregó trietilamina (365,4 mmol) y la mezcla de reacción se dejó agitar durante 18 horas a temperatura ambiente, luego se diluyó con HCl acuoso 1N (250 ml) y se extrajo con acetato de etilo (1,0 L). La fase orgánica sucesivamente se lavó con carbonato de potasio 10% acuoso (200 ml), HCl acuoso 1N (200 ml), y salmuera (200 ml). La fase orgánica luego se secó con sulfato de magnesio, se filtró y concentró in vacuo para proporcionar el compuesto **59A** (23,37 g, 93 %) como un aceite incoloro. M.S. experimental $C_{11}H_{13}NO_3$: 230,11 $(M+Na)^+$.

Paso B – Síntesis del Compuesto 59B

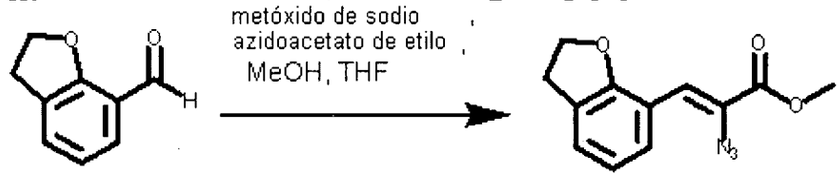


59A **59B**

Una suspensión de hidruro de aluminio y litio (pellet, 5,56 g, 146,5 mmol) en 500 ml de THF seco se dejó agitar a 55°C durante 18 horas bajo atmósfera anhidra, luego se enfrió a 0°C, y se agregó una solución del Compuesto **59A** (23,37 g, 112,7 mmol) en 500 ml de THF seco durante 45 minutos. La mezcla de reacción se dejó agitar a 0°C durante 30 minutos, luego se inactivó por la adición cuidadosa sulfato de hidrógeno sódico acuoso 20% hasta que se detuvo el desarrollo de gas. Se agregó sulfato de hidrógeno sódico acuoso 20% adicional (aprox. 5 ml) y la solución resultante se dejó agitar vigorosamente durante 15 minutos. La mezcla de reacción se diluyó con éter (500 ml) y hexanos (500 ml) y se filtró a través de un trecho corto de celite. El filtrado se concentró in vacuo para suministrar un residuo bruto que se purificó mediante cromatografía líquida de

presión media (columna de gel de sílice Biotage 75-M, gradiente: 0 a 30 % acetato de etilo en hexanos) para proporcionar el compuesto **59B** (9,00 g, 54 %) como un sólido blanco. ^{1}H RMN (400 MHz, d_6-DMSO): δ10,10 (s, 1H), 7,51 (q, J= 7,32 Hz & 5,13 Hz, 2H), 6,95 (t, J= 7,69 Hz, 1H), 4,69 (t, J= 8,79 Hz, 2H), 3,22 (t, J= 8,42 Hz, 2H).

Paso C – Síntesis del Compuesto 59C

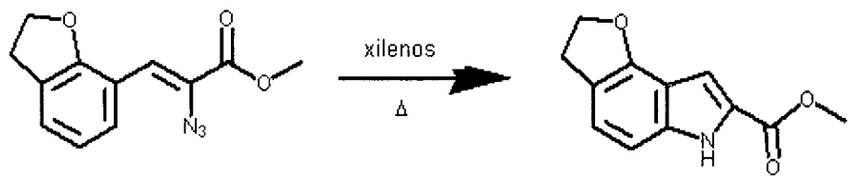


59B **59C**

Una solución de metóxido de sodio recién preparado en metanol (2,5 eq, preparado por disolución de 1,94 g de sodio en 80 ml de metanol) se agregó gota a gota (durante 20 minutos) a una solución enfriada (-20°C, temperatura interna) del Compuesto **59B** (5,0 g, 33,74 mmol) y azidoacetato de etilo (10,9 g, 84,36 mmol) en 20 ml de metanol seco y 20 ml de THF seco. La adición se realizó de modo que no se permitió que la temperatura de reacción interna se elevara por encima de -10°C. Luego la reacción se dejó agitar a -10°C durante 1 hora, luego se dejó calentar a temperatura ambiente durante 1 hora. La mezcla de reacción luego se dejó agitar a temperatura ambiente durante 1 hora (se formó un precipitado blanco), y luego se inactivó con una solución de cloruro de amonio acuoso saturado (10 ml). La solución resultante mixture se dividió entre acetato de etilo (500 ml) y agua (100 ml). La fase orgánica se lavó con salmuera (80 ml), se secó con sulfato de magnesio, se filtró, y concentró in vacuo. El residuo resultante se purificó mediante cromatografía en columna en gel de sílice (columna Biotage 75-M; gradiente: 0 a 25% acetato de etilo en hexanos) para proporcionar el compuesto **59C** (4,20 g, 52%) como un sólido ligeramente amarillo. ^{1}H RMN (400 MHz, d_6-DMSO): δ 7,96 (d, J= 8,06 Hz, 1H), 7,24 (d, J= 6,59 Hz, 1H), 7,01 (s, 1H),

6,88 (t, J= 7,69 Hz, 1H), 4,58 (t, J= 8,79 Hz, 2H), 3,84 (s, 3H), 3,21 (t, J= 8,79 Hz, 2H).

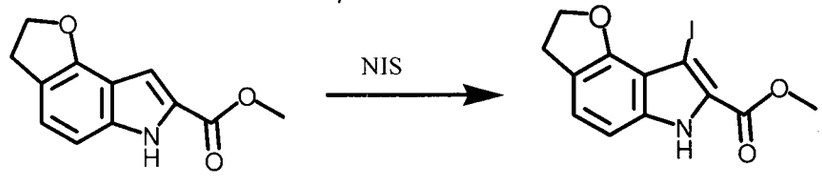
Paso D – Síntesis del Compuesto 59D



59C **59D**

Una solución del Compuesto **59C** (4,0 g, 16,31 mmol) en 60 ml de xilenos se calentó a 150°C y se dejó agitar a esta temperatura durante 10 minutos, luego se enfrió a temperatura ambiente, tiempo durante el cual se formó un sólido blanco. La suspensión se conservó a -20°C en congelador durante 1 hora, luego se filtró para proporcionar el compuesto **59D** como un sólido blanco (1,0 g). El filtrado se concentró in vacuo, y el residuo resultante se purificó mediante cromatografía en columna en gel de sílice (Biotage 40-S column; gradiente: 0 a 35% acetato de etilo in hexanos) para proporcionar una cantidad adicional del compuesto **59D** (290 mg). (Rendimiento total= 1,29 g, 37%). ^{1}H RMN (400 MHz, d_6-DMSO): δ 11,91 (s, 1H), 7,12 (d, J= 8,06 Hz, 1H), 6,96 (s, 1H), 6,95 (d, J= 8,06 Hz, 1H), 4,65 (t, J= 8,79 Hz, 2H), 3,85 (s, 3H), 3,22 (t, J= 8,79 Hz, 2H).

Paso E– Síntesis del Compuesto 59E

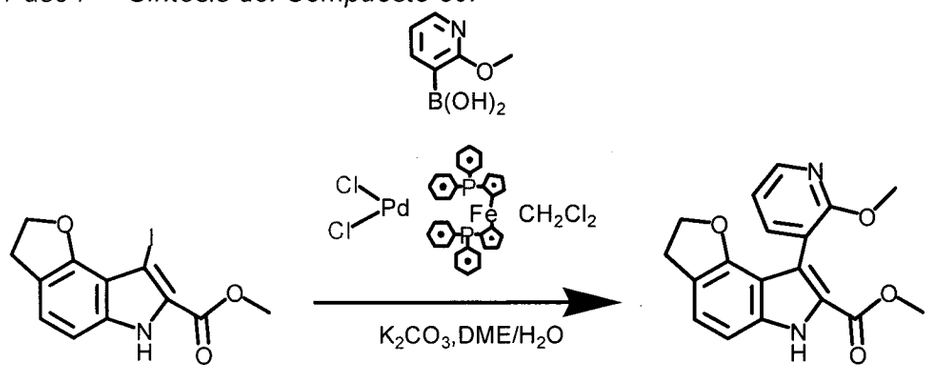


59D **59E**

A una solución del Compuesto **59D** (1,45 g, 6,67 mmol) en 50 ml de cloroformo y 20 ml de THF a 0°C se agregó N-yodosuccinimida (1,65 g, 7,34 mmol). La reacción resultante se dejó agitar a 0°C durante 30 minutos, luego se calentó a temperatura ambiente y se dejó agitar a esta temperatura durante 30

minutos. La mezcla de reacción luego se diluyó con acetato de etilo (100 ml), y la solución resultante se lavó sucesivamente con tiosulfato de sodio acuoso saturado (20 ml), bicarbonato de de sodio acuoso saturado (20 ml) y salmuera (20 ml). La fase orgánica se secó over sulfato de magnesio, se filtró, y concentró in vacuo. El producto bruto se purificó mediante cromatografía en columna en gel de sílice (columna Biotage 40-S; gradiente: 0 a 40 % acetato de etilo en hexanos) para proporcionar el compuesto **59E** (190 mg, 10%) como un sólido blanco. M.S. experimental $C_{12}H_{10}INO_3$: 343,87 $(M+H)^+$.

Paso F – Síntesis del Compuesto 59F

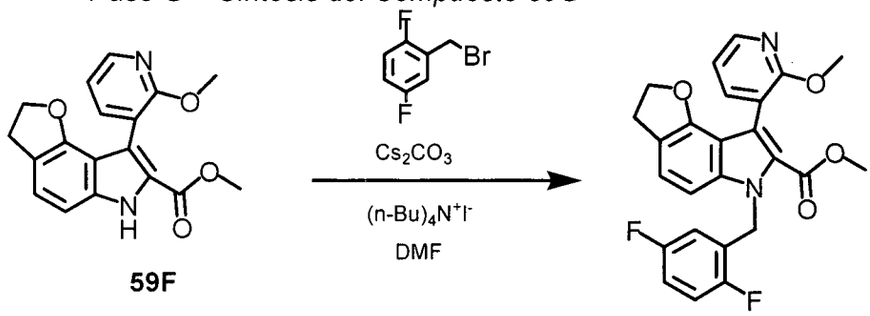


59E **59F**

A una solución de del Compuesto **59E** (180 mg, 0,524 mmol) en 10 ml de 1,2-dimetoxietano se agregó ácido 2-metoxi-3-piridinborónico (240 mg, 1,573 mmol) y se agregó la mezcla resultante se desgasificó (vacío/lavado de argón), y $PdCl_2(dppf)_2$ (10 mol%, 42 mg). La mezcla resultante se dejó agitar durante 15 minutos a temperatura ambiente y se agregó una solución de carbonato de potasio (434 mg, 3,144 mmol). La solución de reacción marrón resultante se calentó a 90°C y se dejó agitar a esta temperatura durante 45 minutos. La mezcla de reacción luego se dejó enfriar temperatura ambiente, y se diluyó con acetato de etilo (80 ml). La fase orgánica se lavó sucesivamente con bicarbonato de sodio acuoso saturado (10 ml) y salmuera (10 ml), luego se secó con sulfato de magnesio, se filtró, y concentró in vacuo. El residuo resultante se purificó

mediante cromatografía en columna en gel de sílice (columna Biotage 25-S; gradiente: 10 a 50 % acetato de etilo en hexanos) para proporcionar el compuesto **59F** (140 mg, 83 %) como un sólido blanco. M.S. experimental $C_{18}H_{16}N_2O_4$: 325,07 $(M+H)^+$.

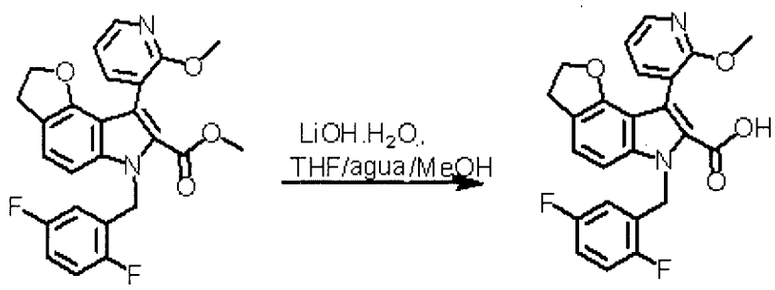
Paso G – Síntesis del Compuesto 59G



59F **59G**

A una solución del Compuesto **59F** (130 mg, 0,400 mmol) en 5 ml de DMF seco a 0°C se agregaron bromuro de 2,5-drifluorobencilo (99 mg, 0,480 mmol), carbonato de cesio (391 mg, 1,200 mmol) y yoduro de tetrabutilamonio (10 mg, catalítica). La reacción resultante se dejó agitar a 0°C durante 45 minutos, luego se calentó a temperatura ambiente. La mezcla luego se diluyó con acetato de etilo (80 ml), y la solución resultante se lavó sucesivamente con agua (10 ml) y salmuera (10 ml). La fase orgánica se secó con sulfato de magnesio, se filtró, y concentró in vacuo para proporcionar un residuo bruto que se purificó mediante cromatografía en columna en gel de sílice (columna Biotage 25-S; gradiente: 0 a 25% acetato de etilo en hexanos) para proporcionar el compuesto **59G**(140 mg, 78 %) como un sólido blanco. M.S. experimental $C_{25}H_{20}F_2N_2O_4$: 451,12 $(M+H)^+$.

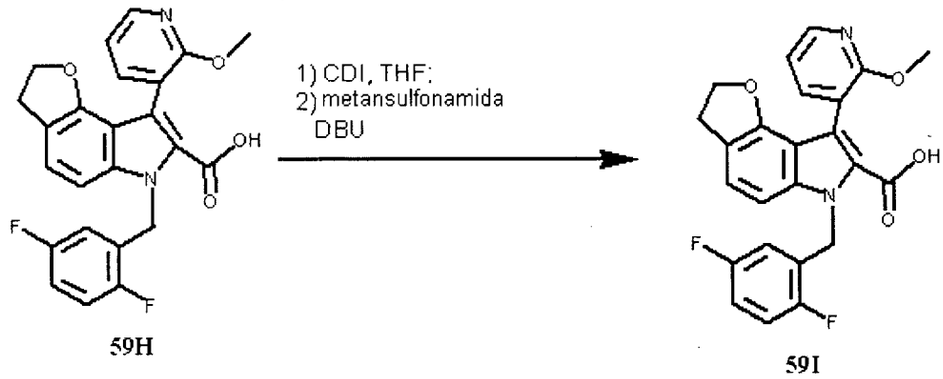
Paso H – Síntesis del Compuesto 59H



59G **59H**

A una solución del Compuesto **59G** (140 mg, 0,310 mmol) en 8 ml de una solución de tetrahidrofurano/agua/metanol (2:1:1) se agregó hidróxido de litio monohidrato (65 mg, 1,554 mmol). La reacción se calentó a 50°C y se dejó agitar a esta temperatura durante 5 horas. La mezcla se diluyó con solución de HCl acuoso 1N (40 ml), y luego se extrajo con diclorometano (3 X 25 ml). Las fases orgánicas combinadas se secaron (sulfito de magnesio), se filtraron y concentraron in vacuo para proporcionar el compuesto **59H** (135 mg, 99%) como un sólido blanco, que se usó sin purificación adicional.

Paso I – Síntesis del Compuesto 59I

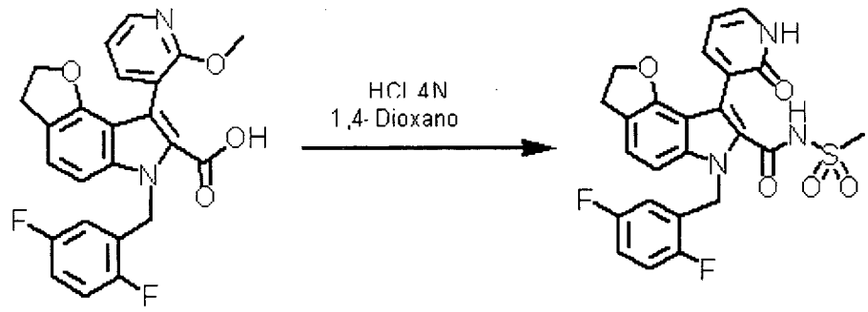


59H **59I**

A una solución del Compuesto **59H** (150 mg, 0,343 mmol) en tetrahidrofurano (4,0 ml) se agregó carbonildiimidazol (69 mg, 0,429 mmol). La mezcla resultante se reflujó a 70 °C durante 2 h y luego se enfrió a temperatura ambiente. Se agregaron metansulfonamida (41 mg, 0,429 mmol) y 1,8-

diazabiciclo(5,4,0)undec-7-eno (78 mg, 0,514 mmol) a la reacción y la mezcla de reacción resultante se calentó a 40°C y se dejó agitar a esta temperatura durante 48 horas. La mezcla de reacción se diluyó con acetato de etilo (60 ml), y se lavó sucesivamente con HCl acuoso 1N (10 ml) y salmuera (10 ml). La fase orgánica se secó (sulfato de magnesio), se filtró, y concentró in vacuo para proporcionar el compuesto **59l** (103 mg, 60%), que se usó sin purificación adicional. ^{1}H RMN (400 MHz, d_6-DMSO): δ 11,71 (s, 1H), 8,14 & 8,13 (dd, J= 2,20 Hz & 5,13 Hz, 1H), 7,79 & 7,77 (dd, J= 2,20 Hz & 7,32 Hz, 1H), 7,34 – 7,26 (m, 1H), 7,20 (d, J= 8,79 Hz, 1H), 7,19 – 7,12 (m, 1H), 7,10 – 7,07 (m, 2H), 6,58 – 6,53 (m, 1H), 5,65 (s, 2H), 4,55 (d, J= 8,79 Hz, 2H), 3,75 (s, 3H), 3,19 – 3,14 (m, 2H), 3,06 (s, 3H).

*Paso J – Síntesis del Compuesto **59***



59l 59

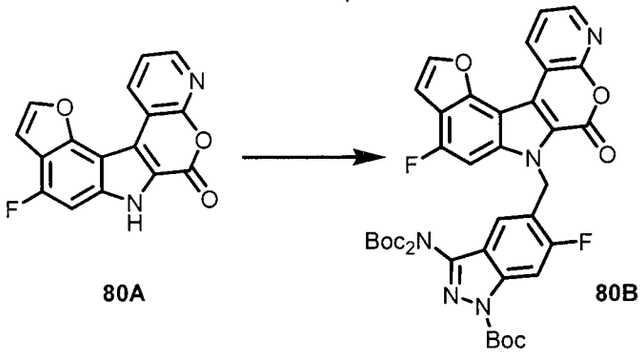
Una solución del Compuesto **59l** (100 mg, 0,194 mmol) en 3 ml de HCl (4M en dioxano) y metanol (1 ml) se colocó en un tubo sellado, se calentó a 90°C y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción se concentró in vacuo para proporcionar un residuo sólido amarillo que se purificó mediante fase reversa HPLC (Delta Pak, C18, 5 micrmnetro, 300A; 300 x 30 mm I.D.; caudal de flujo: 30 ml/min; Gradiente: 40% de acetonitrilo in agua durante 20 min que luego aumenta a 80% durante 30 min y permanece allí por 10 min) para proporcionar el compuesto **59** (62 mg, 65%) como un sólido blanco. ^{1}H RMN (400 MHz, d_6-DMSO): δ7,78 & 7,76 (dd, J= 2,20 Hz & 7,32 Hz, 1H), 7,62 (d, J= 5,86

Hz, 1H), 7,55 & 7,53 (dd, J= 1,47 Hz & 6,59 Hz, 1H), 7,33 – 7,27 (m, 2H), 7,23 - 7,13 (m, 3H), 7,04 (q, J= 4,39 Hz & 3,66 Hz, 1H), 6,57 (q, J= 6,59 Hz, 1H), 5,66 (s, 2H), 3,25 (s, 3H), 3,20-3,15 (m, 4H). ^{13}C RMN (125 MHz, d_6-DMSO): δ162,46, 161,32, 161,00, 153,15, 145,25, 140,18, 138,92, 135,30, 128,30, 125,89, 122,76, 122,25, 121,98, 117,41, 117,06, 115,69, 113,19, 112,00, 106,96, 102,46, 72,11, 51,40, 41,06, 28,66. M.S. experimental $C_{24}H_{19}F_2N_3O_5S$: 500,14 $(M+H)^+$.

Ejemplo 11

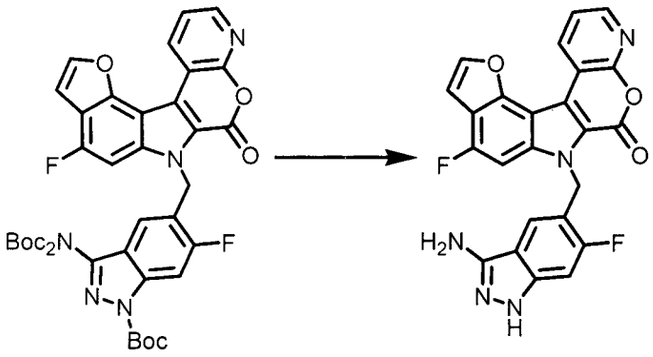
Preparación del Compuesto **80**

Paso A – Síntesis del Compuesto 80B



Una solución del Compuesto **80A** (294,2 mg, 0,99 mmol), carbonato de cesio (488,67 mg, 1,4998 mmol) en DMF (10 ml) se agitó a temperatura ambiente durante 12 horas, se concentró in vacuo. El residuo obtenido se disolvió en EtOAc (200 ml) se lavó con salmuera (100 ml), se secó ($MgSO_4$), se filtró, concentró in vacuo y se purificó mediante cromatografía flash (SiO_2, Acetona/Hexanos) para proporcionar el compuesto **80B** (490 mg; Rendimiento = 65%)

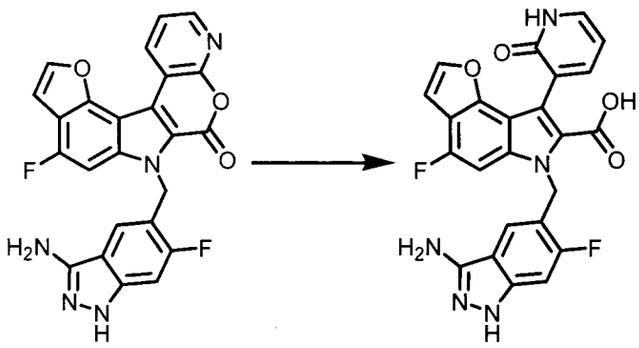
Paso B – Síntesis del Compuesto 80C



80B **80C**

Una solución de **80B** (490,00 mg, 0,646 mmol) en HCl (4 M en dioxano, 25 ml, Proveedor = Aldrich) se agitó a temperatura ambiente durante 4 h y se concentró in vacuo. El residuo obtenido se secó al vacío y se usó sin purificación adicional.

Paso C – Síntesis del Compuesto 80



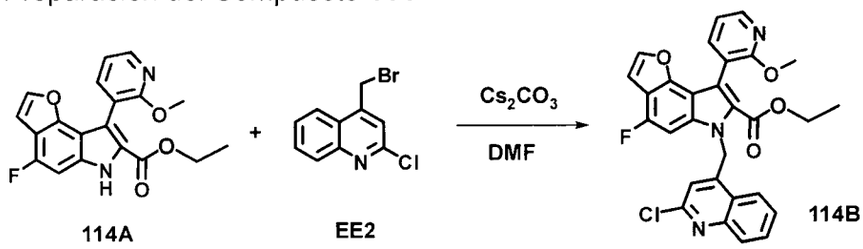
80C **80**

A una solución del Compuesto **80C** (100 mg, 0,219 mmol), en THF (4 ml) y agua (4 ml) se agregó hidróxido de litio monohidrato (64,2 mg, 1,53 mmol) y la reacción se agitó a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró *in vacuo* y el residuo resultante se purificó mediante HPLC (fase reversa) mediante las siguientes condiciones: Columna: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15µM, 300Å, 343K16006 (W): 30 ml/min de flujo; 10-100% aum THF, agua que contiene 0,01% de TFA; Aumento= 0--> 60 minutos, para proporcionar el compuesto **80** como un sólido

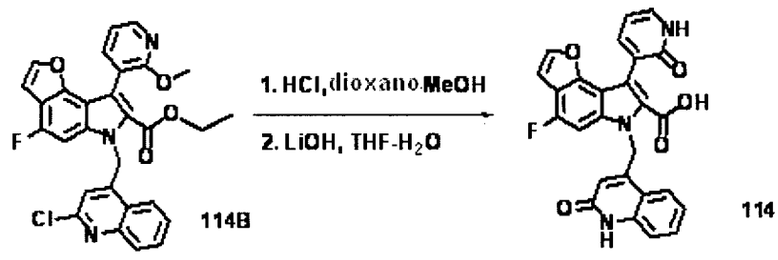
incoloro. ^{1}H RMN (D6-dmso, 400 MHz), δ 12,48 (s, 1 H), 11,74 (b, 2 H), 7,90 (d, 1 H, J = 2,4 Hz), 7,67 (dd, 1 H, J = 1,8 & 6,7 Hz), 7,42 (d, 1 H, J = 10,8 Hz), 7,42 (d, 1 H, J = 2,4 Hz), 7,01 (d, 1 H, J = 11,0 Hz), 6,33 (t, 1 H, J = 6,7 Hz), 5,90 (s, 2 H), 6,00-4,4 (b, 2 H).

Ejemplo 12

Preparación del Compuesto **114**



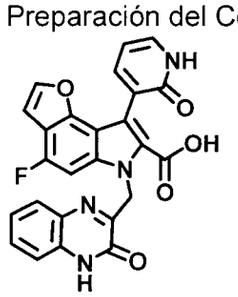
A una suspensión del Compuesto **114A** (200 mg, 0,564 mmol) y carbonato de cesio (600 mg, 1,85 mmol) en DMF (3 ml) se agregó el compuesto **EE2** (520 mg, ~50% de pureza, ~1 mmol) y la mezcla resultante se dejó agitar a temperatura ambiente durante aproximadamente 15 horas. La mezcla de reacción se diluyó con acetato de etilo (100 ml), luego se lavó con agua (3 x 40 ml), se secó con sulfato de sodio, y concentró in vacuo. El residuo obtenido se purificó mediante Combi-cromatografía flash (12 g de columna de sílice) con 0-25% de acetato de etilo en hexanos como eluyente para proporcionar el compuesto **114B** como un sólido blanco (210 mg, 70%).



Un recipiente a presión de 15 ml se cargó con una solución del Compuesto **114B** (210 mg, 0,40 mmol), HCl en dioxano (4M, 5 ml, 20 mmol) y metanol (2 ml) y la reacción resultante se calentó a 90°C y se dejó agitar a esta temperatura durante aproximadamente 15 horas. Después de enfriar a temperatura ambiente, la mezcla de reacción se concentró in vacuo. El residuo obtenido se suspendió con MeOH (~10 ml) y se concentró otra vez *in vacuo* para eliminar el exceso de HCl. El residuo resultante se lavó con metanol (3 x 3 ml) y se secó al vacío para proporcionar un sólido blanco (160 mg, 76%), que se diluyó con THF sólido (8 ml) y solución acuosa de LiOH (2,0 ml, 1,0 M, 2,0 mmol). La reacción resultante se calentó a reflujo y se dejó agitar a esta temperatura durante aproximadamente 7 horas, luego se enfrió a temperatura ambiente. La mezcla de reacción se neutralizó usando HCl (2,0 ml, 1,0 M, 2,0 mmol) y la suspensión resultante se concentró in vacuo. El residuo resultante se lavó con agua (2 x 20 ml) y metanol (3 ml), luego se secó al vacío para proporcionar el compuesto **114** como un sólido blanco (112 mg, 75%). M.S. experimental C26H17FN3O5: 470,3 $(M+H)^+$; ^{1}H RMN (500 MHz, CD3OD, sal de Na): δ 7,85 (1H, dd, J = 6,9, 2,2 Hz), 7,64-7,60 (2H, m), 7,44-7,37 (3H, m), 6,97 (1H, d, J = 10,4 Hz), 6,91 (1H, d, J = 2,2 Hz), 6,51-6,49 (1H, m), 6,34 (2H, s), 5,65 (1H, s).

Ejemplo 13

Preparación del Compuesto **117**



117

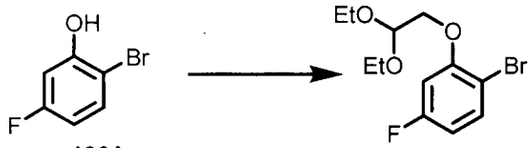
El compuesto **117** se sintetizó usando el método descripto anteriormente en el Ejemplo 12 y utilizando los compañeros de acoplamiento apropiados. M.S.

experimental C25H16FN4O5: 471,3 $(M+H)^+$; ^1H RMN (500 MHz, CD3OD, sal de Na):δ 7,94 (1H, d, J = 1,89 Hz), 7,69 (1H, dd, J = 6,94, 1,89Hz), 7,53-7,40 (4 H, m), 7,32 (1H, d, J = 8,2 Hz), 7,19 (1 H, t, J = 7,57 Hz), 7,09 (1H, d, J = 1,89 Hz), 6,38 (1H, t, J = 6,3 Hz), 5,97 (2H, s).

Ejemplo 14

Preparación del Compuesto **126**

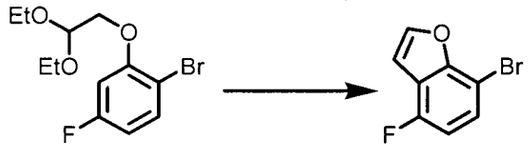
Paso A – Síntesis del Compuesto 126B



126A **126B**

Una solución del compuesto **126A**, (228,00 g, 1,19 mmol), carbonato de potasio (247,47 g, 1,79 mol) en DMF (3,00 L) se trató con 2-Bromo-1,1-dietoxietano (197,54 ml, 1,31 mol) y se calentó a 135°C durante 7 horas. La mezcla de reacción se concentró in vacuo y se extrajo con EtOAc (3x 2L). Las fases orgánicas combinadas se lavaron con NaOH acuoso (2M, 4 L). La fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo para proporcionar el compuesto **126B** (362,00 g, 98%) que se usó sin purificación adicional.

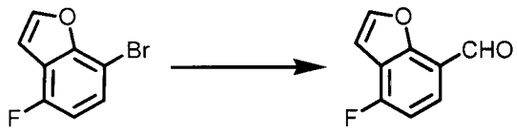
Paso B – Síntesis del Compuesto 126C



126B **126C**

Una solución del Compuesto **126B** (352,00 g, 1,15 mol) eb tolueno (2500 ml, 2,3 mol) se trató con ácido polifosfórico (370,00 g, 3,4 mol) y se calentó a reflujo durante 5 horas. La mezcla de reacción se concentró in vacuo se diluyó con agua (3L) y luego se extrajo con EtOAc (4 L). La fase orgánica se lavó con NaOH acuoso (2L), se filtró, concentró in vacuo y purificó por destilación a presión reducida para proporcionar el compuesto **126C** (125,00 g, 50,8%). Bp. 80°C (1mm/Hg) como un sólido incoloro que se solidificó a temperatura ambiente. ^1H RMN (400 MHz,$CDCl_3$) δ 7,67 (d, 1 H, J = 2,2 Hz), 7,39 (dd, 1 H J =5,1 & 3,7 Hz), 6,94 (d, 1 H, J = 2,2 Hz), 6,86 (t, 1 H, J = 8,8 Hz).

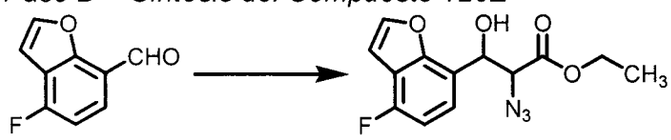
Paso C – Síntesis del Compuesto 126D



126C **126D**

Una solución del compuesto **126C** (124,12 g, 577,25 mmol) en éter (2,0 L) se enfrió a -78°C y se trató gota a gota con una solución de 2,5 M de n-butillitio en hexano (235,5 ml) y se dejó agitar a -78°C durante 15 minutos. A esta mezcla de reacción se agregó DMF (89,393 ml, 1,15 mol) y se dejó agitar a -78°C durante 30 minutos. La mezcla de reacción se inactivó con metanol (23,383 ml, 577,25 mmol) y se calentó a temperatura ambiente. La mezcla de reacción se diluyó con éter (300 ml) y la fase orgánica se lavó con agua (300 ml). la fase orgánica separada se secó ($MgSO_4$) se filtró, concentró in vacuo para proporcionar el compuesto **126D** (89,00 g, 93,9%).

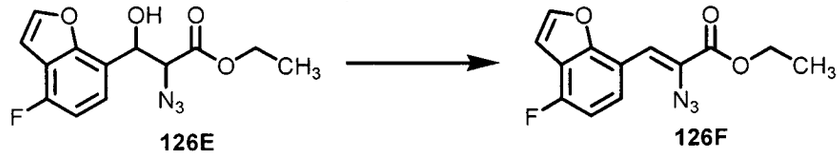
Paso D – Síntesis del Compuesto 126E



126D **126E**

A solución del Compuesto **126D** (12,71 g, 77,45 mmol), litio chloride (6,567 g, 154,9 mmol) y etilo azidoacetate (20,00 g, 154,9 mmol; added as a 30% solución in CH_2Cl_2), diazabiciclo[5,4,0]undec-7-ene (23,16 ml, 154,9 mmol) y stirred durante 2 horas. The compleción of the reacción seguido por TLC (EtOAc/Hexanos 1:4). Upon compleción, la mezcla de reacción se diluyó con acetato de etilo (1L) y se lavó con agua y HCl acuoso(400 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y concentraron in vacuo y el residuo obtenido se purificó mediante cromatografía flash SiO_2 (EtOAc/Hexanos) para proporcionar el compuesto **126E** (18,3 g, 80,6%) como un aceite incoloro.

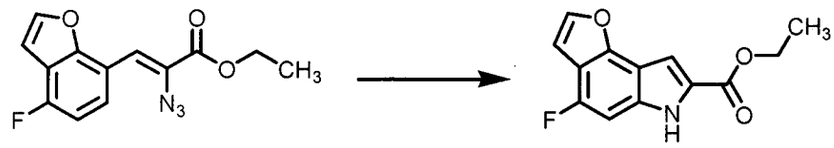
Paso E – Síntesis del Compuesto 126F



126E **126F**

A solución del Compuesto **126E** (15,7 g, 53,5 mmol) y metanosulfonil chloride (8,29 ml, 107 mmol) in cloruro de metileno (87,7 ml, 1,37 mmol) at -30°C was treated gota a gota con a solución of trietilamine (52,2 ml, 375,0 mmol) en cloruro de metileno (100 ml). La mezcla de reacción se dejó agitar a -30°C durante 3 horas, se diluyó con aqueous saturated sodium bicarbonate y cloruro de metileno (400 ml). La fase orgánica se separó y se lavó con agua, HCl acuoso y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo, y se purificó mediante cromatografía flash (SiO_2, 10% EtOAc in (1:1) Hexanos/CH_2Cl_2) para proporcionar el compuesto **126F** (12,6 g, 85,5%).

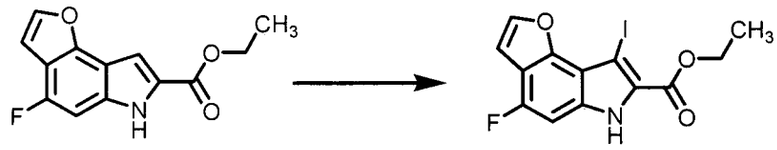
Paso F – Síntesis del Compuesto 126G



126F **126G**

Se calentaron 150 ml de xilenos a 165°C. A esta solución a ebullición se agregó gota a gota una solución del Compuesto **126F** (11,2 g, 40,7 mmol) en xilenos (70 ml, 189,4 mmol). La mezcla de reacción se agitó durante 20,0 minutos adicionales y se dejó enfriar a temperatura ambiente para dar el compuesto **126G** como un precipitado (7,00 g, 69,6%), que se filtró, se lavó con hexanos y se secó al vacío.

Paso G – Síntesis del Compuesto 126H



126G **126H**

A una solución del Compuesto **126G** (15,88 g, 64,23 mmol) en DMF (100 ml) se agregó N-yodosuccinimida (15,90 g, 70,66 mmol) y se dejó agitar a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con agua (1000 ml) y se extrajo en EtOAc (1000 ml). La fase orgánica se lavó con agua (1000 ml), tiosulfato de sodio acuoso (5% de solución acuosa, 1 L) y se secó ($MgSO_4$). La fase orgánica se secó ($MgSO_4$), se filtró, concentró in vacuo para proporcionar el compuesto **126H** (22,30 g, 93,04%) como un sólido.

Paso H – Síntesis del Compuesto 126I

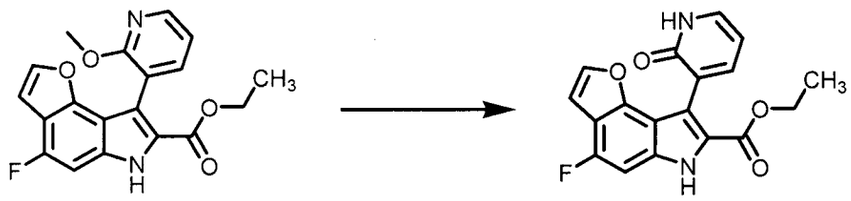


126H **126I**

Una solución del Compuesto **126H** (22,000 g, 58,962 mmol), ácido 2-metoxipiridin-3-ilborónico (13,527 g, 88,444 mmol), $(PPh_3)_2PdCl_2$ (4,13 g, 5,88 mmol) en 1,2-dimetoxietano (250,0 ml) se desgasificó durante 2 min y se dejó agitar a temperatura ambiente durante 15 minutos. La mezcla de reacción anaranjada se trató con una solución de carbonato de potasio (30,53 g, 220,9 mmol) en agua (250,0 ml) y se dejó agitar a 90°C durante 3 horas. La mezcla de reacción amarilla se volvió anaranjada oscura con la desaparición del material de partida (TLC). La mezcla de reacción se diluyó con EtOAc (1000 ml) y se lavó con NaOH acuoso (500 ml, 1M), se secó ($MgSO_4$), se filtró, concentró in vacuo y se purificó mediante cromatografía flash SiO_2 (THF/Hexanos 0--> 60%) para

proporcionar el compuesto **126I** (16,65 g, 79,7%) como un sólido marrón pálido.

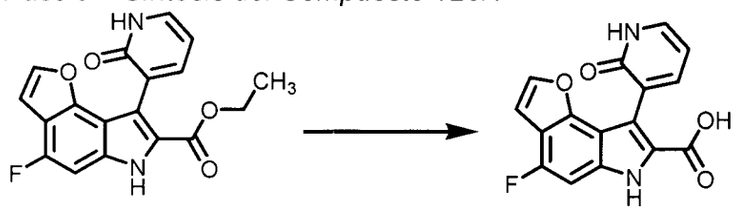
Paso I – Síntesis del Compuesto 126J



126I **126J**

Una solución del Compuesto **126I** (4,50 g, 12,7 mmol) en metanol (10 ml, 246,9 mmol) se trató con una solución de HCl 4 M en dioxano (100 ml) y se calentó a 90°C durante 3 horas en un tubo de presión. La mezcla de reacción se concentró in vacuo y el residuo obtenido se purificó mediante cromatografía flash (SiO_2, THF/Hexanos 0--> 100%) para proporcionar el compuesto **126J** como un sólido incoloro.

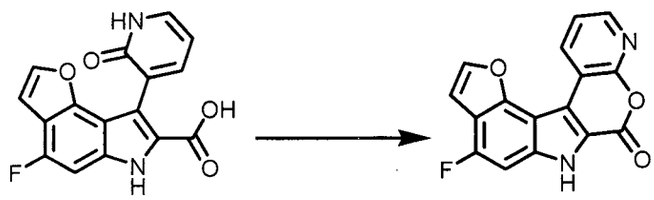
Paso J – Síntesis del Compuesto 126K



126J **126K**

Una solución del Compuesto **126J** (810,00 mg, 2,38 mmol) en agua (25ml), THF (25ml) y metanol (25ml, 780,2 mmol) se trató con hidróxido de litio monohidrato (499,41 mg, 11,901 mmol) y se calentó a 80°C durante 1 hora. La mezcla de reacción luego se acidificó mediante HCl 1N, se filtró y se secó in *vacuo* para proporcionar el compuesto **126K** (627,00 mg, 84,4%) como un sólido incoloro.

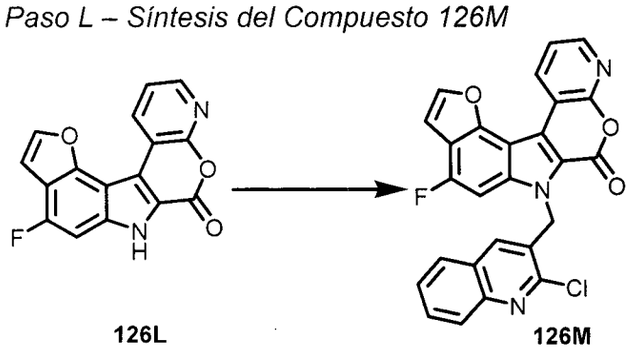
Paso K – Síntesis del Compuesto 126L



126K 126L

A una suspensión del Compuesto **126K** (8,00 g, 25,6 mmol) y clorhidrato de N-(3-dimetilaminopropil)-N'-etilcarbodiimida (9,82 g, 51,2 mmol) en DMF (153,85 ml) se agregó trietilamina (35,71 ml, 256,2 mmol) y la reacción se agitó toda la noche a temperatura ambiente. La mezcla de reacción se concentró in vacuo y el residuo resultante se diluyó con metanol (100 ml). El precipitado resultante se filtró y se secó para proporcionar el compuesto **126L** (5,90 g, 78,3%)

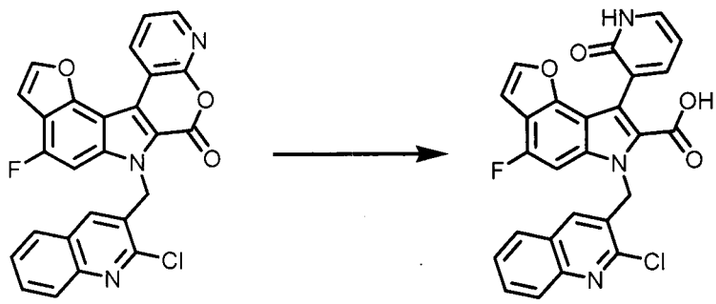
Paso L – Síntesis del Compuesto 126M



126L 126M

Una suspensión del Compuesto **126L** (300 mg, 1 mmol), carbonato de cesio (664,40 mg, 2,0392 mmol) y 2-cloro-3-(clorometil)quinolina (432,46 mg, 2,0392 mmol) en DMF (20 ml, 200 mmol) se dejó agitar a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró in vacuo y el residuo obtenido se agitó con metanol (20 ml). El precipitado resultante se filtró y secó para proporcionar el compuesto **126M** (410 mg, 80%)

Paso M – Síntesis del Compuesto 126

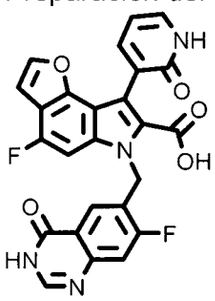


126M **126**

Una solución del Compuesto **126M** (130,00 mg, 0,27668 mmol) en agua (10 ml) y THF (10 ml) se trató con hidróxido de litio monohidrato (58,05 mg, 1,38 mmol) y la reacción se dejó agitar a temperatura ambiente durante 3 horas. La mezcla de reacción se inactivó con HCl acuoso(1M, 3 ml) y mixture se purificó por HPLC (fase reversa) mediante las siguientes condiciones: Columna: Waters: Delta Pk, P/No 11805, Wat 011805, 300x30 mm (L/ID) C18, 15 µM, 300 A, 343K16006 (W): flujo 30 ml/min; 30-70% aumento de acetonitrilo, agua; 0--> 40 minutos, para proporcionar el compuesto **126** (47,00 mg, 34,82%) como sólido incoloro.

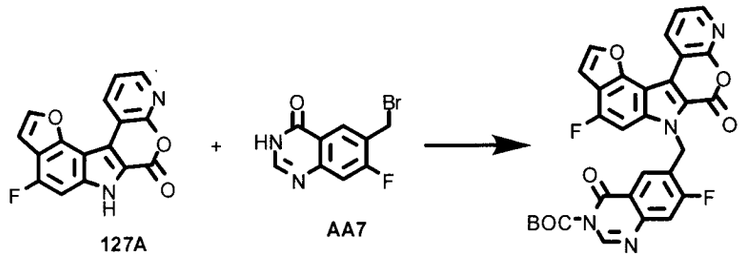
Ejemplo 15

Preparación del Compuesto **127**



127

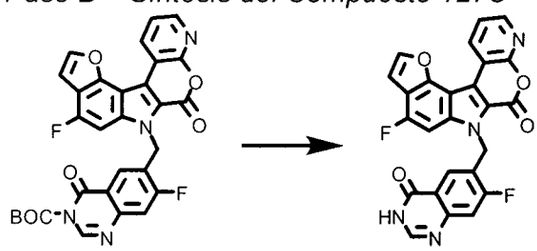
Paso A – Síntesis del Compuesto 127B



127A AA7 127B

A una solución del Compuesto **127A** (130 mg, 0,442) y el compuesto **AA7** (225 mg, < 0,5 mmol) en DMF (10 ml) se agregó carbonato de cesio (330 mg, 1,01 mmol). La reacción resultante se agitó a temperatura ambiente durante 18 horas, luego se diluyó con acetato de etilo (100 ml) y agua (100 ml). La fase orgánica se lavó con agua (2 x 60 ml), se secó (sulfato de magnesio), se filtró y concentró in vacuo para proporcionar el producto **127B** (160 mg, 63 %), que se purificó adicionalmente mediante HPLC en fase reversa en una columna Waters Sunfire C_{18} (10 μM, 50 x 250 mm) usando 20-100% de acetonitrilo/agua como eluyente. MS experimental $C_{30}H_{20}F_2N_4O_6$: 470,9 $(M+H-100)^+$.

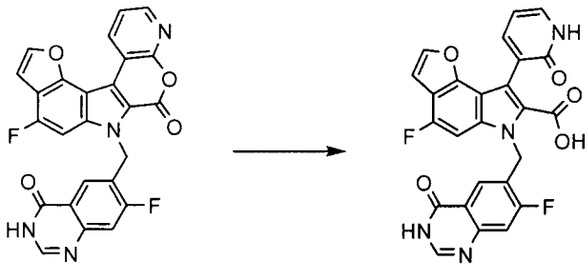
Paso B – Síntesis del Compuesto 127C



127B 127C

El compuesto **127B** (150 mg, 0,263 mmol) se disolvió en 4 M HCl in 1,4-dioxano (15 ml) y la mezcla de reacción se agitó durante 3 horas, luego concentró in vacuo para proporcionar el producto bruto compuesto **127C** (165 mg, cuant.), que se purificó adicionalmente mediante HPLC en fase reversa como se describió anteriormente. MS experimental $C_{25}H_{12}F_2N_4O_4$: 471,0 $(M+H)^+$.

Paso C – Síntesis del Compuesto 127

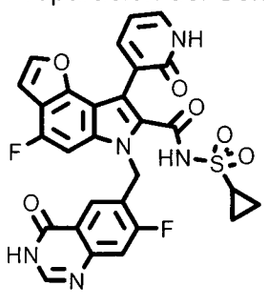


127C 127

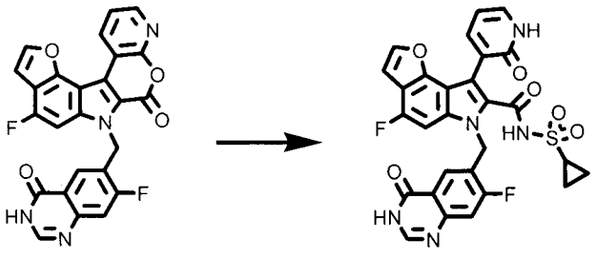
A una solución del producto bruto **127C** (100 mg, < 0,213 mmol, del Paso B anterior) en THF (10 ml) y agua (10 ml) se agregó solución acuosa de LiOH (3,0 ml, 3,0 mmol). La reacción se dejó agitar durante 30 minutos, luego la mezcla de reacción se acidificó usando una solución de HCl acuoso 1N (3,5 ml), y la solución ácida se extrajo con acetato de etilo (3 x 30 ml). Los extractos orgánicos combinados se secaron con sulfato de magnesio, se filtraron y concentraron in vacuo para proporcionar un residuo que se purificó mediante HPLC en fase reversa como se describió anteriormente en el Paso A para proporcionar el compuesto **127** (26 mg, 25 %). ^{1}H RMN (500 MHz, d_6-DMSO): δ 13,0 (bs, 1 H), 12,3 (bs, 1 H), 11,8 (bs, 1 H), 8,08 (s, 1 H), 7,96 (s, 1 H), 7,68-7,66 (m, 1 H), 7,53 (dd, J = 4,0, 11,0 Hz, 2 H), 7,42-7,41 (m, 2 H), 7,10 (s, 1 H), 6,34 (t, J = 6,8 Hz, 1 H), 6,01 (s, 2 H). MS experimental $C_{25}H_{14}F_2N_4O_5$: 489,0 $(M+H)^+$.

Ejemplo 16

Preparación del Compuesto **212**



212

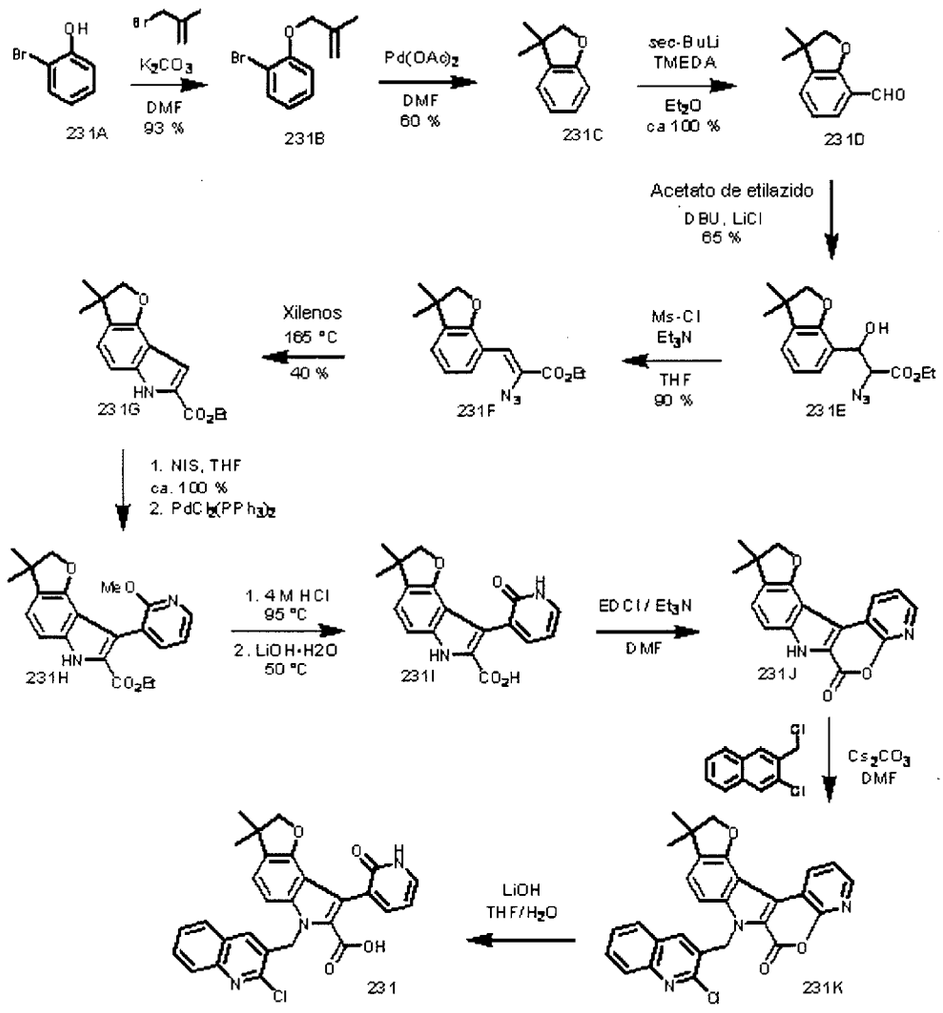


127C 212

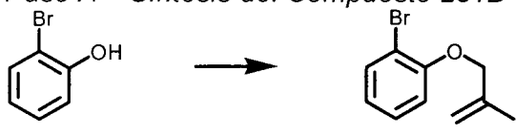
A una solución del compuesto **127C** (15,0 mg, 0,0318 mmol) in THF (10,0 ml) se agregaron sulfonamida ciclopropilsulfonamida (8,0 mg, 0,064 mmol) y NaH (4,0 mg, 0,16 mmol). La reacción resultante se dejó agitar a temperatura ambiente durante 3 horas, luego se diluyó con EtOAc (10 ml) y luna solución resultante se lavó con agua (10 ml). La fase orgánica se secó ($MgSO_4$), se filtró, y concentró in vacuo y el residuo resultante se purificó mediante HPLC en fase reversa como se describió anteriormente in Ejemplo 14, Paso A, para proporcionar el compuesto **212** como un sólido blanco (3,5 mg, 19 %). MS experimental $C_{28}H_{19}F_2N_5O_6S$: 592,3$(M+H)^+$.

Ejemplo 17

Preparación del Compuesto **231**



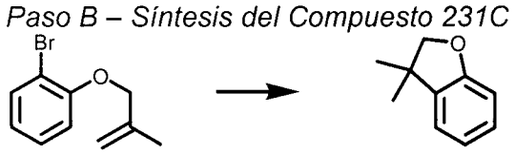
Paso A – Síntesis del Compuesto 231B



Una solución enfriada en hielo de 2-bromofenol (231,2 mmol, 40 g, 26,8 ml, d 1,492) en 460 ml de DMF se trató con 3-bromo-2-metilprop-1-eno (1,1 eq, 24,5 ml, d 1,339) seguido por la adición de carbonato de potasio (2,0 eq, 63,9 g) y yoduro de tetrabutilamonio (1,0 g). Se retiró el baño de enfriamiento y la mezcla de reacción se agitó hasta que todo el material de partida se haya consumido. Después de 6 h la mezcla se concentró a un tercio de su volumen en un evaporador rotatorio (bomba de alto vacío). La mezcla se diluyó con acetato de

etilo (2,0 L) y se lavó con agua (2 x 200 ml) y salmuera (200 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y concentró en un evaporador rotatorio para dar el producto bruto como un aceite ligeramente amarillo. El compuesto **231B** se purificó mediante destilación bulbo a bulbo en lotes de 10 g cada uno (130°C/1 mmHg) para dar el producto (49 g, 93 %) como un aceite incoloro. ^{1}H-RMN (400 MHz, en dmso-d6):δ7,57 (1H, dd, J = 1,83, 7,93 Hz), 7,32 (1H, ddd, J = 1,83, 7,32, 7,93 Hz), 7,10 (1H, dd, J = 1,22, 7,93 Hz), 6,88 (1H, ddd, J = 1,22, 7,32, 7,93 Hz), 5,12 (1H, s), 4,97 (1H, s), 4,55 (2H, s), 1,79 (3H, s); ^{13}C-RMN (125 MHz, en dmso-d6):δ 159,2, 140,3, 132,8, 128,7, 121,9, 113,8, 112,2, 110,9, 71,4, 18,9 ppm.

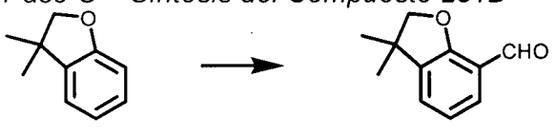
Paso B – Síntesis del Compuesto 231C



Una solución de 1-bromo-2-(2-metilo-aliloxi)-benceno (13,8 g, 60,76 mmol) in 140 ml de DMF (0,1 g / ml) se trató con acetato de sodio (2,5 eq, 12,46 g), formiato de sodio (1,2 eq, 4,95 g) y hidrato del cloruro de tetraetilamonio (1,2 eq, 72,91 mmol [183,72] 13,4 g) y 25 gotas de agua. La mezcla se desgasificó (vacío/lavado de argón) y se agregó acetato de paladio(II) (5% en moles, 682 mg). La mezcla se calentó a 90°C y el flujo de la reacción seguido por TLC (10 % acetato de etilo en hexanos). Después de 3 h la mezcla se enfrió a temperatura ambiente y se diluyó con éter (500 ml). Los sólidos se eliminaron por filtración y el filtrado se lavó con agua (2 x 80 ml) y salmuera (80 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró en evaporador rotatorio. El residuo ligeramente amarillo se adsorbió en gel de sílice y se purificó en una columna de gel de sílice Biotage 65-M. La columna se eluyó con hexanos (200 ml) y un gradiente de 0 a 10 % acetato de etilo en hexanos. El producto **231B** (5,3 g, 60 %) se obtuvo obtenido como un aceite incoloro. ^{1}H-RMN (400 MHz, in

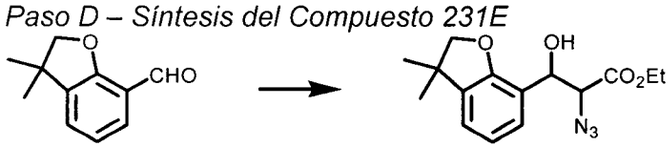
$CDCl_3$):δ 7,13 (1H, m), 7,11 (1H, d, J = 7,32 Hz), 6,89 (1H, ddd, J = 1,22, 7,32, 7,33 Hz), 6,80 (1H, d, J = 7,93 Hz), 4,23 (2H, s), 1,35 (6H, s); ^{13}C-RMN (125 MHz, en $CDCl_3$):δ 159,1, 136,5, 127,9, 122,2, 120,5, 109,6, 84,4, 41,9, 27,5 ppm.

Paso C – Síntesis del Compuesto 231D



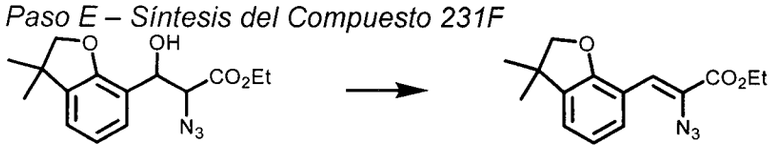
Se agregó gota a gota sec-butillitio (1,2 eq, 36,43 ml de una solución 1,4 M en ciclohexano) a una solución enfriada (-78°C) de TMEDA (1,3 eq, 7,63 ml, d 0,775) in 100 ml de éter seco. Después de 5 min, se agregó gota a gota una solución de 3,3-dimetil-2,3-dihidro-benzofurano (6,3 g, 42,51 mmol) en éter (100 ml). La solución amarilla resultante se agitó a -78°C durante 10 min y a 0°C durante 30 min. La solución ligeramente amarillo se enfrió otra vez a -78°C seguido por la adición de DMF (2,5 eq, 8,19 ml, d 0,948). La mezcla se agitó durante 10 min y luego se calentó a 0°C y se agitó por 30 min adicionales. La reacción se inactivó por la adición de HCl 1M acuoso (1 ml). La mezcla se diluyó con 1:1 éter/hexanos (400 ml) y se lavó con HCl acuoso 1M (3 x 80 ml) y salmuera (80 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró en evaporador rotatorio para proporcionar el compuesto **231C** (ca. 100 %, 7,49 g) como un aceite ligeramente amarillo, que se usó sin purificación adicional. ^{1}H-RMN (400 MHz, en $CDCl_3$):δ10,20 (1H, s), 7,59 (1H, dd, J = 1,22, 7,32 Hz), 7,31 (1H, dd, J = 1,22, 7,32 Hz), 6,97 (1H, dd, J = 7,32, 7,32 Hz), 4,40 (2H, s), 1,37 (6H, s); ^{13}C-RMN (125 MHz, en $CDCl_3$):δ 188,9, 161,3, 139,0, 128,4, 127,6, 120,9, 120,0, 85,9, 41,2, 27,6 ppm. LR-MS (ESI): calculado para $C_{11}H_{13}O_2$ $[M+H]^+$ 177,09, experimental 176,99.

Paso D – Síntesis del Compuesto 231E



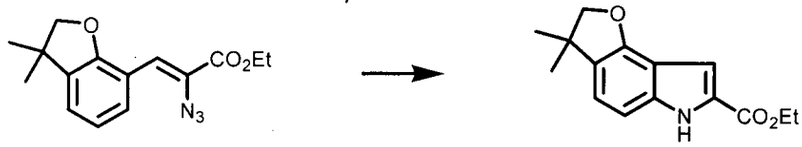
Una solución de 3,3-dimetil-2,3-dihidro-benzofuran-7-carbaldehído (13,6 g; 77,45 mmol) en 380 ml de THF seco se enfrió a 0°C y se trató con cloruro de litio (2,0 eq, 6,56 g). La mezcla se agitó vigorosamente durante 3 min seguido por la adición de una solución de acetato de etilazido (2,0 eq, 80,0 ml de una solución 25% en tolueno). Una solución de DBU (2,0 eq, 23,1 ml, d 1,018) en 38 ml de THF seco se agregó gota a gota. Después de la finalización de la adición la mezcla de reacción se agitó durante 4 h adicionales hasta el punto en que la TLC (20% acetato de etilo en hexanos) demostró consumo casi completo del material de partida. La mezcla de reacción se diluyó con acetato de etilo (1,0 L) y se lavó con 0,5 M de HCl acuoso (3 x 200 ml) y salmuera (100 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró en evaporador rotatorio. El residuo se purificó en una columna de gel de sílice (8 x 18 cm). La columna se eluyó con 4 L de un gradiente de 5 a 20% de acetato de etilo en hexanos para proporcionar el compuesto **231E** (15,4 g; 65 %) como un aceite amarillo pálido. ^{1}H-RMN (400 MHz, en $CDCl_3$, indicado como mezcla diastereomérica mixture) δ 7,19 (0,7H, d, J = 7,93 Hz), 7,12 (0,3H, d, J = 7,32 Hz), 7,09 (1H, m), 6,93 (0,7H, t, J = 7,32 Hz), 6,91 (0,3H, t, J = 7,32 Hz), 5,31 (0,7H, dd, J = 4,27, 7,32 Hz), 5,07 (0,3H, dd, J = 7,32, 7,32 Hz), 4,34 – 4,20 (5H, m), 3,30 (0,3H, d, J = 7,32 Hz), 3,02 (0,7H, d, J = 7,32 Hz), 1,34 (6H, s), 1,26 (3H, t, J = 7,32 Hz); ^{13}C-RMN (125 MHz, in $CDCl_3$, diastereómero mayor):δ 168,7, 155,7, 136,9, 125,7, 122,3, 121,2, 121,1, 85,0, 71,8, 66,1, 62,0, 41,8, 27,4, 14,1 ppm; ^{13}C-RMN (125 MHz, en $CDCl_3$, diastereómero menor):δ 168,9, 156,2, 137,1, 126,4, 122,6, 121,1, 120,8, 85,0, 72,1, 65,3, 61,9, 41,7, 27,5, 14,0 ppm.

Paso E – Síntesis del Compuesto 231F



Una solución de etil éster del ácido 2-azido-3-(3,3-dimetil-2,3-dihidro-benzofuran-7-il)-3-hidroxi-propiónico (18,2 g; 59,61 mmol) en 60 ml de diclorometano seco se enfrió a -30°C y se trató con cloruro de metansulfonilo (2,0 eq, 9,22 ml, d 1,480). Una solución de trietilamina (7,0 eq, 58,1 ml, d 0,726) en 30 ml de diclorometano seco se agregó gota a gota durante 30 min (la temperatura interna se mantuvo entre -40 -30°C). La suspensión resultante se agitó durante 2 h hasta el punto en que la TLC (20% acetato de etilo en hexanos) demostró consumo casi completo del material de partida. La mezcla se diluyó con acetato de etilo (1,5 L) y se lavó con HCl acuoso 0,5 M (2 x 200 ml) y salmuera (100 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró en evaporador rotatorio. El residuo se adsorbió en gel de sílice y se purificó en una columna de gel de sílice (9 x 17 cm). La columna se eluyó con 5 L de 2 % THF en hexanos que contienen 200 ml de DCM para proporcionar el compuesto **231F** (15,25 g; 90 %) como un sólido ligeramente amarillo. ^{1}H-RMN (400 MHz, in $CDCl_3$):δ 8,04 (1H, d, J = 7,93 Hz), 7,18 (1H, s), 7,07 (1H, dd, J = 1,22, 7,32 Hz), 6,92 (1H, dd, J = 7,32, 7,93 Hz), 4,36 (2H, q, J = 7,32 Hz), 4,28 (2H, s), 1,39 (3H, t, J = 7,32 Hz), 1,34 (6H, s); ^{13}C-RMN (125 MHz, in $CDCl_3$): δ 163,6, 158,2, 136,5, 128,2, 125,3, 123,6, 120,7, 118,5, 116,4, 84,7, 62,1, 42,1, 27,5, 14,2 ppm.

Paso F – Síntesis del Compuesto 231G

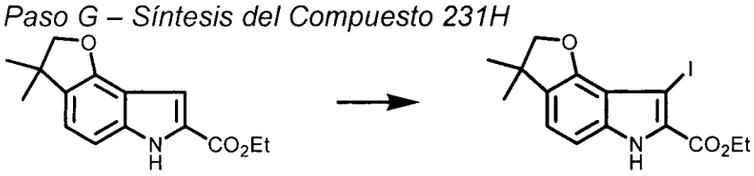


Una solución de etil éster del ácido 2-azido-3-(3,3-dimetil-2,3-dihidro-benzofuran-7-il)acrílico (15,25 g; 53,07 mmol) en 70 ml de xilenos se agregó gota a gota (durante 30 min) agitado xilenos (30 ml) precalentados a 165°C. Después de la finalización de la adición, la mezcla se agitó durante 10 minutos adicionales y luego se enfrió a temperatura ambiente. La mezcla se mantuvo en el congelador-30°C) toda la noche. No se formaron cristales y la mezcla se

concentró en un evaporador rotatorio. El residuo se purificó en una columna de gel de sílice Biotage 65-M. La elución de la columna con 5% de THF en hexanos dio el producto en fracciones que contienen otras impurezas. La concentración de estas fracciones en el evaporador rotatorio proporcionaron el compuesto **231G**, que precipitó como un sólido blanco (4,0 g; 30%). El agua madre se concentró otra vez para dar una segundo lote del producto (1,0 g, 7 %).

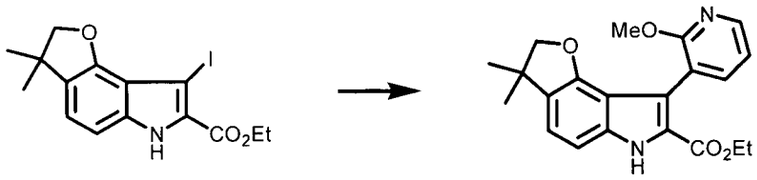
^{1}H-RMN (400 MHz, en dmso-d6):δ11,84 (1H, s), 7,08 (1H, d, J = 8,54 Hz), 6,96 (1H, d, J = 8,54 Hz), 6,95 (1H, s), 4,32 (2H, s), 4,31 (2H, q, J = 7,32 Hz), 1,32 (3H, t, J = 7,32 Hz), 1,29 (6H, s); ^{13}C-RMN (125 MHz, en dmso-d6):δ161,0, 151,4, 138,9, 127,0, 124,5, 119,2, 113,0, 104,6, 103,4, 84,6, 60,3, 41,5, 27,7, 14,2 ppm. LR-MS (ESI): calculado para $C_{15}H_{18}NO_3$ $[M+H]^+$ 260,13, experimental 260,02

Paso G – Síntesis del Compuesto 231H



Una solución de etil éster del ácido 3,3-dimetil-3,6-dihidro-2H-1-oxa-6-aza-indaceno-7-carboxílico (5,0 g, 19,28 mmol) en THF (200 ml) se enfrió a -78°C y se trató con una solución de N-yodosuccinimida (1,1 eq, 4,77 g) in 50 ml de THF. La mezcla se agitó durante 45 min y luego se inactivó por la adición de bicarbonato de sodio acuoso saturado (100 ml). El producto se tomó en acetato de etilo (500 ml) y se lavó con bicarbonato de sodio acuoso saturado (100 ml) y salmuera (80 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y concentró in vacuo para proporcionar el compuesto **231H** (ca. 100 %, 7,42 g)como un sólido marrón oscuro que se usó sin purificación adicional. LR-MS (ESI): calculado para $C_{15}H_{17}INO_3$ $[M+H]^+$ 386,03, experimental 385,86

Paso H – Síntesis del Compuesto 231I

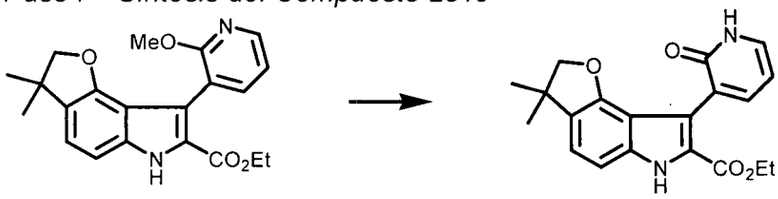


Una solución de etil éster del ácido 8-yodo-3,3-dimetil-3,6-dihidro-2H-1-oxa-6-aza-indaceno-7-carboxílico (7,42 g; 19,28 mmol) en 200 ml de 1,2-dimetoxietano se trató con ácido 2-metoxipiridin-3-borónico (2,0 eq, 5,89 g) y cloruro de bis(trifenilfosfino)paladio (II) (0,1 eq, 1,34 g). La mezcla se agitó durante 10 min seguido por la adición de carbonato de potasio acuoso (4,0 eq, 38,5 ml de solución 2 M). La mezcla se agitó a 90°C y el flujo de la reacción seguido por TLC (30% THF en hexanos). Después de 2 h la mezcla se diluyó con acetato de etilo (700 ml) y se lavó con bicarbonato de sodio acuoso saturado (2 x 100 ml) y salmuera (100 ml). La fase orgánica se secó con sulfato de magnesio, se filtró y se concentró en evaporador rotatorio. El residuo se adsorbió en gel de sílice y purificó en una columna en gel de sílice Biotage 65-M. La elución de la columna con 5 a 20% de THF en hexanos/DCM (9:1)5% dio el producto en fracciones que contenía varias impurezas.

Una muestra (1,0 g, 2,73 mmol) se disolvió en 10 ml de DMF y se purificó en una columna preparativa en fase reversan (Columna: YMC, C18-fase reversa, 120A; 500 x 50 mm I.D); caudal de flujo = 100 ml/min; Gradiente: 20% de solvente B durante 10 min luego aumenta a 90% durante 50 min y permanece durante 5 min (solvente A: agua con 0,01% v/v TFA; solvente B: THF). Se realizaron tres inyecciones y se recolectaron tres fracciones de cada inyección. La fracción A (340 mg) dio 11% de producto puro. La fracción B (850 mg) dio 29% del Compuesto **231l** con pequeña cantidad de impurezas; la fracción C (520 mg) dio 18% de producto C7-metoxipiridilo (regioisomérico). ^{1}H-RMN (400 MHz, en dmso-d6):δ11,86 (1H, s), 8,11 (1H, dd, J = 1,83, 4,88 Hz), 7,64 (1H, dd, J = 1,83, 7,32 Hz), 7,08 (1H, d, J = 7,93 Hz), 6,99 (1H, d, J = 7,93 Hz), 6,98 (1H, dd, J = 4,88, 7,32 Hz), 4,15 (2H, s), 4,11 (2H, q, J = 7,32 Hz), 3,74 (3H, s), 1,25 (6H, s), 1,05

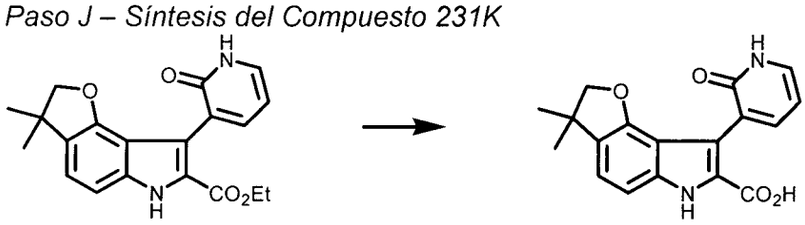
(3H, t, J = 7,32 Hz); ^{13}C-RMN (125 MHz, en dmso-d6):δ161,1, 161,0, 152,0, 145,0, 140,3, 137,7, 125,1, 123,7, 119,2, 118,0, 115,9, 114,4, 113,4, 104,4, 84,5, 59,9, 52,7, 41,0, 27,6, 13,7 ppm. LR-MS (ESI): calculado para $C_{21}H_{23}N_2O_4$ $[M+H]^+$ 367,17, experimental 367,05

Paso I – Síntesis del Compuesto 231J



El etil éster del ácido 8-(2-metoxi-piridin-3-il)-3,3-dimetil-3,6-dihidro-2H-1-oxa-6-aza-indaceno-7-carboxílico (840 mg, 2,292 mmol) se disolvió en una solución de HCl 4M en dioxano (20 ml) y metanol (5 ml). La solución homogénea se calentó en un tubo sellado (95°C) hasta que se consumió todo el material de partida. Después de 3 h, la mezcla se concentró a sequedad en un evaporador rotatorio para proporcionar el compuesto **231J** (ca 100 %, 807 mg) como un sólido ligeramente amarillo que se secó a alto vacío y se usó sin purificación adicional.

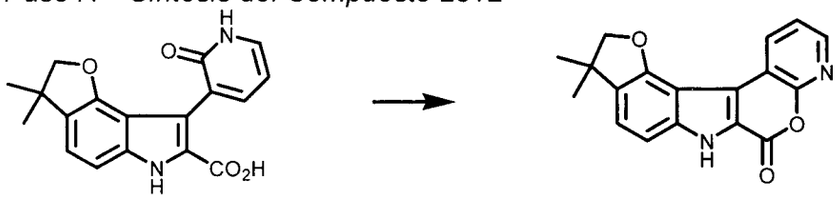
Paso J – Síntesis del Compuesto 231K



El etil éster del ácido 3,3-dimetil-8-(2-oxo-1,2-dihidro-piridin-3-il)-3,6-dihidro-2H-1-oxa-6-aza-indaceno-7-carboxílico (2,292 mmol) se disolvió en 20 ml de 2:1 THF/MeOH y agua se agregó (2 ml). Una solución resultante se trató con hidróxido de litio monohidrato (5,0 eq, 480 mg) y se calentó a 50°C durante 3 horas. La TLC (50 % THF in diclorometano) mostró consumo completo del material de partida. La mezcla se trató con 15 ml de HCl acuoso 1M y se eliminaron los volátiles en un evaporador rotatorio para dar una suispension

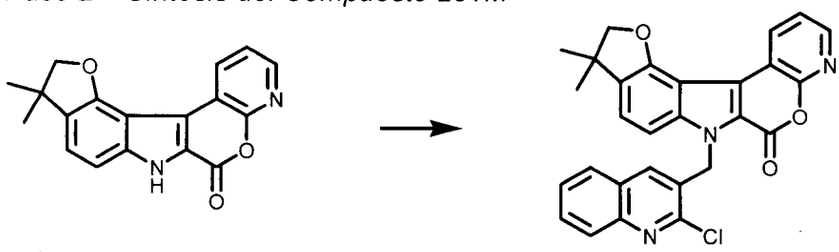
espesa que se diluyó con HCl acuoso 1M (15 ml). Los sólidos se recuperaron por filtración (whatman #1) para proporcionar el compuesto **231K** (480 mg, 67 %) como un sólido verde pálido. El producto contiene impurezas pero no se realizó purificación adicional.

Paso K – Síntesis del Compuesto 231L



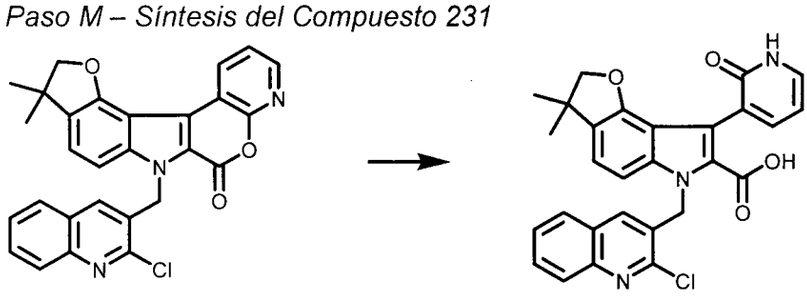
El etil éster del ácido 3,3-dimetil-8-(2-oxo-1,2-dihidro-piridin-3-il)-3,6-dihidro-2H-1-oxa-6-aza-indaceno-7-carboxílico (480 mg, 1,480 mmol) se suspendió en 15 ml de DMF seco y se trató con EDCI (2,0 eq, 567 mg) y trietilamina (10 eq, 2,08 ml, d 0,720). La mezcla se agitó toda la noche a temperatura ambiente. Se eliminaron todos los productos volátiles en un evaporador rotatorio (bomba de alto vacío) y el residuo se trató con 2:1 acetato de etilo/THF (60 ml) y se lavó con HCl acuoso 1M (3 x 10 ml) y salmuera (10 ml). La fase orgánica se separó toda la noche y se formó un precipitado blanco. Este se recuperó por filtración (50 mg; descarte) y el filtrado se concentró a un tercio de su volumen y separó durante 2 horas. Se formó un precipitado y se recuperó por filtración (145 mg) para proporcionar el compuesto **231L** como un sólido blanco. El filtrado se concentró a casi total sequedad y separó durante 1 hora. Se formó una segunda cosecha del producto y se recuperó por filtración (170 mg) para un rendimiento combinado de 73%. ^{1}H-RMN (400 MHz, en dmso-d6):δ 12,83 (1H, s), 9,21 (1H, dd, J = 1,83, 7,93 Hz), 8,39 (1H, dd, J = 1,83, 4,88 Hz), 7,55 (1H, dd, J = 4,88, 7,93 Hz), 7,40 (1H, d, J = 8,54 Hz), 7,16 (1H, d, J = 8,54 Hz), 4,56 (2H, s), 1,39 (6H, s); LR-MS (ESI): calculado para $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307,11, experimental 306,95

Paso L – Síntesis del Compuesto 231M



La lactona (145 mg; 0,473 mmol) se suspendió en 2,5 ml de DMF y se trató con 2-cloro-3-clorometil-quinolina (1,20 eq, 120 mg) y carbonato de cesio (2,0 eq, 308 g). La mezcla de reacción se agitó a temperatua ambiente durante 6 horas. La TLC (40 % THF in hexanos) mostró consumo completo del material de partida. La suspensión se filtró mediante un filtro de papel (whatman #1) y los sólidos se lavaron con diclorometano (20 ml), agua (2 x 20 ml) y éter (2 x 20 ml) para proporcionar el compuesto **231M** (ca. 100 %, 227 mg) como un sólido blanco que se usó sin purificación adicional. ^{1}H-RMN (400 MHz, en dmso-d6):δ9,35 (1H, dd, J = 1,83, 7,93 Hz), 8,44 (1H, dd, J = 1,83, 4,88 Hz), 7,96 (1H, m), 7,76 (2H, m), 7,60 (1H, dd, J = 4,88, 7,93 Hz), 7,53 (1H, d, J = 7,32 Hz), 7,44 (1H, d, J = 8,54 Hz), 7,25 (1H, d, J = 8,54 Hz), 6,08 (2H, s), 4,63 (2H, s), 1,40 (6H, s); LR-MS (ESI): calculado para $C_{28}H_{21}ClN_3O_3$ $[M+H]^+$ 482,13, experimental 481,99

Paso M – Síntesis del Compuesto 231

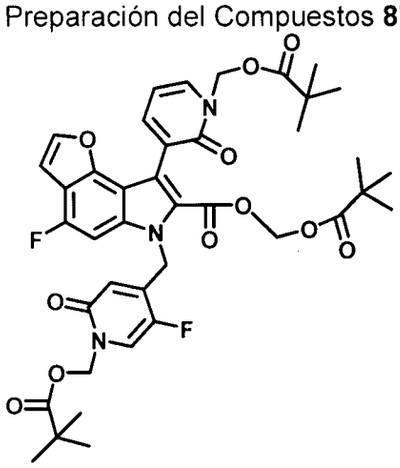


La lactona (40 mg; 0,100 mmol) se suspendió en 5 ml de una mezcla 2:1 de THF/agua y se trató con hidróxido de litio monohidrato (5,0 eq, 99 mg). La mezcla se agitó a temperatura ambiente. La TLC (40 % THF in hexanos) mostró consumo completo del material de partida después de 1 hora. La reacción se inactivó por adición de HCl acuoso 1M (3 ml) y el THF se eliminó en un evaporador rotatorio. El producto precipitó como un sólido blanco y la mezcla se disolvió en DMF (10 ml) y se purificó en HPLC preparativa (reversa C-18) para dar el producto (60 mg, 25 %) como un sólido blanco. El RMN mostró algunas impurezas de cloroquinolina y el compuesto se trató con 10 ml de éter. La mezcla se filtró para proporcionar el compuesto **231** (35 mg) como un sólido blanco. ^{1}H-

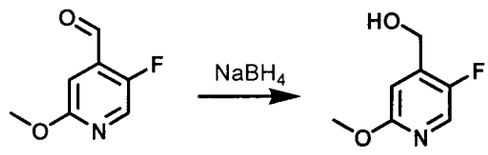
RMN (400 MHz, en dmso-d6):δ 12,90 (1H, ancho, s), 11,68 (1H, broad s), 7,98 (1H, d, J = 8,54 Hz), 7,82 (1H, d, J = 7,93 Hz), 7,78 (1H, dd, J = 7,32, 7,32 Hz), 7,58 (2H, m), 7,37 (1H, d, J = 4,88 Hz), 7,32 (1H, s), 7,13 (1H, d, J = 8,54 Hz), 7,03 (1H, d, J = 8,54 Hz), 6,31 (1H, dd, J = 6,71, 6,71 Hz), 5,90 (2H, s), 4,27 (2H, s), 1,29 (6H, s); LR-MS (ESI): calculado para $C_{28}H_{23}ClN_3O_4$ $[M+H]^+$ 500,14, experimental 499,95.

Ejemplo 18

Preparación del Compuestos **87** y **228**



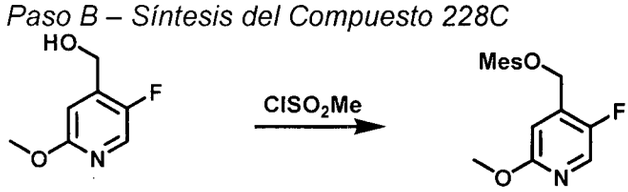
Paso A – Síntesis del Compuesto 228B



228A **228B**

A una solución de 5-Fluoro-2-metoxi-piridine-4-carbaldehído (0,3 g, 1,94 mmol) en etanol (5 ml) se agregó borohidruro de sodio (0,037mg, 0,97 mmol) y la reacción se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró in vacuo. La mezcla de reacción se extrajo con EtOAc (50 ml), se lavó con salmuera, se secó (Na_2SO_4), se filtró, y concentró in vacuo para proporcionar el compuesto **228B** y se usó como tal en el próximo paso.

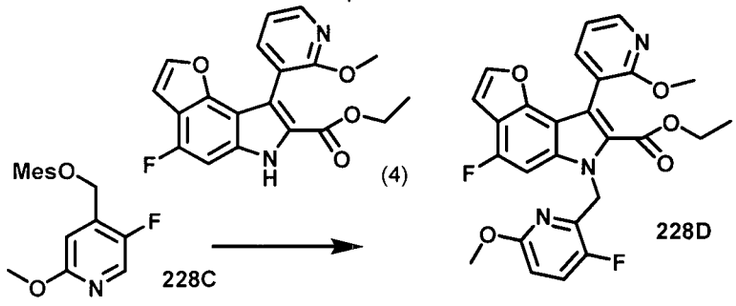
Paso B – Síntesis del Compuesto 228C



228B **228C**

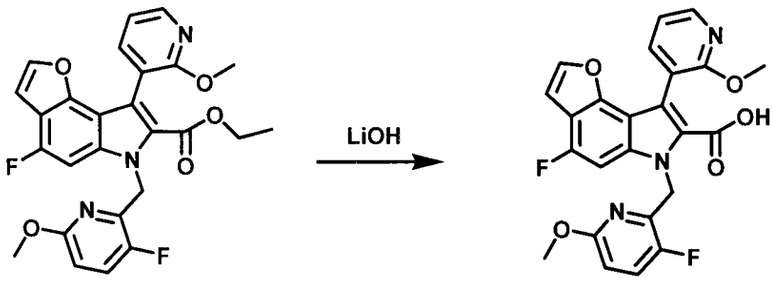
A una solución de (5-Fluoro-2-metoxi-piridin-4-il)-metanol en 5 ml de THF y 1,0 ml TEA se agregó en gotas una solución de 0,45 ml de cloruro de metansulfonilo en 5 ml de THF y la reacción se dejó agitar a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró in vacuo. La mezcla de reacción se extrajo con EtOAc (50 ml), se lavó con salmuera, se secó (Na_2SO_4), se filtró, y concentró in vacuo para proporcionar el compuesto **228C** y se usó como tal en el próximo paso.

Paso C – Síntesis del Compuesto 228D



A una solución del Compuesto (4) (0,687g, 1,94 mmol) en DMF (10 ml) se agregó carbonato de cesio (0,632g, 1,94 mmol) y el compuesto (3) y la reacción resultante se dejó agitar a temperatura ambiente durante 24 hora. La mezcla de reacción se diluyó con EtOAc y se lavó con agua, salmuera. Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y concentraron in vacuo para proporcionar el compuesto **228D** 0,80 g y se usó como tal en el próximo paso.

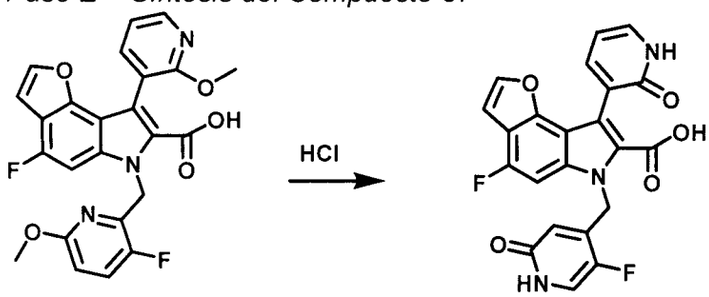
Paso D – Síntesis del Compuesto 228E



228D **228E**

A una solución del Compuesto **228D** agua/THF (15 ml de cada uno) se agregó hidróxido de litio (0,288 g 12 mmol) y la reacción resultante se dejó agitar a 65 ^{0}C toda la noche. La mezcla de reacción se diluyó con HCl acuoso y se extrajo en acetato de etilo. Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron, concentraron in vacuo para proporcionar 0,755 g del producto **228E.**

Paso E – Síntesis del Compuesto 87



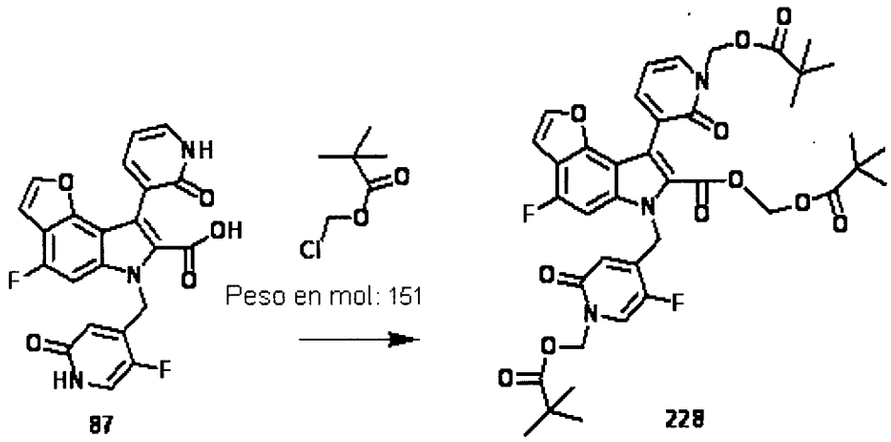
228E **87**

El compuesto **228E** (450 mg, 0,97 mmol) se disolvió en 5 ml de dioxano y 5 ml de HCl 4N en un tubo de presión y la mezcla de reacción resultante se calentó a 90 °C y se dejó estacionar a esta temperatura durante 4 horas. La mezcla de reacción se enfrió a temperatura ambiente, luego se concentró in vacuo para proporcionar un producto bruto que se purificó mediante HPLC preparativa para proporcionar el compuesto **87** (150 mg, 37 %).

M.S. experimental: 438,2 $(M+H)^+$; ^{1}H RMN (500 MHz, DMSO): δ7,97 (d, J = 2,2 Hz, 1H), 7,73 (m, 1H), 7,69 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,54 (d, J = 11,0 Hz,

1H), 7,43 (m, 1H), 7,11 (d, J = 2,2 Hz, 1H), 6,34 (t, J = 6,6 Hz, 1H), 5,85 (s, 2H), 5,27 (s, 1H).

Paso F – Síntesis del Compuesto 228

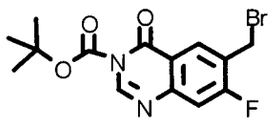


87 228

A una solución del Compuesto **87** (0,06 g, 0,14 mmol) en DMF (5 ml) se agregó carbonato de cesio (0,091g, 0,28 mmol) y clorometil éster del ácido 2,2-dimetil-propiónico (0,042 g, 0,28 mmol) y la reacción resultante se dejó agitar a 40 ^{0}C durante 24 hora. La mezcla de reacción se diluyó con EtOAc y se lavó con agua, luego salmuera. Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y concentraron in vacuo para proporcionar el compuesto **228** (0,003 g). M.S. experimental: 780,4 $(M+H)^+$; ^{1}H RMN (500 MHz, $CDCl_3$): δ7,69 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,63 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,56 - 7.52 (m, 2H), 6.91 (d, J = 2.2 Hz, 1H), 6,83 (d, J = 9,8 Hz, 1H), 6.37 (t, J = 6,9 Hz, 1H), 6,01 (m, 2H), 5,81-5,77 (m, 4H), 5,75 (s, 2H), 5,70 (m, 1H), 1,26-1,22 (m, 18H), 1,16 (s, 9H).

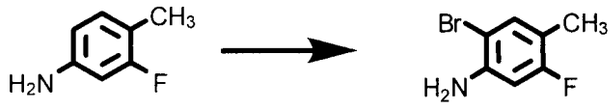
Ejemplo 19

Preparación del intermediario del compuesto **AA7**



AA7

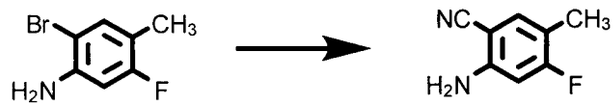
Paso A – Síntesis del Compuesto AA2



AA1 **AA2**

Una mezcla del Compuesto **AA1** (6,00 g, 47,9 mmol) y carbonato de potasio anhidro (6,70 g, 48,5 mmol) en diclorometano anhidro (130 ml) se enfrió a -15 °C en un baño de hielo y sal y luego se agregó gota a gota a una solución de bromo (7,70 g, 48,2 mmol) en diclorometano anhidro (80 ml). Después de finalizar la adición, la reacción se dejó agitar a -15 °C durante 1 hora. Se agregó agua con hielo (100 ml) a la mezcla de reacción y la fase acuosa se extrajo con diclorometano (2 x 100 ml). Las fases orgánicas combinadas se secaron con $MgSO_4$ y concentró in vacuo para proporcionar el compuesto **AA2** (11,0 g, quant.), que se usó sin purificación adicional.

Paso B – Síntesis del Compuesto AA3

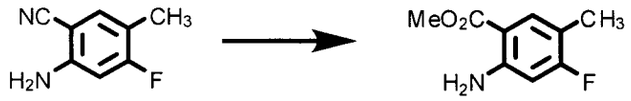


AA2 **AA3**

El compuesto **AA2** se disolvió en DMF (150 ml) y a esta solución se agregó cianuro de cobre (I) (11,0 g, 123 mmol). La mezcla se calentó a 160°C y se dejó agitar a esta temperatura durante 20 horas. Después de enfriarse a temperatura ambiente, con agua (200 ml), cloruro de hierro (III) (42,0 g, 155 mmol) y ácido clorhídrico concentrado (20 ml) se agregaron a la mezcla de reacción y la reacción resultante se agitó durante 45 minutos. La mezcla de reacción luego se alcalinizó a pH > 10 usando solución de hidróxido de amonio. La solución básica luego se extrajo con acetato de etilo (4 x 400 ml). Los extractos orgánicos combinados se lavaron con agua, se secaron con sulfato de magnesio, se filtraron y concentraron in vacuo. El residuo obtenido se purificó mediante cromatografía flash para proporcionar el compuesto **AA3** (5,82 g, 81 %). ^{1}H RMN (400 MHz, d_6-

DMSO): δ 7,34 (d, *J* = 8,4 Hz, 1H), 6,52 (d, *J* = 12,4 Hz, 1H), 6,10 (s, 2 H), 2,08 (s, 3 H).

Paso C – Síntesis del Compuesto AA4



AA3 **AA4**

A la solución de **AA3** (2,0 g, 13,3 mmol) en metanol anhidro (15 ml) a temperatura ambiente se agregó ácido sulfúrico concentrado (4,0 ml). La mezcla de reacción se calentó a 70°C y se agitó durante cuatro días. Después de enfriar a temperatura ambiente, se vertió con agua helada. La mezcla luego se diluyó con acetato de etilo (200 ml) y se volvió básico (pH > 10) con solución de hidróxido de amonio comercial. Las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 100 ml). La solución orgánica combinada se secó con $MgSO_4$ y se concentró in vacuo para proporcionar el producto bruto que, se purificó mediante cromatografía flash para proporcionar el compuesto **AA4** (1,0 g, 41%) y se recuperó algo de **AA3**. ^{1}H RMN (400 MHz, d_6-DMSO): δ 7,61 (d, *J* = 8,8 Hz, 1H), 6,69 (s, 2 H), 6,51 (d, *J* = 12,0 Hz, 1 H), 3,77 (s, 3 H), 2,06 (s, 3 H).

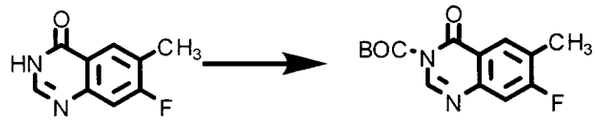
Paso D – Síntesis del Compuesto AA5



AA4 **AA5**

La solución del Compuesto **AA4** (500 mg, 2,73 mmol) en formamida (6,0 ml) se calentó a 150°C en un baño de aceite y se agitó durante 18 horas. Después de enfriar a temperatura ambiente, se agregaron acetato de etilo (100 ml) y agua (100 ml) y las fases se separaron. La solución orgánica se lavó con agua (2 x 60 ml), se secó con $MgSO_4$ y se concentró in vacuo para proporcionar el producto bruto **AA5** (0,50 g, cuant.) que se usó sin purificación adicional. MS experimental $C_9H_7FN_2O$: 179,0 $(M+H)^+$.

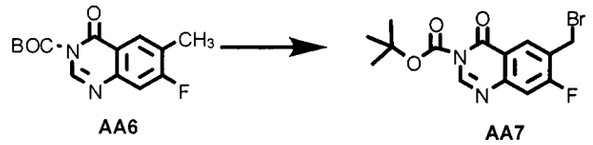
Paso E – Síntesis del Compuesto AA6



AA5 **AA6**

A la solución de **AA5** (del Paso 4) en THF anhidro (20 ml) a temperatura ambiente se agregó bicarbonato de di-*tert*-butilo (1,84 g, 8,43 mmol), 4-dimetilaminopiridina (350 mg, 2,86 mmol) y trietilamina (0,40 ml, 2,87 mmol). La mezcla de reacción se agitó durante 18 horas. Se agregaron acetato de etilo (100 ml) y agua (100 ml) y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 50 ml). La solución orgánica combinada se secó con $MgSO_4$ y se concentró in vacuo para proporcionar el producto bruto que, se purificó mediante cromatografía flash para proporcionar el compuesto **AA6** (285 mg, 36 %). MS experimental $C_{14}H_{15}FN_2O_3$: 179,0 $(M+H-100)^+$.

Paso F – Síntesis del Compuesto AA7

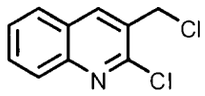


AA6 **AA7**

La mezcla de **AA6** (282 mg, 1,01 mmol), NBS (253 mg, 1,42 mmol) y AIBN (58 mg, 0,353 mmol) en tetracloruro de carbono anhidro (60 ml) se calentó a 90°C en un baño de aceite y se agitó durante 4 horas. Después de enfriar a temperatura ambiente y concentrar in vacuo, el residuo se disolvió en acetato de etilo (100 ml) y agua (100 ml). Las fases se separaron. La solución orgánica se lavó con agua (100 ml), se secó con $MgSO_4$ y concentró in vacuo para proporcionar el producto bruto **AA7** (453 mg, cuant.) que se usó sin purificación adicional.

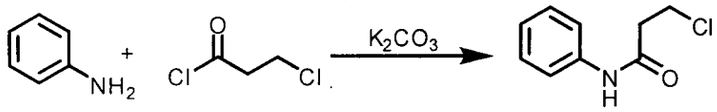
Ejemplo 20

Preparación del intermediario del compuesto **BB2**



BB2

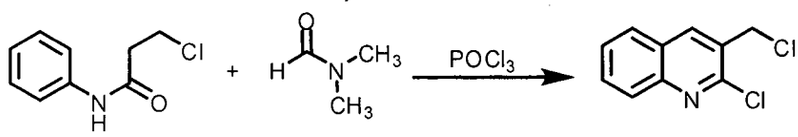
Paso A – Síntesis del Compuesto BB1



BB1

Una mezcla de anilina (65,04 ml, 713,8 mmol), carbonato de potasio (54,4 g, 394 mmol) y agua (300 ml) se agregó a un matraz de 2000 ml. La reacción resultante se mantuvo a temperatura ambiente usando un baño de agua a temperatura ambiente y se agitó con un agitador mecánico. Se agregó gota a gota cloruro de 3-cloro-propionilo (75,18 ml, 787,6 mmol) por medio de un embudo de adición y la suspensión resultante se dejó agitar a temperatura ambiente durante 3 horas. La mezcla de reacción se filtró y el sólido recogido se lavó sucesivamente con agua (300 ml), HCl acuoso (1M, 2 x 300 ml), y agua (300 ml), luego se secó para proporcionar el compuesto **BB1**, que se usó sin purificación (114,5 g, 87%).

Paso B – Síntesis del Compuesto BB2



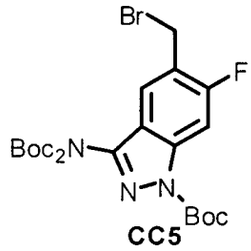
BB1 **BB2**

Se cargó N,N-Dimetilformamida (53,7 ml, 694 mmol) en un matraz de tres bocas y se enfrió a 0°C y se trató gota a gota con cloruro de fosforilo (177,7 ml, 1906 mmol). La reacción se agitó a esta temperatura durante 10 min y se trató con 3-cloro-N-fenilpropanamida **BB1** (50,00 g, 272,3 mmol) y se agitó a temperatura ambiente durante 30 min. La mezcla de reacción se calentó a 80°C durante 3 h y se vertió lentamente en hielo. El sólido que se separó se filtró y lavó extensivamente con agua (2x1000 ml), bicarbonato de sodio acuoso saturado

(500 ml), y se tomó en EtOAc (1L), la solución se secó ($MgSO_4$), se filtró, se concentró in vacuo y el residuo obtenido se recristalizó en hexanos en ebullición para proporcionar el compuesto **BB2** (20 g).

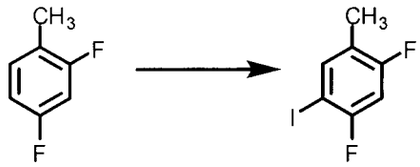
Ejemplo 21

Preparación del intermediario del compuesto **CC5**



CC5

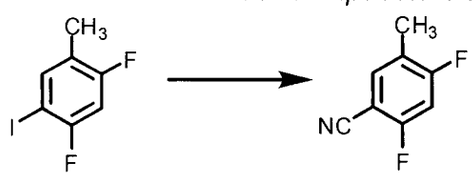
Paso A – Síntesis del Compuesto CC1



CC1

Una solución de 2,4-difluorotolueno (4,72 g, 36,8 mmol) el ácido trifluoroacético (12,29 ml, 159,5 mmol) se enfrió a 0 °C, luego se agregó N-Yodosuccinimida (9,59 g, 42,6 mmol) y la reacción resultante se dejó agitar a temperatura ambiente durante aproximadamente 15 horas. La mezcla de reacción luego se concentró in vacuo y el residuo obtenido se disolvió en hexanos (100 ml), se lavó con tiosulfato de soido acuoso (100 ml), salmuera (100 ml), luego se secó ($MgSO_4$), se filtró y concentró in vacuo. El residuo resultante se purificó mediante destilación bulbo a bulbo para proporcionar el compuesto **CC1** (7,2 g, 77%) como un aceite incoloro.

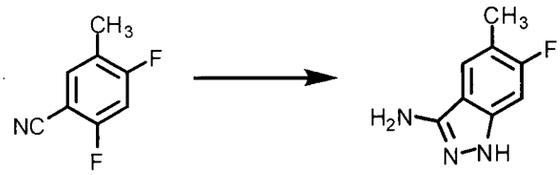
Paso B – Síntesis del Compuesto CC2



CC1 **CC2**

Una solución del Compuesto **CC1** (7,11 g, 28,0 mmol), cianuro de zinc (1,97 g, 16,8 mmol) y tetracis(trifenilfosfino)paladio (0) (3,23 g, 2,80 mmol) en DMF (30 ml) se calentó a 90ºC y se dejó agitar a esta temperatura durante 1,5 horas. La mezcla de reacción se concentró in vacuo y el residuo obtenido se tomó en agua (400 ml) y se extrajo con éter (400 ml). El extracto orgánico se lavó con hidróxido de amonio acuoso solución (1N). La fase orgánica se secó ($MgSO_4$) se filtró, concentró in vacuo para proporcionar un residuo que se purificó mediante cromatografía flash (SiO_2, EtOAc/Hexanos) para proporcionar a una mezcla que contenía producto y trifenilfosfina. Esta mezcla se purificó adicionalmente usando sublimación a 1 mm/Hg a 45 ºC para proporcionar el compuesto **CC2** (1,8 g; Rendimiento = 42%).

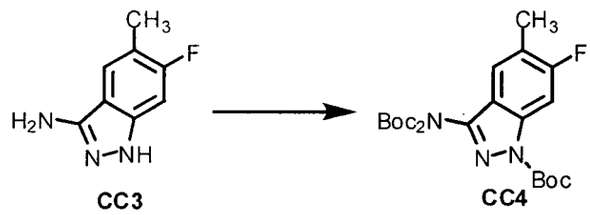
Paso C – Síntesis del Compuesto CC3



CC2 **CC3**

Una solución del Compuesto **CC2** (1,400 g, 9,154 mmol) y hidrazina (0,700 ml, 22,3 mmol) el alcohol isopropílico (50 ml, 653,1 mmol), se calentó a reflujo y se dejó agitar a esta temperatura durante 24 horas. La mezcla de reacción se enfrió a temperatura ambiente, concentró in vacuo y el residuo obtenido se purificó mediante cromatografía flash (SiO_2, Acetona/Hexanos 0→ 50%) para proporcionar el compuesto **CC3** (330 mg, 22%).

Paso D – Síntesis del Compuesto CC4

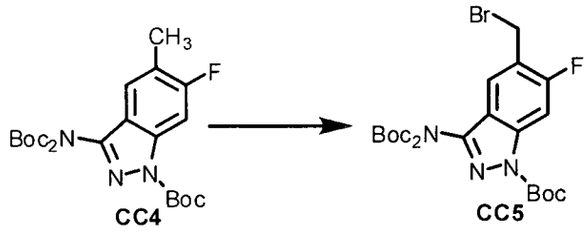


CC3 **CC4**

Una solución del Compuesto **CC3** (330,00 mg, 1,998 mmol), dicarbonato

de di-terbutilo (2,6163 g, 11,98 mmol) y 4-dimetilaminopiridina (48,817 mg, 0,39959 mmol) en acetonitrilo (15 ml, 287,2 mmol) se calentó a reflujo y se dejó agitar a esta temperatura durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente, concentró in vacuo, y el residuo resultante se purificó mediante cromatografía flash (SiO_2, EtOAc/Hexanos 0- 20 %) para proporcionar el compuesto **CC4** (640,00 mg, 68%) como un aceite incoloro.

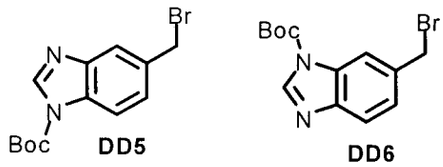
Paso E - Síntesis del Compuesto CC5



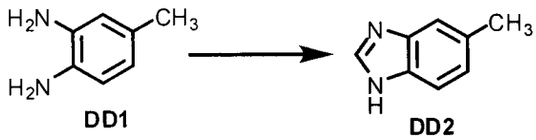
Una solución del Compuesto **CC4** (630,00 mg, 1,3533 mmol), N-bromosuccinimida (337,22 mg, 1,8947 mmol) y peróxido de benzoílo (65,563 mg, 0,27067 mmol) en tetracloruro de carbono (20 ml) se calentó a reflujo y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente, concentró in vacuo y el residuo obtenido se disolvió en EtOAc (300 ml). Una solución resultante se lavó con tiosulfato de sodio acuoso (100 ml), salmuera (100 ml), se secó ($MgSO_4$), se filtró, y concentró in vacuo. El residuo obtenido se purificó mediante cromatografía flash (SiO_2, EtOAc/Hexanos) para proporcionar el compuesto **CC5** como un aceite incoloro.

Ejemplo 22

Preparación del intermediario de los compuestos **DD5** y **DD6**



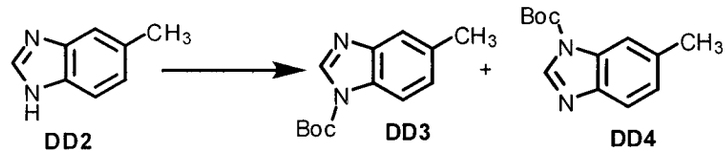
Paso A – Síntesis del Compuesto DD2



DD1 **DD2**

Una solución del Compuesto **DD1** (3 g, 24,5 mmol) en ortoformiato de trimetilo (15 ml) se trató con 2 gotas de HCl concentrado y se calentó a 80 °C durante 2 horas. La mezcla de reacción se enfrió a temperatura ambiente y concentró in vacuo para proporcionar el compuesto **DD2** (3,65 g), que se usó sin purificación adicional. M.S. experimental $C_8H_8N_2$: 133,2 $(M+H)^+$.

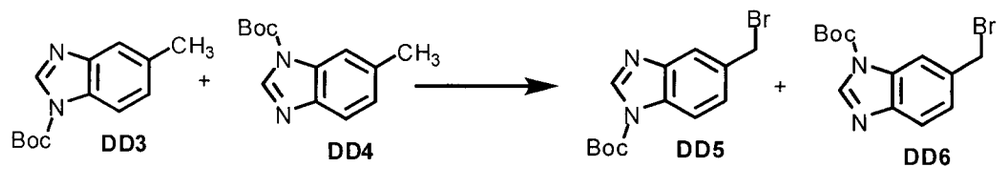
Paso B – Síntesis del Compuestos DD3 y DD4



DD2 **DD3** **DD4**

A una solución del Compuesto **DD2** (24,5 mmol) in CH_3CN (65 ml) se agregó dicarbonato de di-terbutilo (5,89 g, 27,0 mmol), trietilamina (3,76 ml, 27,0 mmol) y 4-dimetilaminopiridina (300 mg, 2,45 mmol) y la reacción resultante se calentó a 80°C y se dejó agitar a esta temperatura durante 1,5 horas. La mezcla de reacción se enfrió a temperatura ambiente, concentró in vacuo, y el residuo obtenido se purificó mediante cromatografía flash (gel de sílice, EtOAc/Hexanos 5-20%) para proporcionar una mezcla isomérica de los compuestos **DD3** y **DD4** (5,38 g, 94,3% rendimiento de los pasos A y B).

Paso C – Síntesis del Compuestos DD5 y DD6



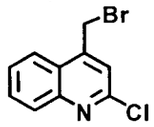
DD3 **DD4** **DD5** **DD6**

A una solución del Compuestos **DD3** y **DD4** (2 g, 8,61 mmol) en tetracloruro de carbono (40 ml) se agregó N-bromosuccinimida (1,6 g, 9,04 mmol) y peróxido de dibenzoílo (41,7 mg, 0,1722 mmol) y la reacción resultante se calentó a 90 °C y se dejó agitar a esta temperatura durante 12 horas. La reacción

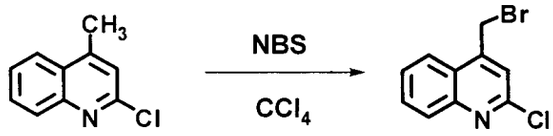
se enfrió a temperatura ambiente, los sólidos se filtraron y el filtrado se lavó con agua, se secó con sulfato de sodio y concentró in vacuo para proporcionar los compuestos **DD5** y **DD6** (2,58 g) que se usaron sin purificación adicional. M.S. experimental $C_{13}H_{15}BrN_2O_2$: 334,7 $(M+Na)^+$.

Ejemplo 23

Preparación del intermediario del compuesto **EE2**



EE2



EE1 **EE2**

Una mezcla del Compuesto **EE1** (1,5 g, 8,44 mmol), NBS (1,8 g, 10,11 mmol) en tetracloruro de carbono (50 ml) se calentó a reflujo, luego se agregó peróxido de dibenzoílo (0,21 g, 0,866 mmol). La suspensión resultante se dejó agitar a reflujo durante 19 horas, luego se enfrió a temperatura ambiente y se filtró. El filtrado se lavó con carbonato de sodio saturado, se secó con sulfato de sodio y concentró in vacuo para proporcionar una mezcla (1,7 g) que contiene aproximadamente 50% del Compuesto **EE2**, y se usó sin purificación adicional.

Ejemplo 24

Ensayo de inhibición de la polimerasa NS5B de VHC

Como se ha demostrado in vitro que el ARN heteropolimérico transcripto conocido como D-ARN o DCoH es un molde eficiente para la polimerasa NS5B de VHC (S.-E. Behrens et al., EMBO J. 15: 12-22 (1996); WO 96/37619). Una versión de 75 mer químicamente sintetizada, designada DCoH75, cuyas secuencias apareadas en el extremo 3' del D-ARN y DCoH75ddC, donde la citidina del

extremo terminal 3' de DCoH75 está reemplazada por didesoxicitidina, se usaron para ensayar la actividad enzimática NS5B descripta en Ferrari *et al.*, *12th International Symposium on VHC and Related Viruses*, P-306 (2005). La secuencia del molde de ARN fue: 5'-UGU GCC GGU CUU UCU GAA CGG GAU AUA AAC CUG GCC AGC UUC AUC GAA CAA GUU GCC GUG UCU AUG ACA UAG AUC-3'. Una forma de la enzima NS5B truncada en el aminoácido 21 C-terminal soluble (NS5BΔCT21, de una cepa VHC-Con 1, genotipo 1b, número de acceso Genbank AJ238799) se produjo y purificó a partir de Escherichia coli como una proteína de fusión marcada en la polihistidin a C-terminal como se describe en Ferrari *et al.*, *J. Virol.* 73:1649-1654 (1999). Un ensayo típico contenía 20 mM de Hepes pH 7,3, 10 mM de $MgCl_2$, 60 mM de NaCl, 100 µg/ml de BSA, 20 unidades/ml de RNasin, 7,5 mM de DTT, 0,1 µM de ATP/GTP/UTP, 0,026 µM de CTP, 0,25 mM de GAU, 0,03 µM de molde de ARN, 20 µCi/ml de [^{33}P]-CTP, 2% de DMSO y 30 o 150 nM de enzima NS5B. Las reacciones se incubaron a 22°C durante 2 horas, luego se detuvo por la adición de 150 mM de EDTA, se lavó en la palca de filtro DE81 en 0,5M de buffer de fosfato de sodio di-básico, pH 7,0, y se contó en un Packard TopCount después de la adición de cóctel de centelleo. Se controló la síntesis de polinucleótidos por la incorporación de CTP radiomarcado. El efecto de los compuestos de fórmula (I)sobre la actividad de polimerasa se evaluó por el agregado de diversas concentraciones de un Compuesto de fórmula (I), normalmente en una serie de 10 diluciones dos veces en la mezcla del ensayo. Las concentraciones iniciales varían de 200 µM a 1 µM. El valor I para el inhibidor, definido como la concentración del compuesto que proporciona 50% de inhibición de actividad polimerasa, se determinó por ajuste de los datos de cpm para la ecuación de Hill Y=100/(1+10^((LogIC50-X)*HillSlope)), donde X es el logaritmo de la concentración del compuesto e Y es el % de inhibición. Ferrari *et al.*, *12th International Symposium on VHC and Related*

Viruses, P-306 (2005) describió en detalle este procedimiento de ensayo. Se debe advertir que tal ensayo se describe como ejemplo y no se considera una limitación del alcance de la invención. El profesional experto puede apreciar que se pueden realizar modificaciones que incluyen, pero sin limitación ARN molde, cebador, nucleótidos, forma de la polimerasa NS5B, composición del buffer para desarrollar ensayos similares que producen el mismo resultado en cuanto a la eficacia de los compuestos y composiciones descriptos en la invención.

Los datos de inhibición de la polimerasa NS5B para los compuestos de fórmula (I) seleccionados se proporciona a continuación en la tabla 2, donde los números del compuesto corresponden a la numeración de compuestos expuesta en la memoria descriptiva anterior. Los datos se denominan de la siguiente manera: "A" para los valores de IC_{50} menores de 25 nanomolares (nM), "B" para los valores de IC_{50} entre 25 a 100 nM y "C" para los valores de IC_{50} mayores de 100 nM.

Ejemplo 25

Ensayo de replicón de VHC basado en células

Para medir la actividad anti-VHC basada en células de un Compuesto de fórmula (I), se sembraron células de replicón a razón de 5000 células/pocillo en placas Nunc recubiertas con colágeno I de 96 pocillos en presencia del compuesto de fórmula (I). Se agregaron varias concentraciones de un Compuesto de fórmula (I), normalmente 10 diluciones seriadas de dos veces a la mezcla de ensayo con concentración que varía de 250 µM a 1 µM. La concentración final de DMSO fue de 0,5%, suero bovino fetal 5%, en el medio de ensayo. Las células se recolectaron el día 3 por la adición de buffer de liis celular 1x (Ambion cat #8721). El nivel de ARN del replicón se midió mediante una PCR de tiempo real (ensayo Taqman). El amplicón se localizó en 5B. Los cebadores de PCR fueron: 5B,2F, ATGGACAGGCGCCCTGA; 5B,2R, TTGATGGGCAGCTTGGTTTC; la secuencia

de la sonda fue marcada con FAM CACGCCATGCGCTGCGG. Se usó ARN GAPDH como control endógeno y se amplificó en la misma reacción que NS5B (PCR multiplex) usando cebadores y sonda marcada con VIC recomendada por el fabricante (PE Applied Biosystem). Las reacciones de RT-PCR de tiempo real se corrieron en un sistema de detección de secuencia ABI PRISM 7900HT usando el siguiente programa: 48°C durante 30 min, 95°C durante 10 min, 40 ciclos de 95°C durante 15 segundos, 60°C durante 1 min. Los valores de ΔCT (CT_{5B}-CT_{GAPDH}) se graficaron contra la concentración de ensayo del compuesto y se ajustó con le modelo de respuesta–dosis sigmoide usando XLfit4 (MDL). La EC_{50} se definió como la concentración de inhibidor necesario para alcanzar ΔCT=1 sobre el valor basal proyectado; EC_{90} la concentración necesaria para obtener ΔCT=3,2 sobre el valor basal. Alternativamente, para cuantificar la cantidad absoluta de ARN de replicón, se estableció una curva estándar por inclusión de transcripto T7 diluidos en forma seriada del ARN del replicón en el ensayo Taíman. Todos los reactivos Taqman eran de PE Applied Biosystems. Tal procedimiento de ensayo se describió en detalle en por ej., Malcolm *et al., Antimicrobial Agents y Chemotherapy* 50: 1013-1020 (2006).

Los datos del ensayo de replicón de VHC para los compuestos de fórmula (I) seleccionados se proporcionan a continuación en la Tabla 1, donde los números del compuesto corresponden a la numeración de compuestos expuesta en la memoria descriptiva anterior. Los datos se denominan de la siguiente manera: "A" para los valores de EC_{50} menores de 0,5 micromolar (μM), "B" para los valores de EC_{50} entre 0,5 y 1,5 μM y "C" para los valores de EC_{50} mayores de 1,5 μM.

Tabla 1

#	IC5	EC5	LR-MS	DATOS DE ^{1}H RMN

	0	0	(M+H)	
1	A	A	403,4	Ver Ejemplo 4 para los detalles y datos experimentales
2	A	B	421,4	1H RMN (400 MHz, D6-dmso), δ 11,75 (s, 1 H), 7,85 (d, 1H, J = 2,2 Hz), 7,66 (dd, 1 H, J = 2,2 & 6,6 Hz), 7,55 & 7,47 (AB, 2 H, J = 8,8 Hz), 7,40 (d, 1 H, J = 5,9 Hz), 7,28 (dt, 1 H, J = 2,2 & 10,9 Hz), 6,96 (d, 1 H, J = 2,2 Hz), 6,95 (dt, 1 H, J = 2,9 & 5,9 Hz), 6,68 (q, 1 H), 6,33 (t, 1 H), 5,91 (s, 2 H).
3	B	A	421,4	1H RMN (400 MHz, D6-dmso), δ 12,8 (s, 1 H), 11,74 (s, 1 H), 7,85 (d, 1H, J = 1,5 Hz), 7,68 (dd, 1 H, J = 2,2 & 6,6 Hz), 7,56 & 7,47 (AB, 2 H, J = 8,8 Hz), 7,40 (d, 1 H, J = 5,2 Hz), 7,30 (dt, 1 H, J = 4,4 & 5,0 Hz), 7,16-7,11 (m, 1 H), 6,97 (d, 1 H, J = 2,2 Hz), 6,36-6,31 (m, 2 H), 5,93 (s, 2 H).
4	A	A	480,5	Ver Ejemplo 5 para los detalles y datos experimentales
5	B	A	498,5	1H RMN (400 MHz, D6-dmso),δ12,8 (s, 1 H), 12,9 (s, 1 H), 7,96 (d, 1H, J = 6,6 Hz), 7,84 (d, 1 H, J = 2,2 Hz), 7,66 (bt, 1 H), 7,59 & 7,51 (AB, 2 H, J = 8,8 Hz), 7,28 (dt, 1 H, J = 2,2 & 8,8 Hz), 6,98 (d, 1 H, J = 2,2 Hz), 6,98-6,87 (m, 2 H), 6,61 (t, 1 H, J = 6,6 Hz), 5,77 (s, 3 H), 3,25 (s, 3 H).
6	A	A	498,5	1H RMN (400 MHz, D6-dmso),δ12,6 (s, 1 H), 12,7 (s, 1 H), 7,99 (d, 1H, J = 6,6 Hz), 7,85 (s, 1H), 7,69-7,65 (m, 1 H), 7,60 & 7,49 (AB, 2 H, J = 8,8 Hz), 7,33-7,24 (m, 1 H), 7,18-7,13 (m, 1 H), 6,99 (s, 1 H),

				6,63–6,53 (m, 2 H), 5,78 (s, 2 H), 3,24 (s, 3 H)
7	A	C	413,5	^{1}H RMN (500 MHz, $CDCl_3$)δ7,59-7,10 (m, 11H), 5,98 (m, 2H), 2,07 (s, 3H), 1,90 (s, 3H).
8	C	C	441,5	1H RMN (500 MHz, CDCl3) δ 9,96 (s, 1H), 7,46-7,10 (m, 11H), 5,98 (ABq, JAB = 16,7 Hz, 2H), 4,03 (m, 2H), 2,30 (s, 3H), 1,46 (s, 3H), 0,84 (t, J = 7,3 Hz, 3H). C28H25FN2O2;
9	A	C	498,5	Ver Ejemplo 3 para los detalles y datos experimentales
10	B	C	590,6	1H RMN (400 MHz, D6-dmso),δ12,9 (s, 1 H), 12,8 (s, 1 H), 7,95 (s, 1 H), 7,79 (m, 2 H), 7,66 (d, 2 H), 7,61 & 7,52 (AB, 2 H, J = 8,8 Hz), 7,15 (t, 1 H, J = 9,5 Hz), 7,02 (d, 2 H, J = 8,8 Hz), 6,81 (t, 1 H, J = 8,8 Hz), 6,64-6,58 (m, 2 H), 6,41 (s, 1 H), 5,65 (s, 2 H), 3,81 (s, 3 H).
11	B	C	653,7	1H RMN (400 MHz, D6-dmso),δ10,22 (s, 1 H), 7,82-7,77 (m, 4 H), 7,62 & 7,53 (AB, 2 H, J = 8,8 Hz), 7,49-7,40 (m, 4 H), 7,15 (dt, 1 H, J = 2,2 & 8,8 Hz), 6,82 (dt, 1 H, J = 3,0 Hz & 8,8 Hz), 6,66 (t, 2 H), 6,42 (d, 1 H, J = 1,5 Hz), 5,64 (s, 2 H), 3,00 (s, 3 H).
12	A	B	498,53	Ver Ejemplo 1 para los detalles y datos experimentales
13	C	C	418,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (s, 1 H), 11,89 (s, 1 H), 9,18 (s, 1 H), 8,04 (d, 1 H, J = 9,2 Hz), 7,95 (bs, 2 H), 7,90 (d, 1 H, J = 5,6 Hz), 7,74 (d, 1 H, J = 9,2 Hz), 7,57 (dd, 1 H, J = 2,0 & 5,2 Hz), 7,52-7,50 (m, 1 H), 6,66 (dd, 1 H, J = 1,6 & 5,2 Hz), 6,36

				(t, 1 H, J = 6,4 Hz), 6,31 (s, 1 H), 5,99 (bd, 2 H).
14	A	B	418,4	1H RMN (500 MHz, d6-DMSO): δ11,7 (s, 1 H), 9,33 (s, 1 H), 8,08 (d, J = 8,8 Hz, 1 H), 7,98-7,87 (m, 2 H), 7,71 (d, J = 8,8 Hz, 1 H), 7,60 (d, J = 6,3 Hz, 1 H), 7,39 (d, J = 5,7 Hz, 1 H), 6,65 (t, J = 6,3 Hz, 1 H), 6,31 (s, 2 H), 5,99 (s, 2 H), 4,46 (s, 1 H), 3,60 (s, 1 H)
16	C	C	438,4	Ver Ejemplo 2 para los detalles y datos experimentales
17	A	C	438,4	1H RMN (400 MHz, D6-DMSO) d, 9,15 (s, 1 H), 8,01 & 7,98 ((d, J = 9,52 Hz, 1H), 7,79 & 7,77 (d, J = 8,79 Hz, 1H), 7,59 & 7,57 (d, J = 6,59 Hz, 1H), 7,497 & 7,48 (d, J = 5,86 Hz, 1H), 7,29 (t, J = 9,52 Hz, 1H), 6,96 (t, J = 9,50 Hz, 1H), 6,70 (q, J = 8,79 & 15,38 Hz, 1H), 6,34 (t, J = 7,32 Hz, 1H), 5,98 (q, J = 16,11 & 46,87 Hz, 2H).
24	C	C	449,4	1H RMN (400 MHz, D6-dmso),δ13,2 (s, 1 H), 11,92 (s, 1 H), 7,75 (d, 1 H, J = 6,6 Hz), 7,57 & 7,44 (AB, 2 H, J = 8,8 Hz), 7,50 (d, 1 H, J = 6,6 Hz), 7,47 (s, 1 H), 7,30 (dt, 1 H, J = 4,4 & 4,3 Hz), 7,15-7,09 (m, 1 H), 6,35 (t, 1 H, J = 6,6 Hz), 6,16-6,13 (m, 1 H), 6,00 (s, 2 H), 2,77 (q, 2 H, J = 7,3 Hz), 1,18 (t, 3 H, J = 7,3 Hz).
33	B	C	437,4	^{1}H RMN (400 MHz, D_6-dmso),δ11,75 (s, 1 H), 7,79 & 7,60 (AB, 2 H, *J* = 8,8 Hz), 7,59 (t, 1 H, *J* = 3,7 Hz), 7,50 -7,46 (m, 3 H), 7,31 (dt, 1 H, *J* = 4,4 Hz), 7,17-7,12 (m, 1H), 6,33 (t, 1 H, *J* = 6,6 Hz), 6,02 & 5,93 (AB, 2 H, *J* = 18,3 Hz).
34	B	B	419,5	^{1}H RMN (400 MHz, D_6-dmso),δ anterior 12 (s, 1 H),

				11,76 (s, 1 H), 7,77 (d, 1 H, J = 8,8 Hz), 7,59-7,57 (m, 2 H), 7,48 & 7,45 (AB, 2 H, *J* = 5,2 Hz), 7,49 -7,44 (bs, 1 H), 7,30-7,20 (m, 2 H), 7,02 (dt, 1 H, *J* = 1,6 & 7,6 Hz), 6,58 (dt, 1 H, *J* = 1,6 & 7,6 Hz), 6,33 (t, 1 H, *J* = 6,8 Hz), 6,07 & 5,94 (AB, 2 H, *J* = 16,0 Hz)
37	A	C	461,3	1H RMN (400 MHz, d6-DMSO): δ, 11,8 (bs, 1 H), 7,62 (dd, J = 6,8, 2,0 Hz, 1 H), 7,47 (d, J = 9,2 Hz, 1 H), 7,43-7,41 (m, 2 H), 7,30 (td, J = 9,2, 4,4 Hz, 1 H), 7,19-7,14 (m, 1 H), 6,52-6,48 (m, 1 H), 6,32 (t, J = 6,6 Hz, 1 H), 5,88 (s, 2 H).
39	B	C	403,4	1H-RMN (400 MHz, en dmso-d6):δ□11,80 (1H, ancho s), 7,94 (1H, s), 7,58 (2H, m), 7,48 (1H, d, J = 9,52 Hz), 7,45 (1H, m), 7,24 (2H, m), 7,01 (1H, t, J = 7,32 Hz), 6,57 (2H, s), 6,34 (1H, dd, J = 5,86, 6,59 Hz), 5,97 (2H, s)
40	B	C	421,4	1H-RMN (400 MHz, en dmso-d6):δ11,81 (1H, ancho s), 7,95 (1H, s), 7,60 (2H, d, J = 8,78 Hz), 7,5 (1H, d, J = 9,5 Hz), 7,46 (1H, d, J = 6,59 Hz), 7,30 (1H, ddd, J = 4,39, 8,78, 9,52 Hz), 7,13 (1H, m), 6,57 (1H, s), 6,32 (1H, m), 5,95 (2H, s)
41	A	A	399,4	^{1}H RMN (400 MHz, D_6-dmso),δ12,8 (s, 1H), 11,72 (s, 1 H), 7,84 (s, 1 H), 7,70 (d, 1 H, *J* = 5,9 Hz), 7,49 &7,19 (AB, 2 H, *J* = 8,8 Hz), 7,40 (d, 1H, *J* = 4,4 Hz), 7,19 (d, 1H, *J* = 6,6 Hz), 7,07 (t, 1 H, *J* = 6,6 Hz), 6,96 (s, 1 H), 6,92 (t, 1 H, *J* = 6,0 Hz), 6,34 (t, 1 H, *J* = 5,9 Hz), 6,03 (d, 1 H, *J* = 7. 3 Hz), 5,86 (s, 2 H), 2,42 (s, 3 H).

43	C	C	431,4	1H RMN (400 MHz, D6-dmso),δ 13,04 (s, 1 H), 11,92 (s, 1 H), 7,75 (dd, 1 H, J = 2,1 & 4,7 Hz), 7,55 & 7,41 (AB, 2 H, J = 8,8 Hz), 7,50 (dd, 1 H, J = 1,7 & 4,7 Hz), 7,46 (s, 1 H), 7,29-7,19 (m, 2 H), 6,97 (dt, 1 H, J = 1,7 & 7,7 Hz), 6,36-6,33 (m, 2 H), 6,0 (s, 2 H), 2,76 (q, 2 H, J = 7,7 Hz), 1,18 (t, 3 H, J = 7,7 Hz).
45	A	A	437,8	1H RMN (400 MHz, D6-dmso),δ13,04 (s, 1 H), 11,75 (s, 1 H), 8,16 (s, 1H), 7,67 (dd, 1H, J = 2,1 & 4,7 Hz), 7,60 & 7,47 (AB, 2 H, J = 9,0 Hz), 7,40 (d, 1 H, J = 6,4 Hz), 7,27 (q, 1 H, J = 7,7 Hz), 7,23 (q, 1 H, J = 10,3 Hz), 7,03 (t, 1 H, J = 7,2 Hz), 6,59 (t, 1 H, J = 7,7 Hz), 6,32 (t, 1 H, J = 6,8 Hz), 5,97 (s, 2 H).
46	A	A	455,8	1H RMN (400 MHz, D6-dmso),δ13,11 (s, 1 H), 11,76 (s, 1 H), 8,18 (s, 1 H), 7,69 (dd, 1 H, J = 2,2 & 4,4 Hz), 7,63 & 7,49 (AB, 2 H, J = 8,8 Hz), 7,41 (d, 1 H, J = 5,5 Hz), 7,30 (dt, 1 H, J = 4,4 & 4,3 Hz), 7,17-7,11 (m, 1 H), 6,38-6,33 (m, 1 H), 6,32 (t, 1 H, J = 6,6 Hz), 5,95 (s, 2 H).
47	C	C	435,4	1H RMN (400 MHz, D6-dmso),δ anterior 12 (s, 1 H), 11,94 (s, 1 H), 7,77 (dd, 1 H, J = 2,0 & 8,5 Hz), 7,54 & 7,47 (AB, 2 H, J = 8,8 Hz), 7,54-7,44 (m, 2 H), 7,33-7,27 (m, 1 H), 7,17-7,08 (m, 1 H), 6,35 (t, 1 H, J = 6,8 Hz), 6,15-6,10 (m, 1H), 5,96 (s, 2 H), 2,28 (s, 3 H).
48	C	C	431,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (s, 1 H), 11,93 (s, 1 H), 7,77 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,51-7,39 (m, 4 H), 7,11 (t, 1 H, J = 8,0 Hz), 6,84 (t, 1 H, J

251

				= 7,6 Hz), 6,35 (t, 1 H, J = 6,8 Hz), 6,13 (t, 1 H, J = 7,2 Hz), 6,00 (s, 2 H), 2,27 (s, 3 H), 2,36 (d, 3 H, J = 1,2 Hz).
49	A	C	514,5	Ver Ejemplo 6 para los detalles y datos experimentales
50	A	A	497,5	1H RMN (400 MHz, d6-DMSO): δ, 9,31 (s, 1 H), 8,09 (d, J = 8,8 Hz, 1 H), 7,94 (dd, J = 6,8, 4,0 Hz, 1 H), 7,81 (d, J = 9,2 Hz, 1 H), 7,66 (d, J = 4,8 Hz, 1 H), 7,34-7,29 (m, 2 H), 7,26-7,21 (m, 1 H), 7,08 (t, J = 7,4 Hz, 1 H), 6,84 (t, J = 7,8 Hz, 1 H), 6,59 (t, J = 6,6 Hz, 1 H), 5,88 (s, 2 H), 3,57 (s, 3 H), 3,60 (s, 1 H).
51	A	A	493,6	Ver Ejemplo 7 para los detalles y datos experimentales
52	A	C	514,5	Ver Ejemplo 8 para los detalles y datos experimentales
53	A	C	480,5	1H-RMN (400 MHz, en dmso-d6):δ12,77 (1H, ancho s), 12,69 (1H, ancho s), 7,97 (1H, s), 7,88 (1H, d, J = 6,84 Hz), 7,75 (1H, m), 7,64 (1H, d, J = 8,79 Hz), 7,54 (1H, d, J = 8,79 Hz), 7,29 (1H, m), 7,22 (1H, m), 7,05 (1H, dd, J = 7,32, 7,32 Hz), 6,82 (1H, dd, J = 7,32, 7,81 Hz), 6,65 (1H, dd, J = 6,35, 6,84 Hz), 6,47 (1H, s), 5,83 (2H, s), 3,23 (3H, s)
56	A	C	520,5	Ver Ejemplo 9 para los detalles y datos experimentales
57	A	A	512,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (s; 1 H), 8,00 (d, 1 H, J = 7,2 Hz), 7,84 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,69 (t, 1 H, J = 6,4 Hz), 7,61 & 7,53 (AB, 2 H, J

				= 9,2 Hz), 7,30 (dt, 1 H, J = 4,0 & 8,8 Hz), 7,18-7,13 (m, 1 H), 6,99 (dd, 1 H, J = 1,2 & 2,4 Hz), 6,64 (t, 1 H, J = 7,6 Hz), 6,57-6,53 (m, 1 H), 5,79 (s, 2 H), 3,35 (q, 2 H, J = 8,0 Hz), 1,04 (d, 3 H, J = 7,6 Hz)
58	A	C	498,5	1H-RMN (400 MHz, en dmso-d6):δ12,92 (1H, ancho s), 11,67 (1H, ancho s), 7,98 (1H, d, J = 2,20 Hz), 7,91 (1H, dd, J = 2,20, 7,32), 7,75 (1H, m), 7,65 (1H, d, J = 9,52 Hz), 7,54 (1H, d, J = 9,52 Hz), 7,30 (1H, ddd, J = 4,39, 9,52, 9,52), 7,15 (1H, m), 6,65 (1H, t, J = 6,59 Hz), 6,57 (1H, ddd, J= 2,92, 5,86, 8,79 Hz), 6,38 (1H, d, J = 1,47 Hz), 5,80 (2H, s) 3,25 (3H, s)
59	A	A	500,5	Ver Ejemplo 10 para los detalles y datos experimentales
60	A	A	490,6	1H RMN (400 MHz, D6-dmso),δ12,70 (s, 1 H), 12,59 (d, 1 H, J = 5,4 Hz), 7,99 (dd, 1 H, J = 1,9 & 4,9 Hz), 7,85 (t, 1 H, J = 1,5 Hz), 7,66 (t, 1 H, J = 4,9 Hz), 7,54 & 7,35 (AB, 2 H, J = 8,8 Hz), 7,00 (bs, 1 H), 6,98 (d, 1 H, J = 2,5 Hz), 6,76 (d, 1 H, J =7,8 Hz), 6,62 (t, 1 H, J = 6,4 Hz), 6,14 (d, 1 H, J = 7,8 Hz), 5,66 (s, 2 H), 3,10 (s, 3 H), 2,31 (s, 3 H), 2,18 (s, 3 H).
61	A	A	476,5	1H RMN (400 MHz, D6-dmso),δ12,69 (s, 1 H), 12,60 (s, 1 H), 8,00 (dd, 1 H, J = 1,5 & 5,4 Hz), 7,85 (d, 1 H, J = 2,5 Hz), 7,66 (t, 1 H, J = 5,9 Hz), 7,55 & 7,36 (AB, 2 H, J = 8,8 Hz), 7,19 (d, 1 H, J = 7,3 Hz), 7,10 (t, 1 H, J = 7,3 Hz), 6,98 (d, 1 H, J = 2,0 Hz), 6,95 (t, 1 H, J =7,8 Hz), 6,62 (t, 1 H, J = 6,8 Hz), 6,22 (d, 1 H, J = 7,8 Hz). 5,71 (s, 2 H), 3,09 (s, 3 H), 2,37 (s, 3 H).

62	A	A	524,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 7,98 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,84 (d, 1 H, J = 2,0 Hz), 7,69 (t, 1 H, J = 5,2 Hz), 7,61 & 7,52 (AB, 2 H, J = 8,4 Hz), 7,30 (dt, 1 H, J = 5,2 & 9,6 Hz), 7,19-7,13 (m, 1 H), 6,99 (d, 1 H, J = 2,0 Hz), 6,63 (t, 1 H, J = 6,4 Hz), 6,60-6,56 (m, 1 H), 5,80 (s, 2 H), 2,96-2,89 (m, 1 H), 0,96 (d, 4 H, J = 6,4 Hz).
63	A	A	526,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 8,00 (td, 1 H, J = 1,6 & 6,8 Hz), 7,84 (m, 1 H), 7,71 (t, 1 H, J = 6,8 Hz), 7,62 & 7,54 (AB, 2 H, J = 8,8 Hz), 7,30 (dt, 1 H, J = 4,4 & 8,8 Hz), 7,18-7,13 (m, 1 H), 6,99-6,98 (m, 1 H), 6,64 (t, 1 H, J = 7,2 Hz), 6,54-6,49 (m, 1 H), 5,80 (s, 2 H), 3,63-3,55 (m, 1 H), 1,14 (d, 6 H, J = 7,2 Hz)
64	A	A	508,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 7,98 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,83-7,26 (m, 1 H), 7,71 (t, 1 H, J = 5,6 Hz), 7,60 & 7,53 (AB, 2 H, J = 8,8 Hz), 7,29 (q, 1 H, J = 9,2 Hz), 7,21 (t, 1 H, J = 8,8 Hz), 7,05 (t, 1 H, J = 7,6 Hz), 6,99-6,98 (m, 1 H), 6,75 (t, 1 H, J = 8,0 Hz), 6,65 (t, 1 H, J = 6,8 Hz), 5,83 (s, 2 H), 3,62-3,55 (m, 1 H), 1,14 (d, 6 H, J = 6,8 Hz)
65	A	A	506,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 7,96 (td, 1 H, J = 1,2 & 9,0 Hz), 7,83-7,82 (m, 1 H), 7,69 (t, 1 H, J = 7,12 Hz), 7,59 & 7,52 (AB, 2 H, J = 8,8 Hz), 7,30 (q, 1 H, J = 6,0 Hz), 7,22 (t, 1 H, J = 8,8 Hz), 7,06 (t, 1 H, J = 7,6 Hz), 6,98-6,97 (m, 1 H), 6,83 (t, 1 H, J = 8,0 Hz), 6,63 (t, 1 H, J = 7,2 Hz), 5,83

				(s, 2 H), 2,93-2,87 (m, 1 H), 0,95 (d, 4 H, J = 6,4 Hz)
66	A	A	494,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 7,97 (dd, 1 H, J = 1,6 & 6,8 Hz), 7,84-7,83 (m, 1 H), 7,66 (t, 1 H, J = 6,4 Hz), 7,58 & 7,48 (AB, 2 H, J = 8,8 Hz), 7,16 (t, 1 H, J = 8,5 Hz), 6,98-6,97 (m, 1 H), 6,92 (t, 1 H, J = 7,6 Hz), 6,61 (t, 1 H, J = 6,8 Hz), 6,57 (t, 1 H, J = 7,2 Hz), 5,79 (s, 2 H), 3,22 (s, 3 H), 2,23 (s, 3 H).
67	A	A	496,9	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 8,02 (dd, 1 H, J = 1,2 & 5,2 Hz), 7,86-7,85 (m, 1 H), 7,68 (t, 1 H, J = 6,4 Hz), 7,57 (d, 1 H, J = 8,8 Hz), 7,51 & 7,33 (AB, 2 H, J = 8,8 Hz), 7,30 (t, 1 H, J = 7,6 Hz), 7,15 (t, 1 H, J = 7,2 Hz), 7,00-6,99 (m, 1 H), 6,64 (t, 1 H, J = 6,8 Hz), 6,40 (d, 1 H, J = 8,0 Hz), 5,79 (s, 2 H), 3,17 (s, 3 H).
68	A	A	494,5	1H RMN (400 MHz, D6-dmso),δ anterior 12 (2 H), 7,97 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,84-7,83 (m, 1 H), 7,70 (t, 1 H, J = 6,8 Hz), 7,60 & 7,53 (AB, 2 H, J = 8,8 Hz), 7,30 (q, 1 H, J = 7,6 Hz), 7,21 (t, 1 H, J = 8,4 Hz), 7,05 (t, 1 H, J = 7,6 Hz), 6,99-6,97 (m, 1 H), 6,78 (t, 1 H, J = 6,8 Hz), 6,64 (t, 1 H, J = 6,8 Hz), 5,82 (s, 2 H), 3,34 (q, 2 H, J = 8,0 Hz), 1,01 (t, 3 H, J = 7,2 Hz)
69	C	A	526,5	1H RMN (400 MHz, D6-dmso),δ12,20 (s, 1 H), 11,95 (s, 1 H), 7,82 (s, 1 H), 7,73 (dd, 1 H, J = 2,2 & 4,7 Hz), 7,62 & 7,46 (AB, 2 H, J = 9,0 Hz), 7,52 (dd, 1 H, J = 1,7 & 4,3 Hz), 7,31 (dt, 1 H, J = 4,3 & 9,3 Hz), 7,16-7,10 (m, 1 H), 6,36 (t, 1 H, J = 6,8 Hz), 6,27-6,22

				(m, 1 H), 5,93 (s, 2 H), 3,32 (s, 3 H), 2,77 (q, 2 H, J = 7,7 Hz), 1,19 (t, 3 H, J = 7,7 Hz).
70	C	C	508,5	1H RMN (400 MHz, D6-dmso), δ12,18 (s, 1 H), 11,94 (s, 1 H), 7,81 (s, 1 H), 7,72 (dd, 1 H, J = 1,7 & 5,1 Hz), 7,59 & 7,44 (AB, 2 H, J = 9,0 Hz), 7,52 (d, 1 H, J = 2,2 Hz), 7,27-7,19 (m, 2 H), 6,99 (t, 1 H, J = 7,7 Hz), 6,46 (t, 1 H, J = 7,7 Hz), 6,35 (t, 1 H, J = 6,8 Hz), 5,95 (s, 2 H), 3,32 (s, 3 H), 2,76 (q, 2 H, J = 7,2 Hz), 1,18 (t, 3 H, J = 7,7 Hz).
74	A	A	532,9	1H RMN (400 MHz, D6-dmso), δ 12,71 (s, 1 H), 12,59 (d, 1 H, J = 5,5 Hz), 8,18 (s, 1 H), 8,00 (dd, 1 H, J = 1,8 & 6,8 Hz), 7,67-7,63 (m, 1 H), 7. 65 & 7,53 (AB, 2 H, J = 8,5 Hz), 7,30 (dt, 1 H, J = 4,2 & 8,9 Hz), 7,18-7,13 (m, 1 H), 6,61-6,56 (m, 2 H), 5,80 (s, 2 H), 3,24 (s, 3 H).
76	B	C	417,4	1H RMN (400 MHz, D6-dmso), δ12,95 (s, 1 H), 11,76 (s, 1 H), 7,69 (dd, 1 H, J = 1,8 & 6,9 Hz), 7,42 & 7,36 (AB, 2 H, J = 8,7 Hz), 7,43-7,40 (m, 1 H), 7,29- 7,18 (m, 2 H), 7,02 (t, 1 H, J = 7,3 Hz), 6,58 (t, 1 H, J = 6,9 Hz), 6,56 (s, 1 H), 6,34 (t, 1 H, J = 6,9 Hz), 5,92 (s, 2 H), 2,34 (s, 3 H).
77	A	A	419,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (1 H), 11,76 (s, 1 H), 7,95 (d, 1 H, J = 2,0 Hz), 7,89 (bs, 2 H), 7,87 (bs, 1 H), 7,64 (dd, 1 H, J = 2,4 & 6,8 Hz), 7,43 (d, 1 H, J = 10,8 Hz), 7,43-7,41 (m, 1 H), 7,09 (d, 1 H, J = 2,4 Hz), 6,62 (dd, 1 H, J = 1,6 Hz), 6,33 (t, 1 H, J = 6,8 Hz), 6,28 (s, 1 H), 5,88 (s, 2 H).

78	B	A	420,4	El compuesto 78 ; 1H RMN (500 MHz, DMSO): 7,95 (bs, 1H), 7,68 (m,1H), 7,44 (m, 2H), 7,31 (m, 1H), 7,09 (bs, 1H), 6,33 (t, 1H, J = 6,6 Hz), 5,95 (m, 1H), 5,72 (s, 2H), 5,64 (bs, 1H)
79	A	A	421,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (1 H), 11,74 (s, 1 H), 7,92 (d, 1 H, J = 2,0 Hz), 7,65 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,44 (d, 1 H, J = 10,8 Hz), 7,41-7,37 (m, 1 H), 7,28 (q, 1 H, J = 6,0 Hz), 7,21 (t, 1 H, J = 8,4 Hz), 7,07 (d, 1 H, J = 2,4 Hz), 7,04 (dt, 1 H, J = 7,6 & 1,2 Hz), 6,58 (t, 1 H, J = 8,8 Hz), 6,31 (t, 1 H, J = 6,4 Hz), 5,93 (s, 2 H)
80	A	A		Ver Ejemplo 11 para los detalles y datos experimentales
81	A	A	432,4	1H RMN (400 MHz, dmso) δ 3,965 (q, 2H, J = 5,5 Hz), 5,885 (s, 2H), 6,326 (t,1H, J = 6,7 Hz), 6,972 (d, 1H, J = 6,1 Hz), 7,0595 (d,1H, J = 2,4 Hz), 7,280 (s, 1H), 7,30-7,39 (m, 3H), 7,413 (d, 1H, J = 7,3 Hz), 7,644 (dd, 1 H, J = 6,7, 1,8 Hz), 7,922 (d, 1H, 2,4 Hz), 8,203 (br s, 3H)
82	A	A	432,4	1H RMN (400 MHz, dmso) δ 3,941 (q, 2H, J = 5,5 Hz). 5,883 (s, 2H), 6,316 (t,1H, J = 6,7 Hz), 7,056 (d, 1H, J = 1,8 Hz), 7,12 (d, 2H, J = 7,9 Hz), 7,369 (d, 2H, J = 7,9 Hz), 7,409 (dd, 1H, J = 6,1, 1,8 Hz), 7,443 (d, 1H, J = 11 Hz), 7,637 (dd, 1H, J = 6,7, 1,8 Hz), 7,915 (d, 1H, J = 1,8 Hz), 8,166 (br s, 3H)
83	A	A	434,4	1H RMN (500 MHz, CD3OD): δ 7,81(dd, 1H, J= 2,2Hz), 7,62 (d,1H, J= 2Hz), 7,42 (m, 1H, 7,24 (bs,

				1H), 6,98 (d, 1H, J=10,7), 6,90 (d, 1H, J = 2,2 Hz), 6,48 (t, 1H, J= 6,3 Hz), 5,91 (s, 2H), 5,50 (bs, 1H), 2,29 (s, 3H)
84	A	A	435,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (1 H), 11,74 (s, 1 H), 7,92 (d, 1 H, J = 2,0 Hz), 7,65 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,42 (d, 1 H, J = 10,8 Hz), 7,39-7,38 (m, 1 H), 7,14 (t, 1 H, J = 7,6 Hz), 7,06 (d, 1 H, J = 2,0 Hz), 6,91 (t, 1 H, J = 7,6 Hz), 6,36 (t, 1 H, J = 7,6 Hz), 6,31 (t, 1 H, J = 6,4 Hz), 5,91 (s, 2 H), 2,23 (d, 3 H, J = 1,2 Hz)
85	A	C	435,4	1H RMN (400 MHz, D6-dmso), δ anterior 12,97 (s, H), 11,75 (s, 1 H), 7,70 (dd, 1 H, J = 1,8 & 6,8 Hz), 7,44 &7,38 (AB, 2 H, J = 8,7 Hz), 7,45-7,36 (m, 1 H), 7,29 (dt, 1 H, J = 4,6 & 9,1 Hz), 7,15-7,10 (m, 1 H), 6,57 (d, 1 H, J = 0,9 Hz), 6,34 (t, 1 H, J = 6,8 Hz), 6,35-6,30 (m, 1 H), 5,89 (s, 2 H), 2,34 (s, 3 H).
87	A	A	438,4	1H RMN (500 MHz, DMSO): δ 7,97 (d, J = 2,2 Hz, 1H), 7,73 (m, 1H), 7,69 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,54 (d, J = 11,0 Hz, 1H), 7,43 (m, 1H), 7,11 (d, J = 2,2 Hz, 1H), 6,34 (t, J = 6,6 Hz, 1H), 5,85 (s, 2H), 5,27 (s, 1H).

#	IC50	EC50	LR-MS (M+H)	DATOS

88	B	B	438,4	1H-RMN (400 MHz, en dmso-d6):δ12,92 (1H, ancho s), 9,74 (1H, s), 7,89 (1H, s), 7,49(1H, d, J = 10,90 Hz), 7,25 (2H, m), 7,04 (3H, m), 6,94 (2H, m), 6,56 (1H, dd, J = 7,266, 7,266 Hz), 5,97 (2H, s)
89	A	A	439,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (1 H), 11,75 (s, 1 H), 7,93 (d, 1 H, J = 2,0 Hz), 7,66 (dd, 1 H, J = 2,4 & 7,5 Hz), 7,48 (d, 1 H, J = 10,8 Hz), 7,41-7,39 (m, 1 H), 7,30 (dt, 1 H, J = 4,8 & 8,2 Hz), 7,17-7,12 (m, 1 H), 7,08 (d, 1 H, J = 2,0 Hz), 6,37-6,33 (m, 1 H), 6,31 (t, 1 H, J = 6,8 Hz), 5,90 (s, 2 H)
91	A	A	443,4	1H RMN (400 MHz, dmso) δ 6,058 (s, 2H), 6,328 (t,1H, J = 6,6 Hz), 7,063 (d, 1H, 2,2 Hz), 7,388 (dd, 1H, J = 8,7, 1,46 Hz), 7,41-7,45 (m, 1H), 7,479 (s, 1H), 7,502 (d, 1H, J = 10,3 Hz), 7,642 (dd, 1H, J = 7,3, 2,2 Hz), 7,796 (d, 1H, 8 Hz), 7,927 (d, 1H, J = 2,2 Hz), 9,456 (s, 1H)
92	A	A	446,4	1H RMN (400 MHz, dmso) δ 5,901 (s, 2H), 6,313 (t, 1H, J = 6,6 Hz), 7,05-7,07 (m, 1H), 7,09 (d, 1H, J = 8 Hz), 7,3-7,375 (m, 2H), 7,398 (d, 1H, J = 6,6 Hz), 7,45 (d, 1H, J = 10,3 Hz), 7,646 (d, 1H, J = 6,6 Hz), 7,712 (m, 2 H), 7,9-7,96 (m, 2H)
93	A	A	446,4	1H RMN (400 MHz, dmso) δ 5,911 (s, 2H), 6,313 (t, 1H, J = 6,6 Hz), 7,05-7,07 (m, 1H), 7,101 (d, 2H, J = 7,3 Hz), 7,306 (s, 1H), 7,402 (d,1H, J = 6,6 Hz), 7,437 (d, 1H, J = 11 Hz), 7,660 (dd, 1H, J = 6,6, 1,5 Hz), 7,50 (d, 2H, J = 7,3 Hz), 7,879 (s, 1H), 7,9-7,94 (m, 1H)

94	A	A	446,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (1 H), 11,75 (s, 1 H), 7,86 (bs, 1 H), 7,84-7,83 (m, 1 H), 7,81-7,77 (m, 1 H), 7,66 (td, 1 H, J = 1,2 & 5,2 Hz), 7,55 (dd, 1 H, J = 1,2 & 8,4 Hz), 7,46 (d, 1 H, J = 8,8 Hz), 7,41 (d, 1 H, J = 5,6 Hz), 7,32-7,28 (m, 3 H), 6,97-6,96 (m, 1H), 6,34 (t, 1 H, J = 6,8 Hz), 5,95 (s, 2 H).
95	A	A	450,4	1H RMN (400 MHz, D6-dmso), δ11,79 (s, 2 H), 8,38 (b, 3 H), 7,93 (d, 1 H, J = 2,0 Hz), 7,65 (dd, 1 H, J = 2,0 & 4,8 Hz), 7,46-7,39 (m, 3 H), 7,15 (d, 1 H, J = 8,0 Hz), 7,07 (d, 1 H, J = 2,0 Hz), 6,62 (t, 1 H, J = 7,6 Hz), 6,32 (t, 1 H, J = 6,8 Hz), 5,93 (s, 2 H), 3,98-3,94 (m, 2 H).
96	A	A	452,4	1H RMN (500 MHz, DMSO): 7,99 (m, 1H), 7,98 (m, 1H), 7,69 (m, 1H), 7,53 (m, 1H), 7,44 (s, 1H), 7,11 (m, 1H), 6,34 (m, 1H), 5,84 (s, 2H), 5,21(m, 1H), 3,33 (s, 3H)
97	A	A	452,4	1H-RMN (400 MHz, en dmso-d6):δ12,94 (1H, ancho s), 11,73 (1H, ancho s), 7,94(1H, Ancho s), 7,90 (1H, dd, J = 0,55, 2,20 Hz), 7,62 (1H, dd, J = 2,2, 6,6 Hz), 7,54 (1H, s), 7,52 (1H, dd, J = 1,1, 1,65 Hz), 7,40 (1H, m), 7,37 (1H, d, 1,1 Hz), 7,31 (1H, Ancho s), 7,06 (1H, d, J = 2,2 Hz), 6,31 (1H, dd, J = 6,6, 7,14), 5,0 (1H, s)
98	B	B	453,4	1H-RMN (400 MHz, en dmso-d6):δ13,09 (1H, ancho s), 11,73 (1H, ancho s), 8,06 (2H, m), 7,90 (1H, s), 7,74 (2H, m), 7,60 (1H, d, J = 6,04 Hz), 7,40 (1H, d,

				J = 4,94 Hz), 7,06 (1H, s), 6,30 (1H, dd, J = 6,04, 6,59 Hz), 6,09 (2H, s)
99	A	B	454,5	1H-RMN (400 MHz, en dmso-d6):δ12,87 (1H, ancho s), 11,64 (1H, ancho s), 7,94 (1H, s), 7,50 (1H, d, J = 1,65 Hz), 7,43 (1H, dd, J = 1,65, 6,59 Hz), 7,33 (1H, d, J = 2,2,0 Hz), 7,31 (2H, s), 7,00 (1H, d, J = 9,89 Hz), 6,24 (1H, t, J = 6,59 Hz), 5,65 (2H, s), 4,60 (2H, t, J = 8,79 Hz), 3,18 (2H, t, J = 8,79 Hz)
100	A	A	458,4	1H RMN (400 MHz, D6-dmso), δ12,96 (s, 1 H), 11,74 (s, 2 H), 7,90 (d, 1 H, J = 2,0 Hz), 7,64 (dd, 1 H, J = 1,2 & 5,6 Hz), 7,51 (s, 1 H), 7,45 (d, 1 H, J = 10,8 Hz), 7,40 (d, 1 H, J = 6,8 Hz), 7,17 (d, 1 H, J = 8,4 Hz), 7,05-7,03 (m, 2 H), 6,32 (t, 1 H, J = 6,4 Hz), 5,88 (s, 2 H), 3,35 (s, 2 H).
101	A	A	458,4	1H RMN (400 MHz, D6-dmso), δ13,02 (s, 1 H), 12,45 (s, 1 H), 12,36 (s, 1 H), 11,75 (s, 1 H), 8,42 (s, 2 H), 7,92 (d, 1 H, J = 2,0 Hz), 7,63 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,48 (d, 1 H, J = 10,8 Hz), 7,41 (d, 1 H, J = 6,0 Hz), 7,27 (d, 1 H, J = 8,4 Hz), 7,08-7,05 (m, 3 H), 6,32 (t, 1 H, J = 6,4 Hz), 5,93 (s, 2 H).
102	A	A	459,4	1H RMN (400 MHz, D6-dmso), δ12,89 (s, 1 H), 11,74 (s, 1 H), 7,91 (dd, 1 H, J = 2,0 & 0,4 Hz), 7,65 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,55 (bs, 1 H), 7,46 (d, 1 H, J = 10,8 Hz), 7,40 (d, 1 H, J = 6,8 Hz), 7,37 (d, 1 H, J = 8,8 Hz), 7,24 (dd, 1 H, J = 1,2 & 8,8 Hz), 7,06 (d, 1 H, J = 2,4 Hz), 6,33 (s, 2 H), 6,32 (t, 1 H, J = 6,8 Hz), 5,93 (s, 2 H).

103	A	A	459,4	1H RMN (400 MHz, d6-DMSO): □ 11,76 (br s, 1H), 10,54 (s, 1H), 10,48 (S, 1H), 7,90 (d, J = 2,0 Hz, 1H), 7,62 (dd, J = 2,0, 6,8 Hz, 1H), 7,48 (d, J = 6,8 Hz, 1H), 7,40 (dd, J = 1,6, 6,4 Hz, 1H), 7,05 (d, J = 2,0 Hz, 1H), 6,83-6,77 (m, 2 H), 6,69 (s, 1 H), 6,31 (t, J = 6,8 Hz, 1H), 5,82 (s, 2 H); LCMS experimental C24H15FN4O5: 459,3 (M+H)+.
104	A	C	460,4	1H RMN (400 MHz, D6-dmso), δ 13,01 (s, 1 H), 11,76 (s, 1 H), 8,17 (dd, 1 H, J = 2,8 & 9,2 Hz), 7,85 (d, 1 H, J = 2,0 Hz), 7,68 (dd, 1 H, J = 2,4 & 6,8 Hz), 7,53 & 7,38 (AB, 2 H, J = 8,8 Hz), 7,43-7,41 (m, 1 H), 7,35 (d, 1 H, J = 2,8 Hz), 7,28 (d, 1 H, J = 9,2 Hz), 6,96 (d, 1 H, J = 2,0 Hz), 6,35 (t, 1 H, J = 6,8 Hz), 5,86 (s, 2 H), 4,01 (s, 3 H)
105	A	A	461,4	1H RMN (400 MHz, dmso) δ 6,058 (s, 2H), 6,335 (t, 1H, J = 6,6 Hz), 6,946 (d, 1H, J = 5,9 Hz), 7,079 (d, 1H, J = 2,2 Hz), 7,425 (dd, 1H, J = 6,6, 2,2 Hz), 7,507 (d, 1H, J = 11 Hz), 7,652 (dd, 1H, J = 6,6, 2,2 Hz), 7,791 (d, 1H, J = 9,5 Hz), 7,944 (d, 1H, J = 2,2 Hz), 9,370 (s, 1H)
106	A	A	499,3	1H RMN (500 MHz, CDCl3): 8,06(d, 1H, J= 6,9 Hz), 7,54 (m,1H), 7,49 (d, 1H, J= 2,2 Hz), 7,29 (m, 1H), 7,14 (d, 1H, J=10,08 Hz), 7,06 (dd, 1H, J = 3,7 Hz), 6,91 (d, 1H, J= 2,2 Hz), 6,73 (t, 1H, J = 6,6 Hz), 5,96 (bs, 2H), 1,90 (m, 1H), 0,85(m, 4H)
107	A	A	464,4	1H RMN (400 MHz, D6-dmso), δ anterior 12,91 (s, H), 11,74 (s, 1 H), 7,92 (d, 1 H, J = 2,4 Hz), 7,87 (s,

				1 H), 7,82-7,78 (m, 1 H), 7,64 (dd, 1 H, J = 2,1 & 6,8 Hz), 7,47 (d, 1 H, J = 10,8 Hz), 7,40 (d, 1 H, J = 7,6 Hz), 7,31-7,27 (m, 3 H), 7,07 (d, 1 H, J = 2,4 Hz), 6,32 (t, 1 H, J = 6,8 Hz), 5,92 (s, 2 H).
108	A	B	465,4	1H RMN (400 MHz, D6-dmso), δ anterior 12,94 (s, H), 11,74 (s, 1 H), 7,93 (d, 1 H, J = 2,0 Hz), 7,89-7,85 (m, 1 H), 7,63 (dd, 1 H, J = 2,4 & 4,4 Hz), 7,49 (d, 1 H, J = 10,8 Hz), 7,42-7,32 (m, 3 H), 7,08 (d, 1 H, J = 2,0 Hz), 6,32 (t, 1 H, J = 6,4 Hz), 5,93 (s, 2 H).
109	A	A	465,4	1H-RMN (400 MHz, en dmso-d6):δ12,96 (1H, ancho s), 11,76 (1H, ancho s), 8,60 (1H, d, J = 1,1 Hz), 8,12 (1H, s), 7,94 (1H, d, J = 2,2 Hz), 7,64 (1H, dd, J = 2,20, 6,59 Hz), 7,59 (1H, s), 7,57 (1H, s), 7,41 (1H, d, J = 5,5 Hz), 7,09 (1H, d, J = 2,2 Hz), 6,32 (1H, dd, J = 6,59, 6,59 Hz), 5,88 (2H, s)
111	A	A	466,4	1H RMN (400 MHz, D6-dmso), δ13,00 (s, 1 H), 11,74 (s, 1 H), 8,23-8,19 (m, 1 H), 7,94 (d, 1 H, J = 2,0 Hz), 7,64 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,58-7,57 (m, 1 H), 7,56, 7,53 (AB, 2 H, J = 3,6 Hz), 7,41 (d, 1 H, J = 7,2 Hz), 7,08 (d, 1 H, J = 2,0 Hz), 6,31 (t, 1 H, J = 6,8 Hz), 5,95 (s, 2 H).
113	A	A	467,4	1H-RMN (400 MHz, en dmso-d6):δ12,90 (1H, ancho s), 11,66 (1H, ancho s), 8,59 (1H, d, J = 1,65 Hz), 8,12 (1H, s), 7,59 (1H, s), 7,55 (1H, dd, J = 1,65, 9,34 Hz), 7,45 (1H, dd, J = 2,2, 6,59 Hz), 7,02 (1H, d, J = 0,89, Hz), 6,25 (1H, dd, J = 6,59, 6,59 Hz), 5,74 (2H, s), 4,63 (2H, t, J = 8,79 Hz), 3,20 (2H, t, J = 8,79

				Hz)
114	A	A		Ver Ejemplo 12 para los detalles y datos experimentales
115	A	A	470,4	1H RMN (400 MHz, dmso) δ 5,686 (s, 2H), 6,338 (t, 1H, J = 6,7 Hz), 6,854 (d, 2H, J = 1,8 Hz), 7,025-7,09 (m, 2H), 7,296 (d, 1H, J = 7,9 Hz), 7,38-7,46 (m, 4H), 7,694 (dd, 1H, J = 6,7, 1,8 Hz), 7,926 (d, 1H, J = 2,4 Hz)
116	A	A	470,9	1H RMN (400 MHz, D6-dmso), δ anterior 12,93 (s, H), 11,77 (s, 1 H), 7,96 (d, 1 H, J = 8,8 Hz), 7,88 (d, 1 H, J = 2,0 Hz), 7,77-7,74 (m, 3 H), 7,55, 7,48 (AB, 2 H, J = 8,4 Hz), 7,56-7,49 (m, 1 H), 7,43 (dd, 1 H, J = 2,0 & 4,8 Hz), 7,18 (s, 1 H), 6,99 (d, 1 H, J = 2,0 Hz), 6,36 (t, 1 H, J = 6,4 Hz), 6,05 (s, 2 H).
117	A	A		Ver Ejemplo 13 para los detalles y datos experimentales
119	A	A	473,8	1H RMN (400 MHz, D6-dmso), δ13,06 (s, 1 H), 11,76 (s, 1 H), 8,20 (s, 1 H), 7,66 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,61 (d, 1 H, J = 11,6 Hz), 7,40 (d, 1 H, J = 6,4 Hz), 7,29 (dt, 1 H, J = 4,4 & 9,2 Hz), 7,17-7,10 (m, 1 H), 6,40-6,35 (m, 1 H), 6,30 (t, 1 H, J = 6,8 Hz), 5,91 (s, 2 H).
120	A	A	477,9	1H RMN (400 MHz, dmso) δ 6,044 (s, 2H), 6,349 (t, 1H, J = 6,6 Hz), 6,535 (s, 1H), 7,091 (d, 1H, J = 2,2 Hz), 7,406 (d, 1H, J = 11 Hz), 7,435 (dd, 1H, J = 6,6, 1,5 Hz), 7,665-7,695 (m, 1H), 7,966 (d, 1H, J =2,2 Hz), 8,049 (s, 1H), 9,305 (s, 1H)

121	A	A	478,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 11,41 (s, 1 H), 8,26 (b, 1 H), 7,80 (s, 1 H), 7,70-7,65 (m, 1 H), 7,54-7,46 (m, 1 H), 7,27 (t, 1 H, J = 8,0 Hz), 7,21-7,14 (m, 1H), 7,12-7,05 (m, 1 H), 6,96 (s, 1 H), 6,19 (b, 1H), 6,04 (b, 2 H), 2,64 (d, 3 H, J = 4,4 Hz).
126	A	A	488,9	1H RMN (400 MHz, D6-dmso), δ anterior 12,90 (s, H), 11,77 (s, 1 H), 7,96-7,94 (m, 2 H), 7,79-7,71 (m, 3 H), 7,56-7,51 (m, 2 H), 7,42 (d, 1 H, J = 6,0 Hz), 7,17 (s, 1 H), 7,09 (d, 1 H, J = 2,8 Hz), 6,34 (t, 1 H, J = 6,4 Hz), 6,01 (s, 2 H).
127	A	A	489,4	Ver Ejemplo 14 para los detalles y datos experimentales
128	C	A	489,9	1H RMN (400 MHz, D6-dmso), δ12,94 (s, 1 H), 7,96 (d, 1 H, J = 8,8 Hz), 7,93- 7,92 (m, 1 H), 7,81 (d, 1 H, J = 7,2 Hz), 7,76 (tt, 1 H, J = 6,8 & 1,2 Hz), 7,65 (tt, 1 H, J = 7,6 & 1,2 Hz), 7,61 (d, 1 H, J = 11,2 Hz), 7,55-7,51 (m, 1 H), 7,45 (q, 1 H, J = 7,2 Hz), 7,31-7,26 (m, 2 H), 7,21 (s, 1 H), 7,10-7,09 (m, 1 H), 6,06 (s, 2 H).
130	B	A	492,5	1H RMN (400 MHz, D6-dmso), δ 11,74 (s, 1 H), 7,95 (dd, 1 H, J = 0,4 & 2,5 Hz), 7,89 (b, 1 H), 7,82-7,78 (m, 1 H), 7,68 (dd, 1 H, J = 1,6 & 6,8 Hz), 7,52 (d, 1 H, J = 10,8 Hz), 7,40 (d, 1 H, J = 6,4 Hz), 7,33-7,27 (m, 3 H), 7,09 (dd, 1 H, J = 0,4 & 1,6 Hz), 6,30 (t, 1 H, J = 6,4 Hz), 5,89 (s, 2 H), 4,02 (q, 2 H, J = 6,8 Hz), 0,98 (t, 2 H, J = 6,8 Hz).
131	A	A	493,9	1H RMN (400 MHz, d6-DMSO): ? 11,75 (br s, 1H), 10,71 (s, 1H), 10,40 (S, 1H), 7,94 (s, 1H), 7,64 (d, J

				= 2,0 Hz, 1H), 7,42 (s, 1H), 7,28 (d, J = 11,2 Hz, 1H), 7,08 (s, 1H), 7,01 (s, 1H), 6,34 (s, 1 H), 5,87 (s, 3 H); LCMS experimental C24H14ClFN4O5: 493,3 (M+H)+.
132	B	B	494,5	1H RMN (400 MHz, D6-dmso), δ anterior 12,80 (s, H), 12,62 (d, 1 H), 7,97 (dd, 1 H, J = 2,0 & 4,8 Hz), 7,69 (dt, 1 H, J = 16 & 6,0 Hz), 7,46, 7,40 (AB, 2 H, J = 8,4 Hz), 7,31-7,26 (m, 1 H), 7,20 (t, 1 H, J = 9,2 Hz), 7,04 (t, 1 H, J = 8,0 Hz), 6,80 (t, 1 H, J = 8,0 Hz), 6,62 (t, 1 H, J = 6,8 Hz), 6,59 (d, 1 H, J = 0,8 Hz), 5,78 (s, 2 H), 3,22 (s, 3 H), 2,33 (s, 3 H).
133	A	A	496,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (dd, 1 H, J = 2,4 & 4,8 Hz), 7,88 (d, 1 H, J = 6,8 Hz), 7,79 (b, 1 H), 7,72 (b, 1H), 7,44 (d, 1 H, J = 10,4 Hz), 7,12 (d, 1 H, J = 2,4 Hz), 6,66 (t, 1 H, J = 6,8 Hz), 6,61 (dd, 1 H, J = 6,4 & 1,6 Hz), 6,37 (s, 1 H), 5,72 (s, 2 H), 3,27 (s, 3 H).
134	A	A	498,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (m, 1 H), 7,92 (d, 1 H, J = 2,0 Hz), 7,66 (b, 1 H), 7,51 (d, 1 H, J = 10,4 Hz), 7,30 (dd, 1 H, J = 7,2 & 14,4 Hz), 7,21 (t, 1 H, J = 8,0 Hz), 7,09 (d, 1 H, J = 2,4 Hz), 7,07 (dt, 1 H, J = 1,2 & 7,2 Hz), 6,83 (t, 1 H, J = 8,4 Hz), 6,60 (b, 1 H), 5,79 (s, 2 H), 3,19 (s, 3 H).
135	A	A	499,3	1H RMN (500 MHz, DMSO): 7,93(bs, 1H), 7,80 (m,1H), 7,66 (m, 1H), 7,41 (m, 2H), 7,08 (m, 1H), 6,34 (m, 1H), 5,76 (bs, 2H), 5,03 (m, 1H). M.S. experimental: 498,3 (M)+.

136	A	A	502,9	1H RMN (500 MHz, DMSO): 7,93(d, 1H, J = 2,2 Hz), 7,60-7,80(m,3H), 7,52(d, 1H, J =10 Hz), 7,42 (m, 1H), 7,09 (d, 1H, J = 2,2 Hz), 6,34 (t, 1H, J = 6,9 Hz, 6,3 Hz), 5,99 (bs, 2H)
138	A	A	502,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,99 (b, 1 H), 7,83 (d, 1 H, J = 2,0 Hz), 7,69 (b, 1 H), 7,55 (d, 1 H, J = 8,0 Hz), 7,37 (d, 1 H, J = 8,8 Hz), 7,20 (d, 1 H, J = 8,4 Hz), 7,11 (t, 1 H, J = 7,6 Hz), 6,98-6,94 (m, 2 H), 6,64 (b, 1 H), 6,22 (d, 1 H, J = 7,6 Hz), 5,74 (s, 2 H), 2,85-2,70 (m, 1 H), 2,38 (s, 3 H), 0,90-0,83 (m, 4 H).
139	A	A	502,9	1H RMN (500 MHz, DMSO): □ 7,98 (d, 1H, J= 2,2 Hz), 7,76 (bs,1H), 7,75(dd, 1H, J= 1,89 Hz, 2,2 Hz), 7,68 (d, 1H, J = 8,5 Hz), 7,57 (d, 1H, J=10,7 Hz), 7,45 (m, 1H), 7,40 (dd, 1H, J= 1,57 Hz), 7,12 (m, 2H), 6,36 (t, 1H, J = 6,3 Hz), 6,01 (bs, 2H), 2,50 (s, 3H, hidden en dmso). M.S. experimental: 502,3 (M+H)+.
140	A	A	502,9	1H RMN (500 MHz, CD3OD): 7,95 - 7,80 (m, 2H), 7,66 (m, 1H), 7,57 (m, 1H), 7,51 (s, 1H), 7,45 (m, 1H), 7,40 (s, 1H), 6,96 (d, J = 10,4 Hz, 1H), 6,91 (m, 1H), 6,53 (m, 1H), 6,15(s, 2H), 2,43 (s, 3H).
141	A	C	504,5	1H RMN (400 MHz, D6-dmso), δ anterior 12,92 (s, H), 11,47 (s, 1 H), 8,36 (d, 1 H, J = 4,0 Hz), 7,93 (d, 1 H, J = 2,4 Hz), 7,75- 7,71 (m, 1 H), 7,40 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,47 (d, 1 H, J = 10,8 Hz), 7,41 (d, 1 H, J = 5,2 Hz), 7,31-7,23 (m, 2 H), 7,08 (d, 1 H, J =

				2,4 Hz), 6,32 (t, 1 H, J = 6,4 Hz), 5,93 (s, 2 H), 2,72-2,66 (m, 1 H), 0,63-0,58 (m, 2 H), 0,49-0,45 (m, 2 H).
143	A	A	506,9	1H RMN (500 MHz, CD3OD): □ 7,88 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,64 (d, J = 2,2 Hz, 1H), 7,45 - 7,41 (m, 2H), 6,94-6,90 (m, 2H), 6,50 (t, J = 6,6 Hz, 1H), 6,05(s, 2H), 3,97 (s, 3H), 2,34 (s, 3H).
145	A	B	511,4	1H RMN (400 MHz, dmso) δ 6,011 (s, 2H), 6,322 (t, 1H, J = 6,7 Hz), 7,055 (d, 1H, J = 1,8 Hz), 7,212 (dd, 1H, J = 8,5, 1,2 Hz), 7,351 (s, 1H), 7,407 (dd, 1H, J = 6,1, 1,8 Hz), 7,508 (d, 1H, J = 11 Hz), 7,642 (d, 1H, J = 1,8 Hz), 7,659 (d, 1H, J = 1,8 Hz), 7,91 (d, 1H, J = 1,8 Hz)
146	A	A	512,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,95 (dd, 1 H, J = 6,4 & 1,2 Hz), 7,91 (d, 1 H, J = 2,0 Hz), 7,66 (t, 1 H, J = 5,2 Hz), 7,49 (d, 1 H, J = 10,8 Hz), 7,17 (t, 1 H, J = 8,0 Hz), 7,08 (d, 1 H, J = 2,0 Hz), 6,94 (t, 1 H, J = 7,6 Hz), 6,64-6,55 (m, 2 H), 5,76 (s, 2 H), 3,19 (s, 3 H), 2,22 (m, 3 H).
147	A	C	512,5	1H RMN (400 MHz, D6-dmso), δ anterior 12,79 (s, 1 H), 12,61 (s, 1 H), 8,00 (td, 1 H, J = 2,0 & 7,2 Hz), 7,67 (t, 1 H, J = 6,0 Hz), 7,50 7,39 (m, 2 H), 7,32-7,26 (m, 1 H), 7,17-7,12 (m, 1 H), 6,62 (t, 1 H, J = 6,8 Hz), 6,59-6,53 (m, 2 H), 5,75 (s, 2 H), 3,24 (d, 3 H, J = 1,2 Hz), 2,34 (s, 3 H).
148	A	A	514,5	1H-RMN (400 MHz, en dmso-d6):δ12,96 (1H, ancho s), 11,76 (1H, ancho s), 7,76 (1H, d, J = 5,86 Hz), 7,59 (1H, m), 7,28 (1H, ddd, J = 3,66, 8,79, 8,79 Hz),

				7,20 (1H, d, J = 8,79), 7,16 (1H, m), 7,03 (1H, d, J = 8,79), 6,59 (1H, m), 6,54 (1H, dd, J = 6,59, 6,59 Hz), 5,64 (2H, s), 4,66 (1H, dd, J = 8,79, 9,52 Hz), 4,04 (1H, dd, J = 7,32, 8,79 Hz), 3,51 (1H, m), 3,23 (3H, s), 1,23 (3H, d, J = 5,86 Hz)
149	A	A	514,9	1H RMN (400 MHz, D6-dmso), δ12,73 (s, 1 H), 12,59 (s, 1 H), 8,17 (s, 1 H), 7,97 (d, 1 H, J = 8,0 Hz), 7,66 & 7,51 (AB, 2 H, J = 9,0 Hz), 7,67-7,36 (bm, 1 H), 7,30 (q, 1 H, J = 7,3 Hz), 7,21 (t, 1 H, J = 8,5 Hz), 7,05 (t, 1 H, J = 7,3 Hz), 6,82 (t, 1 H, J = 7,7 Hz), 6,59 (t, 1 H, J = 6,8 Hz), 5,83 (s, 2 H), 3,22 (s, 3 H).
150	A	A	516,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,98 (d, 1 H, J = 6,4 Hz), 7,93 (d, 1 H, J = 2,4 Hz), 7,66 (t, 1 H, J = 5,2 Hz), 7,52 (d, 1 H, J = 10,8 Hz), 7,30 (dt, 1 H, J = 4,0 & 8,8 Hz), 7,19-7,13 (m, 1 H), 7,10 (d, 1 H, J = 2,4 Hz), 6,62-6,57 (m, 2 H), 5,76 (s, 2 H), 3,22 (m, 2 H).
151	A	B	516,5	1H RMN (400 MHz, D6-dmso), δ12,71 (s, 1 H), 12,54 (s, 1 H), 7,99 (dd, 1 H, J = 6,8 & 2,1 Hz), 7,89 (d, 1 H, J = 2,1 Hz), 7,66 (s, 1 H), 7,42 (d, 1 H, J = 12,8 Hz), 7,30 (dt, 1 H, J = 4,7 & 9,4 Hz), 7,18-7,12 (m, 1 H), 6,96 (d, 1 H, J = 1,7 Hz), 6,60 (t, 1 H, J = 6,8 Hz), 6,55-6,51 (m, 1 H), 5,79 (s, 2 H), 3,27 (s, 3 H).

#	IC50	EC50	LR-MS (M+H)	DATOS
152	A	A	516,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,98 (d, 1 H, J = 6,4 Hz), 7,83 (s, 1 H), 7,69 (b, 1 H), 7,54 (t, 1 H, J = 10,0 Hz), 7,36 (d, 1 H, J = 9,6 Hz), 7,00 (bs, 1 H), 6,97 (bs, 1 H), 6,77 (d, 1 H, J = 9,2 Hz), 6,64 (t, 1 H, J = 11,2 Hz), 6,14 (d, 1 H, J = 8,8 H.z), 5,69 (s, 2 H), 2,83-2,76 (m,1 H), 2,33 (s, 3 H), 2,18 (s, 3 H), 0,89 (bm, 4 H).
153	A	A	518,9	1H RMN (500 MHz, DMSO): □ 7,98 (d, J = 2,0 Hz, 1H), 7,74 (dd, J = 1,9 Hz, J = 6,8 Hz, 1H), 7,71 (d, J = 9,0 Hz, 1H), 7,55 (d, J = 10,8 Hz, 1H), 7,45 (m, 1H), 7,39 (d, J = 2,4 Hz, 1H), 7,19 (dd, J = 2,4 Hz, J = 9,0 Hz, 1H), 7,13 (s, 1H), 7,11 (d, J = 2,0 Hz, 1H), 6,37 (t, J = 6,5 Hz, 1H), 6,0 (s, 2H), 3,91 (s, 3H).
154	A	A	518,9	1H RMN (500 MHz, DMSO): □ 7,99 (d, J = 2,2 Hz, 1H), 7,87 (d, J = 9,2 Hz; 1H), 7,74 (dd, J = 2,1 Hz, J = 6,8 Hz, 1H), 7,55 (d, J = 10,9 Hz, 1H), 7,45 (m, 1H), 7,38 (dd, J = 2,8 Hz, J = 9,2Hz, 1H), 7,21 (m, 1H), 7,13 (d, J = 2,2 Hz, 1H), 7,11 (m, 1H), 6,37 (t, J = 6,6 Hz, 1H), 6,02 (s, 2H), 3,77 (s, 3H).
155	A	A	520,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,95 (d, 1 H, J = 5,6 Hz), 7,82 (bd, 1 H, J = 2,0 Hz), 7,69 (b, 1 H), 7,58, 7,50 (AB, 2 H, J = 8,8 Hz), 7,16 (t, 1 H, J = 7,6 Hz), 6,97 (d, 1 H, J = 2,4 Hz), 6,94 (t, 1 H, J = 6,4 Hz), 6,68-6,57 (m, 2 H), 5,81 (s, 2 H), 2,95-2,88 (m,1 H), 2,22 (s, 3 H), 0,97 (s, 2 H), 0,93

				(s,2 H).
156	A	B	520,9	1H RMN (500 MHz, DMSO): 7,98 (d, J = 2,2 Hz, 1H), 7,72 (dd, J = 2,1 Hz, J = 6,8 Hz, 1H), 7,49 (d, J = 10,9 Hz, 1H), 7,45 (m, 1H), 7,11 (d, J = 2,2 Hz, 1H), 7,03 (m, 1H), 6,36 (t, J = 6,7 Hz, 1H), 5,97 (s, 2H), 5,12 (m, 1H), 1,49 (s, 3H), 1,47 (s, 3H).
158	A	B	522,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (dt, 1 H, J = 2,0 & 6,8 Hz), 7,83 (bd, 1 H), 7,73-7,69 (m, 1 H), 7,59, 7,52 (AB, 2 H, J = 8,8 Hz), 7,16 (t, 1H, J = 8,0 Hz), 6,98 (t, 1 H, J = 2,4 Hz), 6,92 (t, 1 H, J = 8,0 Hz), 6,64 (t, 1 H, J = 6,8 Hz), 6,53 (t, 1 H, J = 8,0 Hz), 5,81 (s, 2 H), 3,60 - 2,54 (m,1 H), 2,22 (s, 3 H), 1,12 (d, 6 H, J = 6,8 Hz).
159	A	A	523,3	1H RMN (400 MHz, D6-dmso), δ12,98 (s, 1 H), 11,77 (s, 1 H), 8,24 (d, 1 H, J = 2,4 Hz), 7,95 (d, 1 H, J = 8,5 Hz), 7,77 (t, 1 H, J = 7,3 Hz), 7,73-7,66 (m, 3 H), 7,53 (t, 1 H, J = 7,9 Hz), 7,42 (d, 1 H, J = 6,1 Hz), 7,17 (s, 1 H), 6,33 (t, 1 H, J = 6,7 Hz), 6,02 (s, 2 H).
161	A	A	523,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,98 (dt, 1 H, J = 2,4 & 7,2 Hz), 7,86 (s, 1 H), 7,82-7,80 (m, 2 H), 7,68 (t, 1H, J = 6,0 Hz), 7,59, 7,52 (AB, 2 H, J = 3,2 Hz), 7,53-7,51 (m, 1 H), 7,33 (s, 1 H), 7,30 (t, 1H, J = 9,2 Hz), 6,98-6,96 (m, 1 H), 6,63 (t, 1 H, J = 7,2 Hz), 5,81 (s, 2 H), 3,25 (s, 3 H).
162	A	A	524,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,95 (d, 1 H, J = 6,4 Hz), 7,92 (d, 1 H, J = 2,0 Hz) 7,69 (s, 1 H), 7,53 (d, 1 H, J = 10,8 Hz), 7,31 (dd, 1

				H, J = 1,5 & 1,4 Hz), 7,21 (t, 1H, J = 8,0 Hz), 7,10-7,06 (m, 2 H), 6,84 (t, 1 H, J = 8,4 Hz), 6,62 (s, 1 H), 5,81 (s, 2 H), 2,91-2,85 (m, 1 H), 0,95 (s, 2 H), 0,93 (s, 2 H).
163	A	A	526,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (dd, 1 H, J = 1,6 & 6,8 Hz), 7,91 (d, 1 H, J = 2,4 Hz) 7,71 (t, 1H, J = 6,4 Hz), 7,55 (d, 1 H, J = 10,8 Hz), 7,30 (dd, 1 H, J = 6,0 & 8,4 Hz), 7,21 (t, 1H, J = 8,4 Hz), 7,08 (d, 1H, J = 2,0 Hz), 7,06 (t, 1H, J = 7,6 Hz), 6,77 (t, 1 H, J = 7,2 Hz), 6,63 (t, 1H, J = 6,8 Hz), 5,81 (s, 2 H), 3,56 (h, 1 H, J = 6,8 Hz), 1,10 (d, 6 H, J = 6,8 Hz).
164	A	A	526,5	1H-RMN (400 MHz, en dmso-d6):δ12,61 (1H, ancho s), 12,53 (1H, ancho s), 7,74 (1H, dd, J = 2,20, 6,59 Hz), 7,62 (1H, ddd, J = 2,2, 6,59, 6,59 Hz), 7,29 (1H, ddd, J = 4,39, 8,79, 8,79 Hz), 7,21 (1H, d, J = 8,79 Hz), 7,15 (1H, m), 7,03 (1H, d, J = 8,79 Hz), 6,55 (2H, m), 5,66 (2H, s), 4,52 (2H, t, J = 8,79 Hz), 3,15 (2H, t, 8,79 Hz), 2,90 (1H, dt, J = 5,86, 12,45 Hz), 0,94 (4H, d, J = 5,86 Hz)
164	A	A	526,5	1H-RMN (400 MHz, en dmso-d6):δ12,61 (1H, ancho s), 12,53 (1H, ancho s), 7,74 (1H, dd, J = 2,20, 6,59 Hz), 7,62 (1H, ddd, J = 2,2, 6,59, 6,59 Hz), 7,29 (1H, ddd, J = 4,39, 8,79, 8,79 Hz), 7,21 (1H, d, J = 8,79 Hz), 7,15 (1H, m), 7,03 (1H, d, J = 8,79 Hz), 6,55 (2H, m), 5,66 (2H, s), 4,52 (2H, t, J = 8,79 Hz), 3,15 (2H, t, 8,79 Hz), 2,90 (1H, dt, J = 5,86, 12,45 Hz),

				0,94 (4H, d, J = 5,86 Hz)
				1H-RMN (400 MHz, en dmso-d6):δ12,67 (2H, m), (7,93 (1H, dd, J = 2,2., 7,14 Hz), 7,91 (1H, d, J = 2,20 Hz), 7,87 (1H, s), 7,65 (1H, ddd, J = 1,10, 5,49
165	A	A	529,5	Hz), 7,59 (1H, d, J = 10,99 Hz), 7,50 (1H, s), 7,49 (1H, d, J = 11,54 Hz), 7,34 (1H, s), 7,09 (1H, d, J = 2,20 Hz), 6,60 (1H, t, J = 6,59 Hz), 5,66 (2H, s), 3,23 (3H, s)
				1H-RMN (400 MHz, en dmso-d6):δ12,61 (1H, ancho s), 12,53 (1H, ancho s), 7,87 (1H, s), 7,68 (1H, dd, J = 2,20, 7,14 Hz), 7,58 (1H, d, J = 6,04 Hz), 7,49 (1H,
167	A	A	531,6	d, J= 1,65 Hz), 7,42 (1H, s), 7,33 (1H, s), 7,05 (1H, d, J = 10,44 Hz), 6,51 (1H, dd, J = 6,59, 7,14 Hz), 5,52 (2H, s), 4,61 (2H, t, J = 8,79 Hz), 3,26 (3H, s), 3,19 (2H, t, J = 8,79 Hz)
				1H RMN (500 MHz, DMSO): 7,84 (t, 1H, J= 2,2 Hz), 7,68 (bs,1H), 7,61(d, 1H, J= 8,2 Hz), 7,57 (m, 1H),
168	A	A	535,0	7,38 (d, 1H, J= 8,8 Hz), 7,29 (m, 1H), 7,17 (m, 1H), 7,11 (bs, 1H), 6,99 (m, 1H), 6,20 (m, 1H), 6,10 (bs, 2H), 2,60 (s, 3H)
				1H RMN (400 MHz, D6-dmso), δ12,73 (s, 1 H), 12,62 (s, 1H), 12,42 (s, 2 H), 8,42 (s, 1 H), 7,95 (s, 1
169	A	A	535,5	H), 7,92 (d, 1 H, J = 7,9 Hz), 7,69-7,66 (m, 1 H), 7,54 (d, 1 H, J = 11,0 Hz), 7,27 (d, 1 H, J = 7,9 Hz), 7,14 (s, 1 H), 7,09-7,07 (m, 2 H), 6,59 (t, 1 H, J = 6,7 Hz), 5,77 (s, 2 H), 3,26 (s, 3 H).
170	A	A	536,5	1H RMN (400 MHz, D6-dmso), δ12,63 (s, 2 H), 7,95

				(dd, 1 H, J = 2,0 & 6,8 Hz), 7,91 (d, 1 H, J = 2,4 Hz), 7,65 (t, 1 H, J = 4,4 Hz), 7,58 (bs, 1 H), 7,54 (d, 1 H, J = 10,8 Hz), 7,38 (d, 1 H, J = 8,4 Hz), 7,30 (dd, 1 H, J = 2,0 & 8,4 Hz), 7,09 (d, 1 H, J = 2,0 Hz), 6,60 (t, 1 H, J = 7,6 Hz), 6,31 (s, 2 H), 5,79 (s, 2 H), 3,22 (s, 3 H).
171	A	A	538,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,94 (dd, 1 H, J = 1,2 & 6,4 Hz), 7,91 (d, 1 H, J = 2,0 Hz) 7,69 (t, 1H, J = 6,0 Hz), 7,52 (d, 1 H, J = 10,8 Hz), 7,17 (t, 1 H, J = 8,8 Hz), 7,08 (d, 1H, J = 2,4 Hz), 6,96 (t, 1H, J = 7,6 Hz), 6,62 (q, 2H, J = 6,8 Hz), 5,79 (s, 2 H), 2,89 (h, 1 H, J = 1,3 Hz), 2,21 (s, 3 H), 0,95 (s, 2 H), 0,94 (s, 2 H).
173	A	A	540,6	
174	A	A	541,5	1H RMN (500 MHz, DMSO): 7,96 (d, J = 2,2 Hz, 1H), 7,73 (m, 2H), 7,59 (d, J = 10,9 Hz, 1H), 7,13 (d, J = 2,2 Hz, 1H), 6,66 (m, 1H), 5,72 (s, 2H), 5,53 (s, 1H), 2,94 (m, 1H), 1,02 - 0,96 (m, 4H).
175	A	A	541,5	1H RMN (400 MHz, D6-dmso), δ12,72 (s, 1 H), 12,68 (s, 1H), 7,96 (dd, 1 H, J = 2,2 & 7,1 Hz), 7,92 (d, 1 H, J = 2,2 Hz), 7,88 (d, 1 H, J = 2,2 Hz), 7,84-7,80 (m, 1 H), 7,69-7,64 (m, 1 H), 7,58-7,50 (m, 3 H), 7,36-7,27 (m, 2 H), 7,09 (d, 1 H, J = 2,2 Hz), 6,62 (t, 1 H, J = 7,1 Hz), 5,79 (s, 2 H), 3,21 (s, 3 H).
176	A	A	542,5	1H-RMN (400 MHz, en dmso-d6):δ12,74 (1H, ancho s), 12,73 (1H, ancho s), 8,61 (1H, d, J = 1,65 Hz), 8,11 (1H, s), 8,00 (1H, dd, J = 2,2, 7,14 Hz), 7,94

				(1H, d, J = 2,2 Hz), 7,77 (1H, dd, J = 2,2, 9,3 Hz), 7,70 (1H, ddd, J = 2,2, 6,59, 6,04 Hz), 7,60 (1H, s), 7,57 (1H, s), 7,11 (1H, d, J = 2,2 Hz), 6,64 (1H, dd, J = 6,59, 7,14 Hz), 5,76 (2H, s), 3,23 (3H, s)
177	A	A	542,5	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,92 (d, 1 H, J = 2,4 Hz) 7,69 (t, 1H, J = 6,8 Hz), 7,54 (d, 1 H, J = 10,8 Hz), 7,29 (dt, 1 H, J = 4,8 & 9,2 Hz), 7,18 -7,14 (m, 1 H), 7,09 (d, 1H, J = 2,0 Hz), 6,63-6,59 (m, 2 H), 5,78 (s, 2 H), 2,93-2,86 (m, 1 H), 0,95 (d, 4 H, J = 6,4 Hz)
178	A	A	542,5	1H RMN (400 MHz, D6-dmso), d, 12,71 (s, 1 H), 12,60 (s, 1 H), 7,97 (dd, 1 H, J = 1,7 & 6,8 Hz), 7,89 (d, 1 H, J = 2,1 Hz), 7,68 (bs, 1 H), 7,43 (d, 1 H, J = 12,8 Hz), 7,31 (dt, 1 H, J = 9,3 & 4,3 Hz), 7,19-7,13 (d, 1 H, J = 2,2 Hz), 6,97 (d, 1 H, J = 2,2 Hz), 6,61 (t, 1 H, J = 6,4 Hz), 6,56-6,51 (m, 1 H), 5,81 (s, 2 H), 2,97-2,91 (m, 1 H), 0,99 (d, 2 H, J = 3,0 Hz), 0,97 (s, 2 H).
179	A	A	543,5	1H RMN (400 MHz, D6-dmso), d, 12,67 (s, 2 H), 8,25-8,21 (m, 1 H), 7,98-7,97 (m, 1H), 7,94 (d, 1 H, J = 2,4 Hz), 7,74 (dd, 1 H, J = 3,0 & 6,1 Hz), 7,68-7,66 (m, 1 H), 7,61 (d, 1 H, J = 10,3 Hz), 7,55 (t, 1 H, J = 9,2 Hz), 7,11 (d, 1 H, J = 2,4 Hz), 6,62-6,59 (m, 1 H), 5,86 (s, 2 H), 3,22 (s, 3 H).
180	A	A	548,0	
181	A	A	552,5	
182	A	A	555,0	1H RMN (400 MHz, dmso) δ 3,17 (s, 3H), 5,885 (s,

				2H), 6,653 (t, 1H, J = 6,6), 6,747 (s, 1H), 7,111 (d, 1H, J = 2,2 Hz), 7,411 (d, 1H, J = 10,3 Hz), 7,68-7,74 (br s, 1H), 7,959 (d, 1H, J = 2,2 Hz), 7,985 (s, 1H), 7,995-8,03 (m, 1H), 9,09 (br s, 1H)
183	A	A	555,6	1H-RMN (400 MHz, en dmso-d6):δ12,65 (1H, ancho s), 11,60 (1H, ancho s), 7,91 (2H, m), 7,86 (1H, ancho s), 7,67 (1H, ddd, J = 2,2, 6,04, 6,6 Hz), 7,62 (1H, d, J= 10,99 Hz), 7,50 (1H, s), 7,46 (1H, s), 7,34 (1H, ancho s), 7,09 (1H, d, J = 2,2 Hz), 6,60 (1H, dd, J = 6,59, 6,59 Hz), 5,68 (2H, s), 3,02 (1H, m), 1,1 (4H, d, J = 7,7 Hz)
184	A	A	557,6	1H RMN (400 MHz, D6-dmso), δanterior 12 (s, 1 H), 12,36 (bd, 1 H, J = 6,4 Hz), 7,96 (d, 1 H, J = 2,1 Hz), 7,91 (dd, 1 H, J = 2,2 Hz), 7,80 (dd, 1 H, J = 1,5 & 8,1 Hz), 7,67 (t, 1 H, J = 7,7 Hz), 7,59 (d, 1 H, J = 10,4 Hz), 7,60-7,55 (m, 1 H), 7,46 (t, 1 H, J = 8,1 Hz), 7,28-7,23 (m, 1 H), 7,19 (d, 1H, J = 8,1 Hz), 7,17 – 7,11 (m, 1 H), 7,12 (d, 1 H, J = 2,2 Hz), 7,03 (t, 1 H, J = 7,3 Hz), 6,97 (t, 1 H, J = 7,3 Hz), 6,50 (t, 1 H, J = 6,6 Hz), 5,98 (s, 2 H).
185	A	A	557,6	1H-RMN (400 MHz, en dmso-d6):δ12,60 (2H, ancho m), 7,87 (1H, s), 7,68 (1H, dd, J = 1,65, 6,59 Hz), 7,60 (1H, m), 7,48 (1H, s), 7,40 (1H, s), 7,35 (1H, s), 7,09 (1H, d, J = 9,89 Hz), 6,53 (1H, t, J = 6,59 Hz), 5,54 (2H, s), 4,61 (2H, t, J = 8,79 Hz), 3,19 (2H, t, J = 8,79 Hz), 2,99 (1H, m), 0,98 (4H, m)
186	A	A	557,6	1H-RMN (400 MHz, en dmso-d6):δ12,74 (1H, d, J =

5,49 Hz), 12,54 (1H, s), 7,93 (1H, dd, J = 1,65, 7,14 Hz), 7,91 (1H, d, J = 2,20 Hz), 7,87 (1H, s), 7,69 (1H, ddd, J = 1,65, 6,04, 6,59 Hz), 7,64 (1H, d, J = 10,44 Hz), 7,49 (1H, d, J = 1,10 Hz), 7,41 (1H, d, J = 1,10 Hz), 7,35 (1H, s), 7,09 (1H, d, J = 2,20 Hz), 6,62 (1H, t, J = 6,59 Hz), 5,67 (2H, s), 3,67 (2H, s), 1,15 (6H, d, J = 6,59 Hz)

187	A	A	558,5	1H-RMN (400 MHz, en dmso-d6):δ12,67 (1H, ancho s), 12,54 (1H, ancho s), 7,88 (1H, s), 7,70 (1H, dd, J = 2,20, 7,14 Hz), 7,62 (1H, m), 7,48 (1H, d, J = 1,10
188	A	A	559,6	Hz), 7,35 (1H, s), 7,11 (1H, d, J = 9,89 Hz), 6,54 (1H, dd, J = 6,59, 7,14 Hz), 5,53 (2H, s), 4,61 (2H, t, J = 8,79 Hz), 3,64 (1H, h, J = 7,12 Hz), 3,19 (2H, t, j = 8,79 Hz), 1,13 (6H, d, J = 7,12 Hz)
190	A	A	562,6	1H RMN (400 MHz, D6-dmso), □12,67 (d, 1 H, J = 5,5 Hz), 12,59 (s, 1 H), 8,00 (dd, 1 H, J = 1,9 & 7,3 Hz), 7,91 (d, 1 H, J = 2,4 Hz), 7,70-7,65 (m, 1 H), 7,61-7,58 (m, 2 H), 7,38 (d, 1 H, J = 8,5 Hz), 7,29 (dd, 1 H, J = 1,2 & 8,5 Hz), 7,09 (d, 1 H, J = 2,4 Hz), 6,61 (t, 1 H, J = 6,7 Hz), 6,32 (s, 2 H), 5,81 (s, 2 H), 2,99-2,95 (m, 1 H), 0,93-0,89 (m, 4 H).
192	A	A	564,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,97 (d, 1 H, J = 8,0 Hz), 7,93-7,89 (m, 1 H), 7,84 (d, 1H, J = 2,0 Hz), 7,72 (t, 1 H, J = 6,0 Hz), 7,61, 7,54 (AB, 2 H, J = 8,8 Hz), 7,58 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,39 (dd, 1 H, J = 8,8 & 9,6 Hz), 6,99 (d, 1H, J =

				2,0 Hz), 6,65 (t, 1 H, J = 4,4 Hz), 5,86 (s, 2 H), 3,73 (s, 3 H), 2,93-2,86 (m, 1 H), 0,96-0,92 (m, 4 H).
193	A	B	566,0	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 8,32 (d, 1 H, J = 8,4 Hz), 8,10 (d, 1 H, J = 8,0 Hz), 8,03 (dd, 1 H, J = 0,8 & 8,4 Hz), 7,96 (d, 1 H, J = 2,0 Hz), 7,91 (ddd, 1 H, J = 1,6, 7,2 & 6,8 Hz), 7,79 (ddd, 1 H, J = 1,6, 7,2 & 6,8 Hz), 7,71 (t, 1 H, J = 8,0 Hz), 7,47 (d, 1 H, J = 10,8 Hz), 7,12 (d, 1 H, J = 2,0 Hz), 6,66 (t, 1 H, J = 5,2 Hz), 6,34 (s, 1 H), 6,28 (s, 2 H), 3,11 (s, 3 H).
194	A	A	566,0	1H RMN (400 MHz, D6-dmso), □12,69 (s, 2 H), 8,06 (dd, 1 H, J = 1,8 & 6,7 Hz), 7,97-7,95 (m, 2 H), 7,81-7,74 (m, 2 H), 7,71 (t, 1 H, J = 4,9 Hz), 7,56 (dt, 1 H, J = 4,2 & 1,2 Hz), 7,54 (s, 1 H), 7,38 (s, 1 H,), 7,11 (d, 1 H, J = 1,8 Hz), 6,67 (t, 1 H, J = 6,7 Hz), 5,87 (s, 2 H), 3,12 (s, 3 H).
195	A	A	567,5	1H RMN (400 MHz, D6-dmso), □12,75 (d, 1 H, J = 5,5 Hz), 12,71 (s, 1 H), 7,95 (dd, 1 H, J = 1,8 & 6,7 Hz), 7,92 (d, 1 H, J = 1,8 Hz), 7,88 (s, 1 H) 7,70 (t, 1 H, J = 4,9 Hz) 7,57 (d, 1 H, J =11,0 Hz), 7,53 (t, 1H, J = 6,1 Hz), 7,40 (s, 1 H), 7,29 (t, 1H, J = 8,5 Hz) 7,09 d, 1 H, J = 1,8 Hz), 6,63 (t, 1 H, J = 6,7 Hz), 5,82 (s, 2 H), 2,92-2,83 (m, 1 H), 0,95 (s, 2 H), 0,93 (s, 2 H).
196	A	A	568,0	1H-RMN (400 MHz, en dmso-d6):δ12,92 (1H, ancho s), 11,67 (1H, ancho s), 7,96 (1H, d, J = 8,06 Hz), 7,83 (1H, d, J = 7,32 Hz), 7,82 (1H, d, J = 7,32), 7,77

				(1H, m), 7,63 (1H, ddd, J = 2,2, 6,6, 6,6 Hz), 7,57 (1H, dd, J = 7,32, 7,32 Hz), 7,38 (1H, s), 7,01 (1H, d, J = 9,52 Hz), 6,59 (1H, dd, J = 6,59, 6,59 Hz), 5,73 (2H, s), 4,66 (2H, t, J = 8,79 Hz), 3,21 (2H, t, J = 8,79 Hz), 3,09 (3H, s)
197	A	A	568,5	1H-RMN (400 MHz, en dmso-d6):δ12,75 (2H, ancho s); 8,62 (1H, d, J = 1,95 Hz), 8,11 (1H, s), 7,98 (1H, dd, J = 1,95, 6,84 Hz), 7,93 (1H, d, J = 1,95 Hz), 7,80 (1H, dd, J = 1,95, 9,77 Hz), 7,72 (1H, d, J = 5,37 Hz), 7,62 (1H, s), 7,60 (1H, s), 7,19 (1H, d, J = 2,44 Hz), 6,64 (1H, t, J = 6,35, 6,84 Hz), 5,79 (2H, s), 2,88 (1H, q, J = 6,35 Hz), 0,95 (4H, d, J = 6,35 Hz); LR-MS (ESI)
197	A	A	568,5	1H-RMN (400 MHz, en dmso-d6):δ12,75 (2H, ancho s); 8,62 (1H, d, J = 1,95 Hz), 8,11 (1H, s), 7,98 (1H, dd, J = 1,95, 6,84 Hz), 7,93 (1H, d, J = 1,95 Hz), 7,80 (1H, dd, J = 1,95, 9,77 Hz), 7,72 (1H, d, J = 5,37 Hz), 7,62 (1H, s), 7,60 (1H, s), 7,19 (1H, d, J = 2,44 Hz), 6,64 (1H, t, J = 6,35, 6,84 Hz), 5,79 (2H, s), 2,88 (1H, q, J = 6,35 Hz), 0,95 (4H, d, J = 6,35 Hz); LR-MS (ESI): calculado para C26H20F2NO6S+ [M+H]+ 568,11, experimental 567,97
198	A	A	569,5	1H RMN (400 MHz, D6-dmso), δ12,71 (s, 2 H), 8,25-8,21 (m, 1 H), 7,97 (dd, 1 H, J = 1,8 & 7,3 Hz), 7,93 (d, 1 H, J = 2,4 Hz), 7,75-7,69 (m, 2 H), 7,62 (d, 1 H, J = 10,4 Hz), 7,55 (t, 1 H, J = 9,8 Hz), 7,10 (d, 1 H, J = 2,4 Hz), 6,63 (t, 1 H, J = 6,7 Hz), 5,88 (s, 2 H),

				2,91-2,84 (m, 1H), 0,94 (d, 4 H, J = 6,7 Hz).
199	A	A	569,6	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,98 (d, 1 H, J = 7,2 Hz), 7,93-7,92 (m, 1 H), 7,89 (b, 1 H), 7,84-7,81 (m, 1H), 7,72 (t, 1 H, J = 5,2 Hz), 7,60 (d, 1 H, J =11,0 Hz), 7,50 (d, 1 H, J = 6,8 Hz), 7,38 (b, 1 H), 7,29 (t, 1 H, J = 9,6 Hz), 7,10 – 7,09 (m, 1H), 6,64 (t, 1 H, J = 6,8 Hz), 5,82 (s, 2 H), 3,53 (h, 1 H, J = 7,2 Hz), 1,07 (d, 6 H, J = 6,8 Hz).
200	A	A	570,5	1H-RMN (400 MHz, en dmso-d6):δ12,67 (1H, ancho s), 8,60 (1H, s), (8,12 (1H, s), 7,76 (2H, m), 7,63 (1H, m), 7,60 (1H, s), 7,06 (1H, d, J = 9,77 Hz), 6,56 (1H, dd, J = 6,35, 6,84 Hz), 5,64 (2H, s), 4,62 (2H, t, J = 8,79 Hz), 3,20 (2H, t, J = 8,79 Hz), 2,87 (1H, m), 0,92 (4H, d, J = 5,86 Hz)
201	A	A	574,0	1H RMN (400 MHz, D6-dmso), d, 12,74 (s, 1 H), 12,70 (d, 1 H, J = 5,5 Hz) 8,05 (dd, 1 H, J = 1,8 & 6,7 Hz), 7,96 (d, 1 H, J = 8,0 Hz), 7,87 (d, 1 H, J = 2,5 Hz), 7,79-7,75 (m, 2 H), , 7,71 (dt, 1 H, J = 1,8 & 6,1 Hz), 7,58 (t, 2 H, J = 9,2 Hz), 7,53 (t, 1 H, J = 9,2 Hz), 7,38 (s, 1 H), 7,00 (d, 1 H, J = 2,4 Hz), 6,68 (t, 1 H, J = 6,7 Hz), 5,92 (s, 2 H), 2,79-2,74 (m, 1 H), 0,83 -0,79 (m, 2 H), 0,76-0,71 (m, 2 H).
202	A	A	575,6	1H RMN (400 MHz, dmso) δ 5,656 (s, 2H), 6,546 (t, 1H, J = 7,3 Hz), 6,60-6,69 (m, 2H), 6,729 (d, 1H, J = 7,3 Hz),6,979 (t, 1H, J = 7,3 Hz), 7,066 (d, 1H, J = 2,2 Hz), 6,95-7,00 (m, 1H), 7,22-7,3 (m, 2H), 7,445 (d, 1H, J = 11 Hz), 7,480 (dd, 1H, J = 8, 1,5 Hz),

				7,70-7,756 (m, 1H), 7,87-7,91 (m, 2H).
204	A	A	577,0	1H RMN (400 MHz, D6-dmso), δ 12,70 (d, 1 H, J = 4,9 Hz), 12,45 (d, 1 H) 8,04 (dd, 1 H, J = 1,8 & 6,7 Hz), 7,96 (d, 1 H, J = 9,2 Hz), 7,87 (d, 1 H, J = 2,4 Hz), 7,79-7,75 (m, 2 H), 7,70 (t, 1 H, J = 6,7 Hz), 7,59-7,52 (m, 3 H), 7,34 (s, 1 H), 7,00 (d, 1 H, J = 2,4 Hz), 6,66 (t, 1 H, J = 6,7 Hz), 5,92 (s, 2 H), 2,52 (s, 6 H).
205	A	A	581,0	1H RMN (400 MHz, dmso) δ 0,82-0,92 (m, 4H), 2,78-2,86 (m, 1H), 5,907 (s, 2H), 6,664 (t, 1H, J = 6,6 Hz), 6,714 (s, 1H), 7,109 (d, 1H, J = 2,2 Hz), 7,445 (d, 1H, J = 11 Hz), 7,731 (br s, 1H), 7,953 (d, 1H, J = 2,2 Hz), 7,97-8,03 (m, 2H), 9,087 (br s, 1H).

#	IC50	EC50	LR-MS (M+H)	DATOS
206	A	B	581,6	1H RMN (400 MHz, D6-dmso), d, 12,75 (s, 1H), 12,70 (d, 1 H, J = 4,9 Hz), 8,38 (d, 1 H, J = 4,3 Hz), 7,96 (dd, 1 H, J = 2,4 & 7,3 Hz), 7,93 (d, 1 H, J = 2,4 Hz), 7,78-7,43 (m, 1 H), 7,69 (dt, 1 H, J = 1,8 & 6,1 Hz), 7,55 (d, 1 H, J = 10,4 Hz), 7,51 (d, 1 H, J = 7,3 Hz), 7,29 (t, 1 H, J = 9,1 Hz), 7,10 (d, 1 H, J = 1,8 Hz), 6,63 (t, 1 H, J = 6,1 Hz), 5,80 (s, 2 H), 3,23 (s, 3 H), 2,75-2,69 (m, 1 H), 0,65-0,60 (m, 2 H), 0,51-0,46 (m, 2 H).
207	A	A	584,6	1H RMN (400 MHz, d6-DMSO): ? 12,71 (s, 1H),

				12,67 (s, 1H), 7,94 (dd, J = 2,0, 6,8 Hz, 1H), 7,91 (d, J = 2,0 Hz, 1H), 7,70 (m, 1H), 7,54 (d, J = 10,8 Hz, 1H), 7,26 (m, 1H), 7,13 (dd, J = 8,4, 10,0 Hz, 1H), 7,09 (d, J = 2,0 Hz, 1H), 6,91 (dd, J = 2,0, 7,2 Hz, 1H), 6,62 (t, J = 6,8 Hz, 1H), 5,80 (s, 2 H), 4,37 (t, J = 6,0 Hz, 1H), 3,26 (d, J = 6,4 Hz, 2H), 2,86 (m, 1H), 0,95-0,92 (M, 4H)
208	A	A	588,5	1H RMN (400 MHz, dmso) δ 3,253 (s, 3H), 5,857 (s, 2H), 6,597 (t, 1H, J = 6,6 Hz), 7,076 (d, 1H, J = 2,2 Hz), 7,242 (dd, 1H, J = 8,8, 1,5 Hz), 7,456 (s,1H), 7,558 (d, 1H, J = 11 Hz), 7,653 (d, 2H, J = 8 Hz), 7,912 (d, 1H, J = 2,2 Hz), 7,959 (dd, 1H, J = 7,3, 2,2 Hz)
209	A	A	591,1	1H RMN (400 MHz, d6-DMSO): d, 9,34 (s, 1 H), 8,09 (d, J = 9,2 Hz, 1 H), 8,02-8,01 (m, 1 H), 7,98 (d, J = 8,8 Hz, 1 H), 7,85-7,77 (m, 3 H), 7,72-7,70 (m, 1 H), 7,57 (t, J = 7,0 Hz, 1 H), 7,40 (s, 1 H), 6,64 (t, J = 6,0 Hz, 1 H), 6,00 (s, 2 H), 2,79-2,76 (m, 1 H), 0,81-0,74 (m, 4 H).
210	A	B	592,0	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 8,34 (d, 1 H, J = 8,8 Hz), 8,08 (d, 1 H, J = 8,0 Hz), 8,02 (d, 1 H, J = 8,4 Hz), 7,96 (d, 1 H, J = 2,4 Hz), 7,91 (t, 1 H, J = 7,2 Hz), 7,79 (t, 1 H, J =8,0 Hz), 7,72 (t, 1 H, J = 4,0 Hz), 7,52 (d, 1 H, J = 10,4 Hz), 7,11 (d, 1 H, J = 2,0 Hz), 6,66 (t, 1 H, J = 6,4 Hz), 6,32 (s, 1 H), 6,30 (s, 2 H), 2,74-2,69 (m, 1 H), 0,85 (b, 2 H), 0,75 (b, 2 H).

211	A	A	592,0	
212	A	A		Ver Ejemplo 15 para los detalles y datos experimentales
213	A	A	594,0	1H RMN (500 MHz, DMSO): δ 8,07 (dd, 1H, J= 1,89 Hz), 7,98 (m,2H), 7,80 (m, 2H), 7,74(m, 1H), 7,65 (d, 1H, J= 10,7Hz), 7,58 (t, 1H, J = 8,19 Hz), 7,14 (d, 1H, J = 2,2 Hz), 6,69 (t, 1H, J = 6,3 Hz), 5,93 (s, 2H), 3,16 (t, 2H, J= 7,5 Hz), 1,23 (p, 2H), 0,60 (t, 3H). M.S. experimental: 593,3 (M)+.
215	A	A	595,0	1H RMN (400 MHz, D6-dmso), δ, 12,70 (d, 1 H, J = 5,5 Hz), 12,38 (d, 1 H) 8,03 (dd, 1 H, J = 1,8 & 7,3 Hz), 7,97-7,95 (m, 2 H), 7,79-7,74 (m, 2 H), 7,70 (dt, 1 H, J = 1,2 & 6,1 Hz), 7,61 (d, 1 H, J.= 11,0 Hz) 7,56 (dt, 1 H, J = 7,3 & 1,2 H), 7,33 (s, 1 H), 7,11 (d, 1 H, J = 1,8 Hz), 6,65 (t, 1 H, J = 6,7 Hz), 5,89 (s, 2 H), 2,48 (s, 6 H).
216	A	A	596,1	1H-RMN (400 MHz, en dmso-d6):δ12,96 (1H, ancho s), 11,76 (1H, ancho s), 7,95 (1H, d, J = 8,79 Hz), 7,74 (2H, m), 7,58 H1H, dd, J = 4,39, 7,32 Hz), 7,50 (1H, dd, J = 7,32, 8,06 Hz), 7,35 (1H, s), 7,26 (1H, d, J = 10,25 Hz), 6,63 (2H, s), 6,02 (2H, s), 5,01 (2H, t, J = 8,79 Hz), 3,40 (2H, t, J = 8,79 Hz), 1,21 (6H, d, J = 6,6 Hz)
218	A	C	599,4	1H RMN (400 MHz, D6-dmso), δ anterior 12 (2 H), 7,95 (d, 1 H, J = 6,0 Hz), 7,92 (dd, 1 H, J = 1,2 & 2,4 Hz), 7,79 (d, 1 H, J = 10,4 Hz), 7,70-7,66 (b, 1 H), 7,57 (d, 1 H, J = 7,6 Hz), 7,49 (d, 1 H, J = 8,0 Hz),

				7,14 (dt, 1 H, J = 0,8 & 7,6 Hz), 7,10 (dd, 1 H, J = 0,8 & 2,0 Hz), 6,84 (s, 1 H), 6,60 (t, 1 H, J = 7,6 Hz), 5,99 (s, 2 H), 3,15 (s, 3 H).
219	C	A	603,0	1H RMN (400 MHz, cdcl3) δ 1,232 (s, 9H), 5,940 (s, 2H), 6,094 (s, 2H), 6,705-6,752 (m, 1H), 6,819 (d, 1H, J = 9,5 Hz), 6,911 (d, 1H, J = 2,2 Hz), 7,382 (s, 1H), 7,418-7,437 (m, 1H), 7,494 (d, 1H, J = 2,2 Hz), 7,565 (d, 1H, J = 7,3 Hz), 7,65-7,71 (m, 1H), 7,871 (dd, 1H, J = 6,6, 1,5 Hz), 8,02 (d, 1H, J = 8 Hz), 8,06-8,11 (m, 1H)
221	A	C	607,6	1H RMN (400 MHz, D6-dmso), δ12,76 (d, 1 H, J = 5,6 Hz) 12,74 (s, 1H), 8,39 (d, 1 H, J = 4,0 Hz), 7,95 (dd, 1 H, J = 2,0 & 6,8 Hz), 7,92 (d, 1 H, J = 2,4 Hz), 7,78-7,43 (m, 1 H), 7,71 (dt, 1 H, J = 1,6 & 6,0 Hz), 7,57 (d, 1 H, J = 10,8 Hz), 7,53 (dd, 1 H, J = 2,0 & 7,2 Hz), 7,28 (dd, 1 H, J = 1,2 & 8,8 Hz), 7,09 (d, 1 H, J = 2,4 Hz), 6,64 (t, 1 H, J = 6,4 Hz), 5,80 (s, 2 H), 2,92-2,86 (m, 1 H), 2,72 (m, 1H), 0,95 (s, 2 H), 0,94 (m, 2 H), 0,65-0,61 (m, 2 H), 0,50-0,47 (m, 2 H).
222	A	A	614,6	1H RMN (400 MHz, dmso) δ 0,93-0,97 (m, 4H), 2,47-2,495 (m, 1H), 5,88 (s, 2H), 6,615 (t, 1H, J = 6,6 Hz), 7,077 (d, 1H, J = 2,2 Hz), 7,248 (dd, 1H, J = 8,8, 1,5 Hz), 7,471 (s, 1H), 7,607 (d, 1H, J = 11 H), 7,635-7,715 (m, 2H), 7,904 (d, 1H, J = 2,2 Hz), 7,948 (dd, 1H, J = 7,3, 2,2 Hz)
223	A	A	643,1	1H RMN (400 MHz, dmso) δ 4,09-4,14 (m, 2H), 5,703 (s, 2H), 6,28-6,35 (m, 1H), 6,538 (d, 1H, J =

				8,8Hz), 6,66-6,74 (m, 1H), 7,06-7,13 (m, 2H), 7,26-7,34 (m, 2H), 7,48 (d, 1H, J = 11 Hz), 7,52-7,58 (m, 1H), 7,64-7,72 (m, 2H), 7,72-7,8 (m, 2H), 7,91-8,04 (m, 2H)
225	A	B	671,7	1H RMN (400 MHz, D6-dmso), δ, 12,76 (s, 2 H) 12,13 (s, 1H), 7,96-7,92 (m, 3 H), 7,71 (bs, 1 H), 7,66 (d, 1 H, J = 6,8 Hz), 7,60 (d, 1 H, J = 10,8 Hz), 7,38 (t, 1 H, J = 8,0 Hz), 7,10 (s, 1 H), 6,38 (t, 1 H, J = 7,6 Hz), 5,84 (s, 2 H), 3,09-3,01 (m, 1 H), 2,90-2,83 (m, 1H), 1,16-1,05 (m, 4 H), 1,00-0,90 (m, 4 H)
226	C	A	680,7	1H RMN (500 MHz, CDCl3): δ 8,02 (s, 1H), 7,72 (dd, J = 7,25 Hz, J = 2,21 Hz, 1H), 7,63 (dd, J = 7,25 Hz, J = 2,21 Hz, 1H), 7,52 (d, J = 2,20 Hz, 1H), 6,905 (d, J = 2,20 Hz, 1H), 6,85 (d, J = 9,8 Hz 1H), 6,37 (t, J = 6,9 Hz 1H), 6,01 (s, 2H), 5,99 (s, 1H), 5,84 (s, 2H), 5,79 (s, 2H), 3,79 (s, 3H), 1,244(s, 9H), 1,135 (s, 9H).
227	C	A	740,8	1H RMN (500 MHz, CDCl3) δ 8,50 (s, 1H), 7,96 (m, 2H), 7,73 (m, 1H), 7,53 (d, J = 8,0 Hz, 1H), 7,11 (s, 1H), 6,67 (m, 1H), 6,53 (s, 1H), 5,91 (s, 1H), 5,77 (s, 2H), 1,16 (m, 18H), 0,98 (m, 4H)
228	C	A	780,8	M.S. experimental: 780,4 (M+H)+; 1H RMN (500 MHz, CDCl3): δ 7,69 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7,63 (dd, J = 2,2 Hz, J = 6,9 Hz, 1H), 7. 56 - m, 2H), d, J = 2,2 Hz, 1H), 6,83 (d, J = 9,8 Hz, 1H), 6,37 (t, J = 6,9 Hz, 1H), 6,01 (m, 2H), 5,81-5,77 (m, 4H), 5,75 (s, 2H), 5,70 (m, 1H), 1,26-1,22 (m,

			18H), 1,16 (s, 9H).
231	A	A	Ver Ejemplo 16 para los detalles y datos experimentales

Usos de los compuestos de fórmula (I)

Los compuestos de fórmula (I) son útiles en la medicina humana y veterinaria para el tratamiento o prevención de una infección viral o un trastorno relacionado con un virus en paciente. De acuerdo con la invención, los compuestos de fórmula (I) se pueden administrar a un paciente que necesita un tratamiento o prevención de una infección viral o trastorno relacionado con el virus.

Por consiguiente, en una realización, la invención proporciona métodos para tratar una infección viral en un paciente comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de fórmula (I) o sal, solvato, éster o profármaco aceptables para uso farmacéutico de los mismos. En otra realización, la invención proporciona métodos para tratar un trastorno relacionado con un virus en paciente que comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de fórmula (I) o sal, solvato, éster o profármaco aceptables para uso farmacéutico de los mismos.

Tratamiento o prevención de una ilnfección viral

Los compuestos de fórmula (I) se pueden usar para tratar o prevenir una infección viral. En una realización, los compuestos de fórmula (I) pueden ser inhibidores de la replicación viral. En una realización especifica, los compuestos de fórmula (I) pueden ser inhibidores de la replicación de VHC. Por consiguiente, los compuestos de fórmula (I) son útiles para tratar enfermedades virales y trastornos relacionados con la actividad de un virus, tal como la polimerasa de VHC.

Los ejemplos de infecciones virales que se pueden tratar o prevenir mediante los presentes métodos, que incluyen pero sin limitación, infección de hepatitis A, infección de hepatitis B e infección de hepatitis C.

En una realización, la infección viral es infección de hepatitis C.

En una realización, la hepatitis C infección es hepatitis C aguda. En otra realización, la infección de hepatitis C es hepatitis C crónica.

Las composiciones y combinaciones de la presente invención pueden ser útiles para tratar un paciente que sufre de la infección relacionada con algún genotipo de VHC. Los tipos y subtipos de VHC pueden diferir en sus antigenicidad, nivel de viremia, severidad de la enfermedad producida y respuesta a la terapia de interferón descripta en Holland *et al.*, *Pathology*, 30(2):192-195 (1998). La nomenclatura expuesta en Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391-2399 (1993) está ampliamente usada y clasifica las cepas en seis genotipos principales, 1 a 6, con dos o más subtipos relacionados, por ej., 1a, 1b. Se han propuesto que los genotipos adicionales 7-10 y 11, sin embargo la base filogenética en la que se basa esta clasificación ha sido cuestionada y de este modo se han reasignado las cepas 7, 8, 9 y 11 como cepas de tipo 6, y tipo 10 como tipo 3 (ver Lamballerie *et al, J Gen Virol*, 78(Pt1):45-51 (1997)). Se han definido que los genotipos principales presentan similitudes de secuencia de entre 55 y 72% (media 64,5%), y los subtipos dentro de los tipos que tienen similitud de 75%-86% (media 80%) cuando se secuencian en la región NS-5 (ver Simmonds *et al.*, *J Gen Virol*, 75(Pt 5):1053-1061 (1994)).

Tratamiento o prevención de un Trastorno Relacionado con el Virus

Los compuestos de fórmula (I) se pueden usar para tratar o prevenir un trastorno relacionado con el virus. Por consiguiente, los compuestos de fórmula (I) son útiles para tratar trastornos relacionados con la actividad de un virus, tales como inflamación o cirrosis hepática. Los trastornos relacionados con el virus

incluyen, pero sin limitación, trastornos relacionados con la polimerasa dependiente de ARN y trastornos relacionados con la infección con VHC.

Tratamiento o prevención de un trastorno relacionado con la polimerasa dependiente de ARN

Los compuestos de fórmula (I) son útiles para el tratamiento o prevención de un trastorno relacionado con la polimerasa dependiente de ARN (RdRp) en una paciente. Tales trastornos incluyen infecciones virales donde el virus infectivo contiene una enzima RdRp.

Por consiguiente, en una realización, la presente invención proporciona un método para tratar un trastorno relacionado con la polimerasa dependiente de ARN en un paciente, que comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de fórmula (I) o sal, solvato, éster o profármaco aceptables para uso farmacéutico de los mismos.

Tratamiento o prevención de un trastorno relacionado con la infección con VHC

Los compuestos de fórmula (I) también pueden ser útiles para el tratamiento o prevención de un trastorno relacionado con una infección con VHC. Los ejemplos de tales trastornos incluyen, pero sin limitación, cirrosis, hipertensión portal, ascitis, dolor óseo, várices, ictericia, encefalopatía hepatica, tiroiditis, porfiria cutánea tardía, crioglobulinemia, glomerulonefritis, síndrome sicca, trombocitopenia, lichen planus y diabetes mellitus.

Por consiguiente, en una realización, la invención proporciona métodos para tratar un trastorno relacionado con con VHC en un paciente, donde el método comprende administrar al paciente una cantidad terapéuticamente efectiva de por lo menos un compuesto de fórmula (I), o sal, solvato, éster o profármaco aceptables para uso farmacéutico de los mismos .

Terapia combinada

En otra realización, los presentes métodos para el tratamiento o prevención de una infección viral además puede comprender la administración de uno o más agentes terapéuticos adicionales que no son compuestos de fórmula (I).

En una realización, el agente terapéutico adicional es un agente antiviral.

En otra realización, el agente terapéutico adicional es un agente inmunomodularo, tal como un agente inmunosupresor.

Por consiguiente, en una realización, la presente invención proporciona métodos para tratar una infección viral en una paciente, el método comprende administrar al paciente : (i) por lo menos un compuesto de fórmula (I), o sal, solvato, éster o profármaco aceptables para uso farmacéutico de los mismos , y (ii) por lo menos otro agente antiviral que es diferente de un compuesto de fórmula (I), donde las cantidades administradas son en conjunto efectivas para tratar o prevenir una infección viral.

Cuando se administra una terapia combinada de la invención a un paciente, los agentes terapéuticos en la combinación, o una composición farmacéutica o composiciones que comprenden los agentes terapéuticos, se pueden administra en cualquier orden tal como, por ejemplo, en forma sucesiva, concurrente, conjunta, simultánea y similares. Las cantidades de los diversos componentes activos en tal terapia combinada pueden ser cantidades diferentes (cantidades de dosis diferentes) o cantidades iguales (cantidades de dosis iguales). De este modo, con propósitos de ilustración no limitantes, un compuesto de fórmula (I) y un agente terapéutico adicional puede estar presente en cantidades fijas (cantidades de dosis) en una unidad de dosis simple (por ej., una cápsula, un comprimido y similares). Un ejemplo comercial de tales unidades de dosis simples que contienen cantidades fijas de dos compuestos activos

diferentes es VYTORIN® (disponible en Merck Schering-Plough Pharmaceuticals, Kenilworth, New Jersey).

En una realización, el por lo menos un compuesto de fórmula (I) se administra durante el tiempo en el que el agente antiviral adicional ejerce su efecto profiláctico o terapéutico, o *vice versa*.

En otra realización, el por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) se administran en dosis comúnmente empelados cuando tales agentes se usan como monoterapia para tratar una infección viral.

En otra realización, el por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) se administran en dosis menores que las dosis comúnmente empelados cuando tales agentes se usan como monoterapia para tratar una infección viral.

En aún otra realización, el por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) se actúan en forma sinérgica y se se administran en dosis menores que las dosis comúnmente empelados cuando tales agentes se usan como monoterapia para tratar una infección viral.

En una realización, el por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) están presentes en la misma composición. En una realización, esta composición es adecuada para la administración oral. En otra realización, esta composición es adecuada para la administración intravenosa.

Las infecciones virales y trastornos relacionados con el virus que se pueden tratar o prevenir mediante los métodos de la terapia combinada de la presente invención incluyen, pero sin limitación, a los listados con anterioridad.

En una realización, la infección viral es una infección con VHC.

El por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) actúan en forma aditiva o sinérgica. Una combinación sinérgica puede permitir el uso de dosis inferiores de uno o más agentes y/o administración menos frecuente de uno o más agentes de una terapia de combinación. Una dosis inferior o administración menos frecuente de uno o más agentes puede reducir la toxicidad de la terapia sin reducir la eficacia de la terapia.

En una realización, la administración de por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es) pueden inhibir la resistencia de una infección viral a estos agentes.

Los ejemplos no limitantes de otros agentes terapéuticos útiles en las presentes composiciones y métodos incluyen un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un agente antisentido; una vacuna terapéutica; un inhibidor de proteasa; un inhibidor de la producción del virion, una terapia de anticuerpo (monoclonal o policlonal); y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

En una realización, el otro agente antiviral es un inhibidor de la proteasa viral.

En otra realización, el otro agente antiviral es es un inhibidor de la proteasa de VHC.

En otra realización, el otro agente antiviral es un interferón.

En aún otra realización, el otro agente antiviral es un inhibidor de la replicación viral.

En otra realización, el otro agente antiviral es un agente antisentido.

En otra realización, el otro agente antiviral es una vacuna terapéutica.

En una realización adicional, el otro agente antiviral es un inhibidor de la producción del virion.

En otra realización, el otro agente antiviral es la terapia de anticuerpo.

En otra realización, los otros agentes antivirales comprenden un inhibidor de proteasa y un inhibidor de polimerasa.

En aún otra realización, los otros agentes antivirales comprenden un inhibidor de proteasa y un agente inmunosupresor.

En aún otra realización, los otros agentes antivirales comprenden un inhibidor de polimerasa y un agente inmunosupresor.

En una realización adicional, los otros agentes antivirales comprenden un inhibidor de proteasa, un inhibidor de polimerasa y un agente inmunosupresor.

En otra realización el otro agente es ribavirina.

Los inhibidores de polimerasas de VHC útiles en los métodos y composiciones presentes incluyen, pero sin limitación VP-19744 (Wyeth/ViroPharma), VHC-796 (Wyeth/ViroPharma), NM-283 (Idenix/Novartis), R-1626 (Roche), MK-0608 (Merck), A848837 (Abbott), GSK-71185 (Glaxo SmithKline), XTL-2125 (XTL Biopharmaceuticals), y los descriptos en Ni *et al.*, *Current Opinion in Drug Discovery and Development*, 7(4):446 (2004); Tan *et al.*, *Nature Reviews*, 1:867 (2002); y Beaulieu *et al.*, *Current Opinion in Investigational Drugs*, 5:838 (2004).

Los interferones útiles en los métodos y las composiones presentes incluyen, pero sin limitación, interferón alfa-2a, interferón alfa-2b, interferón alfacon-1 y conjugados de PEG-interferón alfa. Los "conjugados de PEG-interferón alfa" son moléculas de interferón alfa unidas en forma covalente a una molécula de PEG. Los conjugados de PEG-interferón alfa ilustrativos incluyen interferón alfa-2a (Roferon™, Hoffman La-Roche, Nutley, New Jersey) en la forma de interferón alfa-2a pegilado (*por ej.,* comercializado con la marca registrada Pegasys™), interferón alfa-2b (Intron™, de Schering-Plough Corporación) en la forma de interferón alfa-2b pegilado (*por ej.,* comercializado con la marca registrada PEG-Intron™), interferón alfa-2c (Berofor Alpha™, Boehringer

Ingelheim, Ingelheim, Germany), polipéptidos de fusión interferón alfa o interferón de consenso definido por la determinación de una secuencia de consenso de interferones alfa naturales (Infergen™, Amgen, Thousand Oaks, California).

Los agentes de la terapia de anticuerpos útiles en los métodos y las composiciones presentes incluyen, pero sin limitación, anticuerpos específicos para IL-10 (tales como los descriptos en la publicación de la Patente Estadounidense No. US2005/0101770, anticuerpo humanizado 12G8, anticuerpo monoclonal humanizado contra IL-10 humana, plásmidos que contienen los ácidos nucleicos que codifican las cadenas livianas y pesadas 12G8 humanizadas se depositaron con la América n Type Culture Collección (ATCC) como números de depósito PTA-5923 y PTA-5922, respectivamente, y similares). Los inhibidores de la proteasa viral útiles en los métodos y las composiciones presentes incluyen, pero sin limitación, inhibidores de serina proteasa NS3 (que incluyen, pero sin limitación, las descriptas en las Patentes Estadounidenses Nos. 7.012.066, 6.914.122, 6.911.428, 6.846.802, 6.838.475, 6.800.434, 5.017.380, 4.933.443, 4.812.561 y 4.634.697; y publicación de las Patentes Estadounidenses Nos. US20020160962, US20050176648 y US20050249702), inhibidores de proteasa de VHC (*por ej.,* SCH503034 (Schering-Plough), VX-950 (Vertex), GS-9132 (Gilead/Achillion), ITMN-191 (InterMune/Roche)), amprenavir, atazanavir, fosemprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir y TMC114.

Los inhibidores de la replicación viral útiles en los métodos y las composiciones presentes incluyen, pero sin limitación, inhibidores de helicasa NS3, inhibidores de NS5A, ribavirina, viramidina, A-831 (Arrow Therapeutics); un agente antisentido o una vacuna terapéutica.

En una realización, viral replicación inhibidores útiles en los métodos y las composiciones presentes incluyen, pero sin limitación, inhibidores de helicasa NS3 o inhibidores de NS5A.

Los ejemplos de inhibidores de proteasa útiles en los métodos presentes incluyen, pero sin limitación, un inhibidor de proteasa de VHC y un inhibidor de serina proteasa NS-3.

Los ejemplos de inhibidores de proteasa de VHC útiles en los métodos presentes incluyen, pero sin limitación, los descriptos en Landro *et al.*, *Biochemistry*, 36(31):9340-9348 (1997); Ingallinella *et al.*, *Biochemistry*, 37(25):8906-8914 (1998); Llinàs-Brunet *et al.*, *Bioorg Med Chem Lett*, 8(13):1713-1718 (1998); Martin *et al.*, *Biochemistry*, 37(33):11459-11468 (1998); Dimasi *et al.*, *J Virol*, 71(10):7461-7469 (1997); Martin *et al.*, *Protein Eng*, 10(5):607-614 (1997); Elzouki *et al.*, *J Hepat*, 27(1):42-48 (1997); *BioWorld Today*, 9(217):4 (November 10, 1998); y

Publicaciones Internacionales Nos. WO 98/14181; WO 98/17679, WO 98/17679, WO 98/22496 y WO 99/07734.

Otros ejemplos inhibidores de proteasa útiles en los métodos presentes incluyen, pero sin limitación.

Ejemplos adicionales de otros agentes terapéuticos útiles de los presentes métodos incluyen, pero sin limitación, Levovirin™ (ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (Viropharma, Incorporated, Exton, Pennsilvania), ISIS 14803™ (ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (Ribozyme Pharmaceuticals, Boulder, Colorado), VX-950™ (Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), NKB-122 (JenKen Bioscience Inc., North Carolina), micofenolato de mofetilo (Hoffman-LaRoche, Nutley, New Jersey).

Las dosis y esquema de dosis de los otros agentes usados en las terapias de combinación de la presente invención para el tratamiento o prevención de una infección viral puede ser determinada por el clínico asistente, que toma en consideraciónla dosis y esquemas aprobados en el prospecto del envase; la edad, sex y salud general del paciente y el tipo y gravead de la infección viral o enfermedad o trastorno relacionado. Cuando se administra en combinación, el compuesto de fórmula (I)(s) y el/los otro(s) agente(s) para tratar enfermedades o afecciones enumeradas anteriormente se pueden administrar en forma simultánea (es decir, en la misma composición o en composiciones separadas uno después de la otra) o sucesiva. Es particularmente útil cuando los componentes de la combinación se dan en esquemas de dosis diferentes, *por ej.,* un componente se administra una vez por día y otro cada seis horas o cuando las composiciones farmacéuticas preferidas son diferentes, *por ej.,* una es un comprimido y otro es cápsula. Un kit que comprende las formas de dosis separadas es en consecuencia, ventajosa.

Generalmente, una dosis diaria total de por lo menos un compuesto de fórmula (I) y el/los agente(s) antiviral(es) adicional(es), cuando se admnistra como terapia combinada, puede variar de aproximadamente 0,1 a aproximadamente 2000 mg por día, aunque las variaciones necesariamente se producirán de acuerdo con el blanco de la terapia, el paciente y la vía de administración. En una realización, la dosis es de aproximadamente 10 a aproximadamente 500 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En otra realización, la dosis es de aproximadamente 1 a aproximadamente 200 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En aún otra realización, la dosis es de aproximadamente 1 a aproximadamente 100 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En aún otra realización, la dosis es de aproximadamente 1 a aproximadamente 50 mg/día, administrada en una dosis

única o en 2-4 dosis divididas. En una realización adicional, la dosis es de aproximadamente 1 a aproximadamente 20 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En otra realización, la dosis es de aproximadamente 500 a aproximadamente 1500 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En aún otra realización, la dosis es de aproximadamente 500 a aproximadamente 1000 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En aún otra realización, la dosis es de aproximadamente 100 a aproximadamente 500 mg/día, administrada en una dosis única o en 2-4 dosis divididas.

En una realización, cuando el otro agente terapéutico es INTRON-A interferón alfa 2b (disponible en el mercado en Schering-Plough Corp.), este agente se administra por inyección subcutánea a razón de 3MIU(12 mcg)/0,5 ml/TIW durante 24 semanas o 48 semanas para el primer tiempo de tratamiento.

En otra realización, cuando el otro agente terapéutico es PEG-INTRON interferón alfa 2b pegilado (disponible en el mercado en Schering-Plough Corp.), este agente se administra por inyección subcutánea a 1,5 mcg/kg/semana, dentro de un rango de 40 a 150 mcg/semana, durante por lo menos 24 semanas.

En otra realización, cuando el otro agente terapéutico es ROFERON A interferón alfa 2a (disponible en el mercado en Hoffmann-La Roche), este agente se administra por inyección subcutánea o intramuscular a razón 3MIU(11,1 mcg/ml)/TIW durante por lo menos 48 a 52 semanas, o alternativamente 6MIU/TIW durante 12 semanas seguido por 3MIU/TIW durante 36 semanas.

En aún otra realización, cuando el otro agente terapéutico es PEGASUS interferón alfa 2a pegilado (disponible en el mercado en Hoffmann-La Roche), este agente se administra por inyección subcutánea at 180mcg/1ml o 180mcg/0,5ml, una vez por semana durante por lo menos 24 semanas.

En aún otra realización, cuando el otro agente terapéutico es INFERGEN interferón alphacon-1 (disponible en el mercado en Amgen), este agente se administra por inyección subcutánea a 9 mcg/TIW es 24 semanas para el primer tiempo de tratamiento y hasta 15 mcg/TIW durante 24 semanas para una tratamiento que no responde o recaídas.

En una realización adicional, cuando el otro agente terapéutico es Ribavirina (disponible en el mercado como REBETOL ribavirina de Schering-Plough o COPEGUS ribavirina de Hoffmann-La Roche), este agente se administra con una dosis diaria de aproximadamente 600 a aproximadamente 1400 mg/día durante por lo menos 24 semanas.

Composiciones y administración

Debido a su actividad, los compuestos de fórmula (I) son útiles en la medicina veterinaria y humana. Como se describió anteriormente, los compuestos de fórmula (I) son útiles para el tratamiento o prevención a infección viral o a trastorno relacionado con un virus en paciente que lo requiere.

Cuando se administra a un paciente, se pueden administrar los ID como un componente de una composición que comprende un vehículo o transportador aceptable para uso farmacéutico. La presente invención proporciona composiciones farmacéuticas que comprende una cantidad efectiva de por lo menos un compuesto de fórmula (I) y un vehículo aceptable para uso farmacéutico. En las composiciones farmacéuticas y los métodos de la presente invención, los ingredientes activos normalmente se administrarán en una mezcla con materiales de vehículo adecuados seleccionados con respecto a la forma prevista de administración, es decir, comprimidos orales, cápsulas (ya sea rellenas con sólido, rellenas con semisólidos o rellenas con líquido), polvos por constitución, geles orales, elixires, gránulos dispersables jarabes, suspensiones y similares y compatibles con las practicas farmacéuticas convencionales. Por

ejemplo, para la administración oral en la forma de comprimidos o cápsulas, el componente fármaco activo se puede combinar con cualquier vehículo oral inerte aceptable para uso farmacéutico no tóxico, tal como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato dicálcico, sulfato de calcio, talco, manitol, alcohol etílico (formas líquidas) y similares. Las preparaciones de formas sólidas incluyen polvos, comprimidos, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y comprimidos pueden estar compuestos de aproximadamente 5 a aproximadamente 95 por ciento de la composición de la invención. Los comprimidos, polvos, sellos y cápsulas se pueden usar como formas de dosis sólidas adecuadas para administración oral.

Además, cuando se desee o necesite, también se pueden incorporar aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes adecuados en la mezcla. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales, edulcorantes de maíz, gomas naturales y sintéticas tales como acacia, alginato de sodio, carboximetilcelulosa, polietilenglicol y ceras. Entre los lubricantes se pueden mencionar para el uso en estas formas de dosis mencionadas, ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio y similares. Los desintegrantes incluyen almidón, metilcelulosa, goma de guar y similares. También se pueden incluir edulcorantes y agentes saborizantes, según corresponda.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones y pueden incluir agua o soluciones agua-propilenglicol para inyección parenteral.

Las preparaciones en forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para la inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden estar en combinación con un vehículo aceptable para uso farmacéutico, tales como un gas inerte comprimido.

También se incluyen preparaciones en forma sólida que están destinadas a convertirse, inmediatamente antes de usar, a las preparaciones en forma líquida tanto para administración oral como parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Para preparar supositorios, una cera de baja fusión tal como una mezcla de glicéridos de ácidos grasos o manteca de cacao se funde primero y el componente activo se dispersa homogéneamente en estos como por agitación. La mezcla homogénea fundida luego se vierte en moldes de tamaño conveniente, se deja enfriar y de este modo se solidifica.

Los compuestos de fórmula (I) de la presente invención también se pueden administrar en forma transdérmica. Las composiciones transdérmicas pueden adoptar la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluir en un parche transdérmico de la matriz o tipo reservorio que son convencional en el arte para este propósito.

Adicionalmente, las composiciones de la presente invención se pueden formular en forma de liberación sostenida para proporcionar la velocidad de liberación controlada de uno o más de los componentes o ingredientes activos para optimizar los efectos terapéuticos, es decir, actividad antiinflamatoria y similares. Las formas de dosis adecuadas para la liberación sostenida incluyen los comprimidos en capas que contienen capas de variadas velocidades de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y configurados en la forma de comprimido o cápsulas que contienen matrices poliméricas impregnadas o porosas encapsuladas.

En una realización, uno o más compuestos de fórmula (I) se administran por vía oral.

En otra realización, uno o más compuestos de fórmula (I) se administran por vía intravenosa.

En otra realización, uno o más compuestos de fórmula (I) se administran por vía tópica.

En aún otra realización, uno o más compuestos de fórmula (I) se administran por vía sublingual.

En una realización, una preparación farmacéutica que comprende por lo menos un compuesto de fórmula (I) es una forma de dosis unitaria. En tal forma, la preparación se subdivide en dosis unitarias que contienen cantidades apropiadas del componente activo, por ej., una cantidad efectiva para obtener el propósito deseado.

Las composiciones se pueden preparar de acuerdo con métodos convencionales de mezclado, granulación o recubrimiento, respectivamente y las presentes composiciones pueden contener, en una realización, de aproximadamente 0,1% a aproximadamente 99% del compuesto(s) de fórmula (I) en peso o volumen. En diversas realizaciones, las presentes composiciones pueden contener en una realización, de aproximadamente 1% a aproximadamente 70% o de aproximadamente 5% a aproximadamente 60% del Compuesto(s) de fórmula (I) en peso o volumen.

La cantidad de compuesto de fórmula (I) en una dosis unitaria de preparación puede ser variado o ajustado de aproximadamente 0,1 mg a aproximadamente 2000 mg. En diversas realizaciones, la cantidad es de aproximadamente 1 mg a aproximadamente 2000 mg, 100 mg a aproximadamente 200 mg, 500 mg a aproximadamente 2000 mg, 100 mg a aproximadamente 1000 mg, y 1 mg a aproximadamente 500 mg.

Por conveniencia, la dosis diaria total se puede subdividir y administrar en porciones durante el día, según corresponda. En una realización, la dosis diaria se administra en una porción. En otra realización, la dosis diaria total se administra en dos dosis divididas durante un período de 24 horas. En otra realización, la dosis diaria total se administra en tres dosis divididas durante un período de 24 horas. En aún otra realización, la dosis diaria total se administra en cuatro dosis divididas durante un período de 24 horas.

La cantidad y frecuencia de administración de los compuestos de fórmula (I) se regulará de acuerdo con el criterio del médico asistente que considera factores tales como edad, enfermedad y tamaño del paciente además de la gravedad de los síntomas tratados. Generalmente, una dosis diaria total de los compuestos de fórmula (I) varía de aproximadamente 0,1 a aproximadamente 2000 mg por día, si bien las variaciones necesariamente se producirán de acerado con el blanco de la terapia, el paciente y la vía de administración. En una realización, la dosis es de aproximadamente 1 a aproximadamente 200 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En otra realización, la dosis es de aproximadamente 10 a aproximadamente 2000 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En otra realización, la dosis es de aproximadamente 100 a aproximadamente 2000 mg/día, administrada en una dosis única o en 2-4 dosis divididas. En aún otra realización, la dosis es de aproximadamente 500 a aproximadamente 2000 mg/día, administrada en una dosis única o en 2-4 dosis divididas.

Las composiciones de la invención además pueden comprender uno o más agentes terapéuticos adicionales, seleccionados de los enumerados anteriormente en la presente memoria. Por consiguiente, en una realización, la presente invención proporciona composiciones que comprenden: (i) por lo menos un compuesto de fórmula (I) o sal, solvato, éster o profármaco aceptables para

uso farmacéutico de los mismos ; (ii) uno o más agentes terapéuticos adicionales que no son un compuesto de fórmula (I); y (iii) un vehículo aceptable para uso farmacéutico, donde las cantidades de la composición son en conjunto efectivas para tratar una infección viral o trastorno relacionado con el virus.

Kits

En un aspecto, la presente invención proporciona un kit que comprende una cantidad terapéuticamente efectiva de por lo menos un compuesto de fórmula (I), o una sal, solvato, éster o profármaco aceptables para uso farmacéutico de dicho compuesto y un vehículo, transportador o diluyente aceptables para uso farmacéutico.

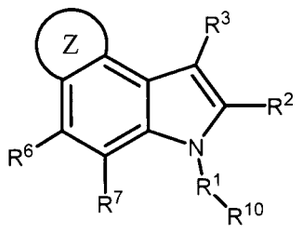
En otro aspecto La presente invención proporciona un kit que comprende una cantidad de por lo menos un compuesto de fórmula (I), o una sal, solvato, éster o profármaco aceptables para uso farmacéutico de dicho compuesto y una cantidad de por lo menos un agente terapéutico adicional enumerado anteriormente, donde las cantidades de los dos o más ingredientes producen un efecto terapéutico deseado.

La presente invención no está limitada por las realizaciones específicas descriptas en los ejemplos que se consideran como ilustraciones de uno pocos aspectos de la invención y cualquiera de las realizaciones que son funcionalmente equivalentes está dentro del alcance de esta invención. En efecto, varias modificaciones de la invención además de las se muestran y describen en la presente memoria serán evidentes para los expertos en el arte y se consideran que se incluyen en el alcance de las reivindicaciones anexas.

Se han mencionado numerosas referencias en la presente memoria, cuyas descripciones completas están incorporadas en la presente memoria como referencia.

REIVINDICACIONES

1. Un compuesto que tiene la fórmula:



(I)

y sus sales y solvatos aceptables para uso farmacéutico,

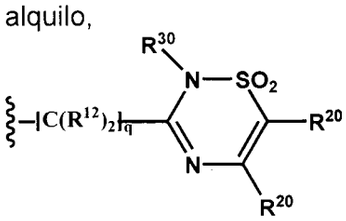
donde

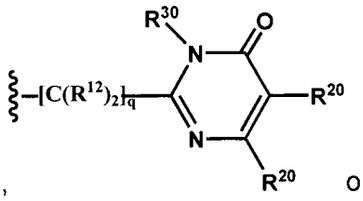
el anillo Z de la fórmula (I) es un ciclopentilo, ciclopentenilo, heterocicloalquilo de 5 miembros, heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros, donde el anillo Z puede estar: (i) opcionalmente sustituido en uno o más átomos de carbono anulares con sustituyentes, que son iguales o diferentes, y que se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$; y/o (ii) opcionalmente sustituido en un átomo de nitrógeno del anillo con sustituyentes, que son iguales o diferentes, y que se seleccionan de alquilo, arilo, haloalquilo, heteroarilo, hidroxialquilo, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_r-OR^9$, $-[C(R^{12})_2]_r-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$;

R^1 es un enlace, $-[C(R^{12})_2]_r-$, $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$, $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$ o $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$;

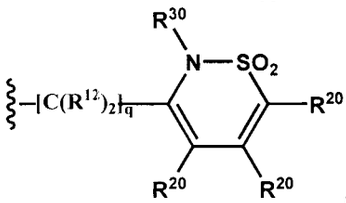
R^2 es $-C(O)R^9$, $-C(O)OR^9$, $-C(O)OCH_2OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-C(O)N(R^9)C=N(R^9)_2$, $-[C(R^{12})_2]_q-$arilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$cicloalquenilo, $-[C(R^{12})_2]_q-$heterocicloalquilo, $-[C(R^{12})_2]_q-$heteroarilo, $-[C(R^{12})_2]_q-$heterocicloalquenilo, $-[C(R^{12})_2]_q-$

$C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$, alquilo,



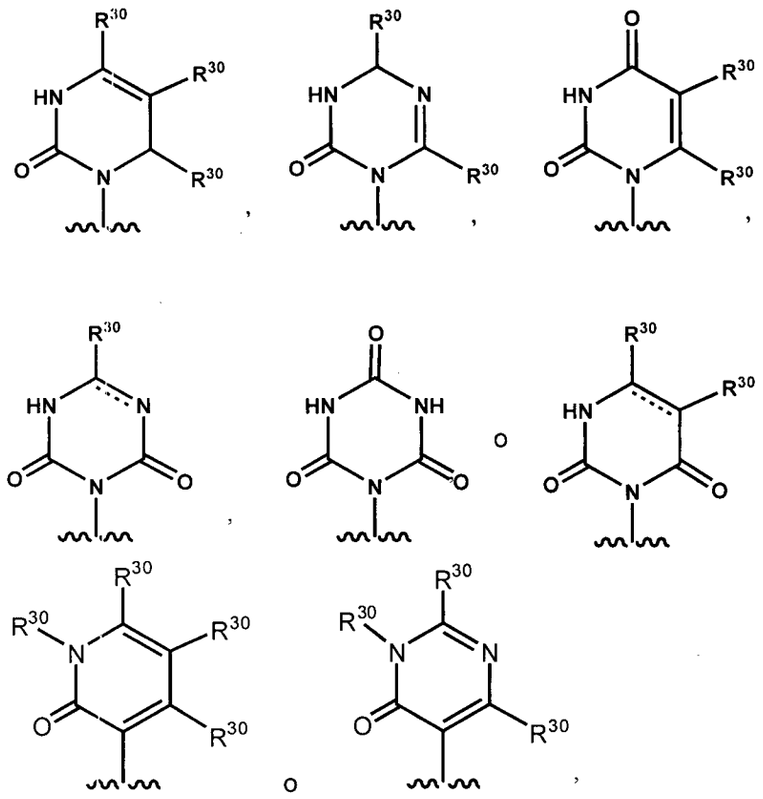


o



, donde un grupo arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona en forma independiente de alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$;

R^3 es –H, $-[C(R^{12})_2]_q$-alquilo, $-[C(R^{12})_2]_q$-arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heteroarilo o $-[C(R^{12})_2]_q$-heterocicloalquenilo,



donde un grupo arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo o heteroarilo puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heteroarilo, heterocicloalquilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$;

cada R^6 y R^7 son independientemente, H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ o $-SO_2N(R^9)C(O)N(R^9)_2$;

cada aparición de R^8 es independientemente H, alquilo, alquenilo, alquinilo, -$[C(R^{12})_2]_q$-arilo, -$[C(R^{12})_2]_q$-cicloalquilo, -$[C(R^{12})_2]_q$-cicloalquenilo, -$[C(R^{12})_2]_q$-heterocicloalquilo, -$[C(R^{12})_2]_q$-heterocicloalquenilo, -$[C(R^{12})_2]_q$-heteroarilo, haloalquilo o hidroxialquilo;

cada aparición de R^9 es independientemente H, alquilo, alquenilo, alquinilo, -$[C(R^{12})_2]_q$-arilo, -$[C(R^{12})_2]_q$-cicloalquilo, -$[C(R^{12})_2]_q$-cicloalquenilo, -$[C(R^{12})_2]_q$-heterocicloalquilo, -$[C(R^{12})_2]_q$-heterocicloalquenilo, -$[C(R^{12})_2]_q$-heteroarilo, haloalquilo o hidroxialquilo, o dos grupos R^9 que están unidos a un átomo de nitrógeno común, junto con el átomo de nitrógeno al cual están unidos, se combinan para formar un grupo heterocicloalquilo, heterocicloalquenilo o heteroarilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona en forma independiente de H, alquilo, alquenilo, alquinilo, arilo, -$[C(R^{12})_2]_q$-cicloalquilo, -$[C(R^{12})_2]_q$-cicloalquenilo, -$[C(R^{12})_2]_q$-heterocicloalquilo, -$[C(R^{12})_2]_q$-heterocicloalquenilo, -$[C(R^{12})_2]_q$-heteroarilo, -$[C(R^{12})_2]_q$-haloalquilo, -$[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, -OR^9, -CN, -$[C(R^{12})_2]_q$-$C(O)R^8$, -$[C(R^{12})_2]_q$-$C(O)OR^9$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-OR^9, -$[C(R^{12})_2]_q$-$N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHC(O)R^8$, -$[C(R^{12})_2]_q$-$NR^8C(O)N(R^9)_2$, -$[C(R^{12})_2]_q$-$NHSO_2R^{11}$, -$[C(R^{12})_2]_q$-$S(O)_pR^{11}$, -$[C(R^{12})_2]_q$-$SO_2N(R^9)_2$ y -$SO_2N(R^9)C(O)N(R^9)_2$, de modo tal que cuando R^1 es un enlace, R^{10} no es H;

cada aparición de R^{11} es independientemente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar

opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona en forma independiente de –H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2$alquilo, $-[C(R^{12})_2]_q-NHSO_2$cicloalquilo, $-[C(R^{12})_2]_q-NHSO_2$arilo, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$;

cada aparición de R^{12} es independientemente H, halo, $-N(R^9)_2$, $-OR^9$, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona en forma independiente de alquilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, -C(O)Oalquilo -C(O)NHalquilo $-C(O)N(alquilo)_2$, -O-alquilo, $-NH_2$, -NH(alquilo), $-N(alquilo)_2$, -NHC(O)alquilo, $-NHSO_2$alquilo $-SO_2$alquilo o $-SO_2$NH-alquilo, o dos grupos R^{12}, junto con los átomos de carbono a los que están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

cada aparición de R^{20} es independientemente H, alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los que están unidos, se unen para formar un grupo cicloalquilo, cicloheteroalquilo, arilo o heteroarilo donde un cicloalquilo, cicloheteroalquiloo, arilo o heteroarilo puede estar sustituido con hasta 4 grupos, cada uno de los cuales se selecciona en forma independiente de alquilo, alquenilo, alquinilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo,

$-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$;

cada aparición de R^{30} es independientemente H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ o $-SO_2N(R^9)C(O)N(R^9)_2$, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los que están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

cada aparición de p es independientemente 0, 1 o 2;

cada aparición de q es independientemente un número entero que varía de 0 a 4; y

cada aparición de r es independientemente un número entero que varía de 1 a 4.

2. El compuesto de la reivindicación 1, donde R^1 es un enlace o $-[C(R^{12})_2]_r-$.

3. El compuesto de la reivindicación 2, donde R^{10} es fenilo, piridilo o pirimidinilo, cada uno de cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

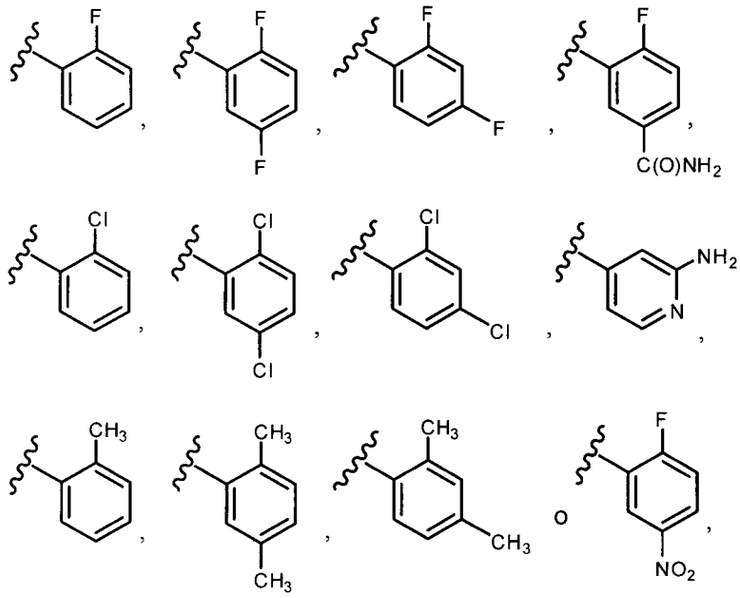
4. El compuesto de la reivindicación 2, donde R^{10} es un arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u

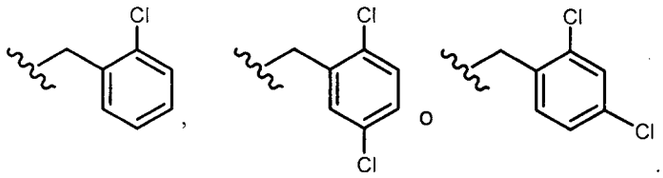
opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, -C(O)N(R^9)$_2$, -alquilen-OR^9, -OR^9, -N(R^9)$_2$, -NHC(O)R^8, -NHSO_2R^{11}, -S(O)$_p R^{11}$ o -SO_2N(R^9)$_2$.

5. El compuesto de la reivindicación 2, donde R^{10} es fenilo, piridilo, benzoimidazol, benzoimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, -NH_2, -NH-alquilo, -N(alquilo)$_2$ o –NHSO_2-alquilo.

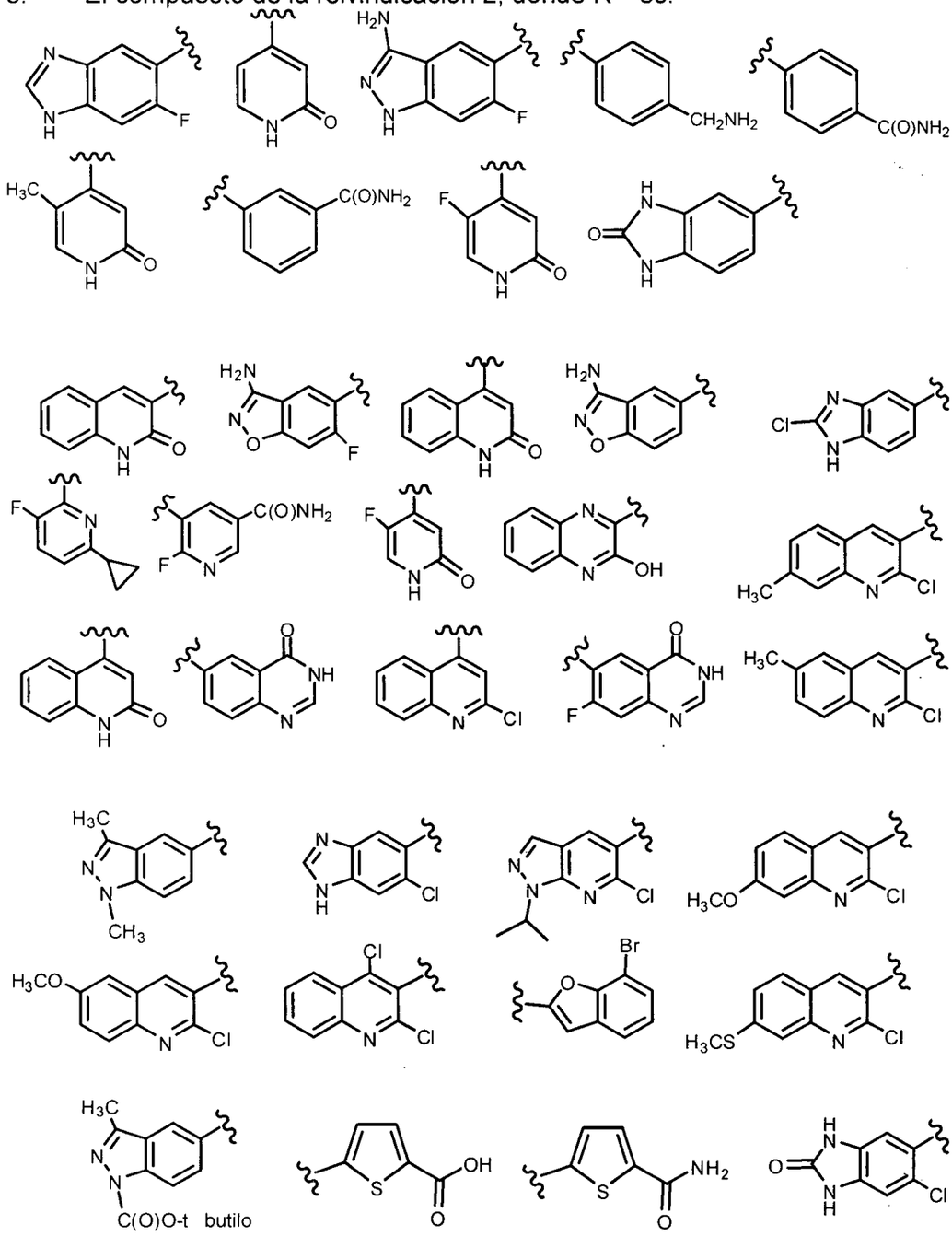
6. El compuesto de la reivindicación 5, donde el grupo R^{10} puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de metilo, ciclopropilo, halo, -OH, -NH_2, -$NHCH_3$ y –N(CH_3)$_2$.

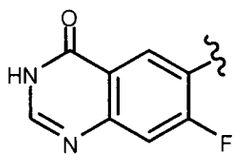
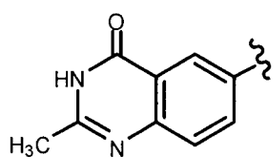
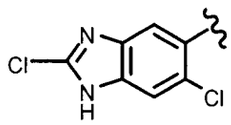
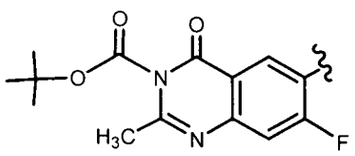
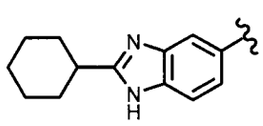
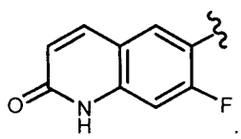
7. El compuesto de la reivindicación 2, donde R^{10} es:



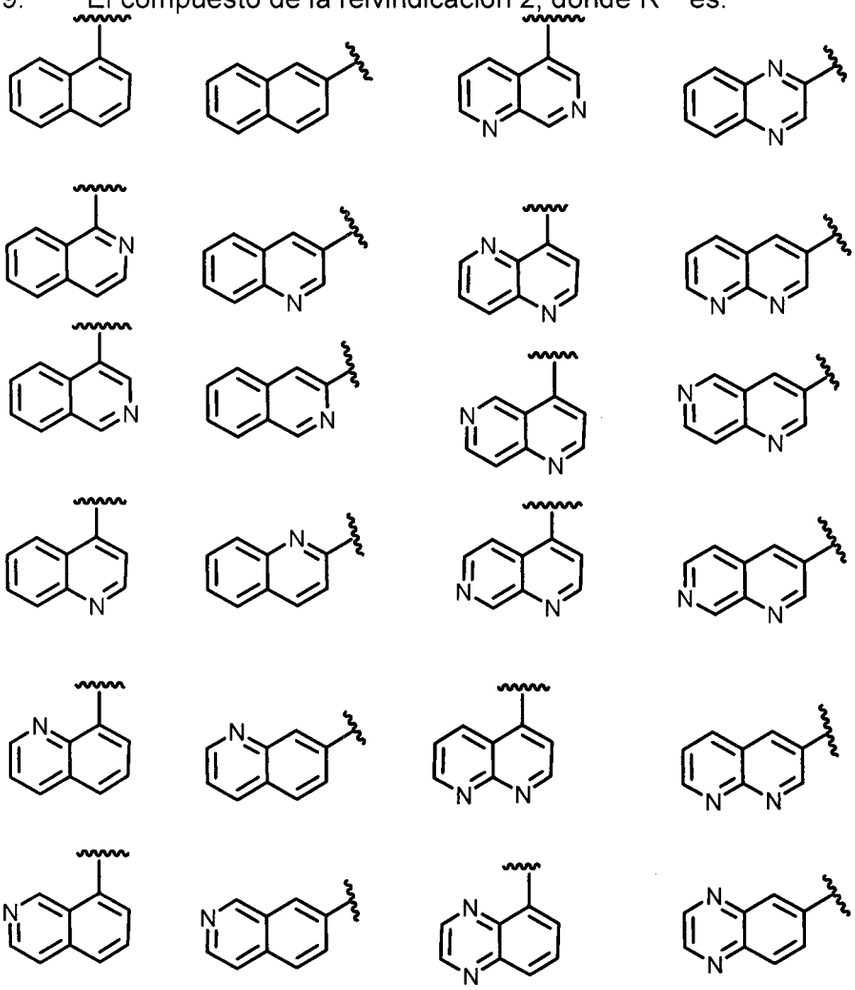


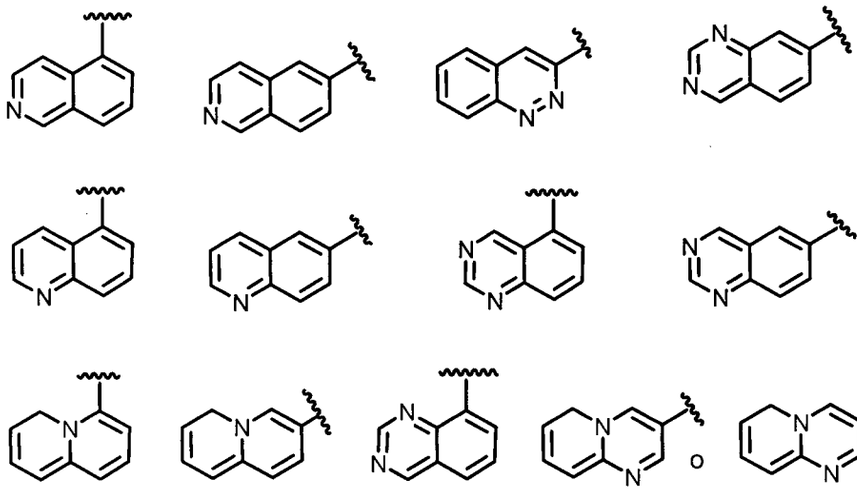
8. El compuesto de la reivindicación 2, donde R^{10} es:








o


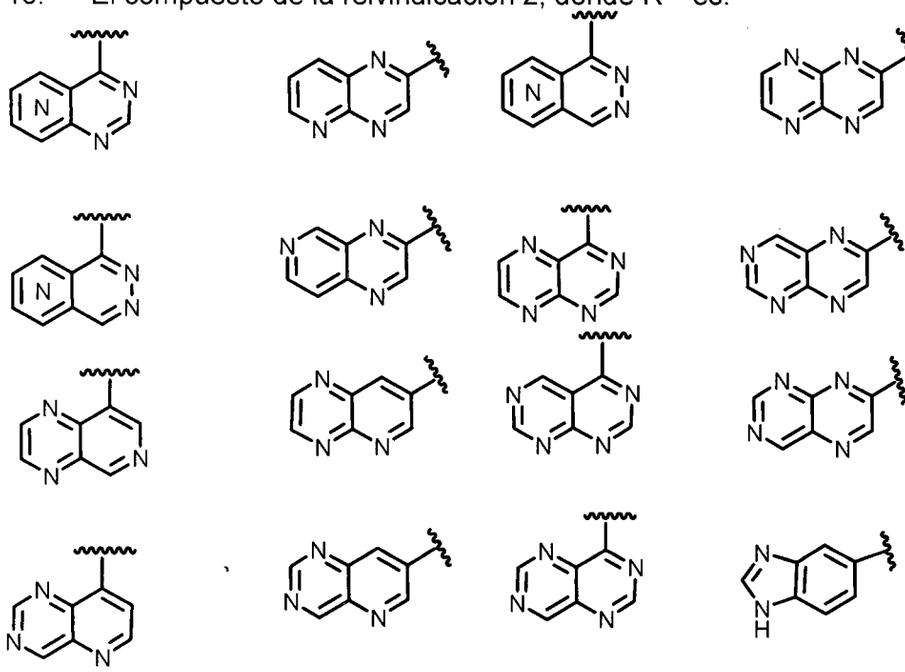
9. El compuesto de la reivindicación 2, donde R^{10} es:

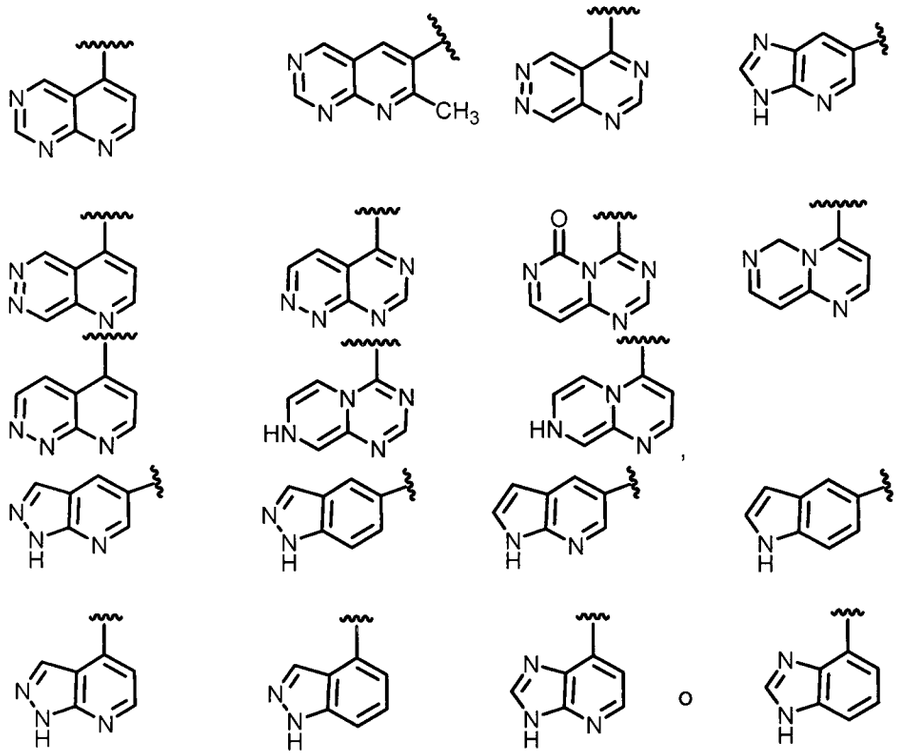




cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

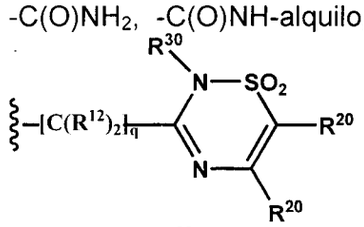
10. El compuesto de la reivindicación 2, donde R^{10} es:



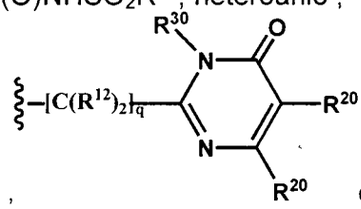


, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro de un anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno anulares.

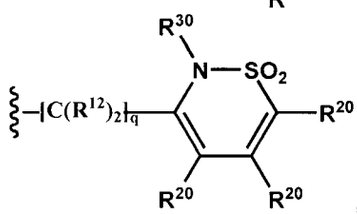
11. El compuesto de la reivindicación 1, donde R^2 es -C(O)OH, -C(O)Oalquilo, $-C(O)NH_2$, -C(O)NH-alquilo, -C(O)NH-cicloalquilo, $-C(O)NHSO_2R^{11}$, heteroarilo ,



,



o



,

donde el grupo ariltiazin-il- o ariltiadiazol-il- puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$; de modo tal que si Z es tiofenilo, R^2 es diferente de –C(O)O-alquilo.

12. El compuesto de la reivindicación 4, donde R^2 es $-C(O)NHSO_2$-alquilo, $-C(O)NHSO_2$-arilo, $-C(O)NHSO_2$-cicloalquilo o $-C(O)NHSO_2$-alquilen-cicloalquilo.

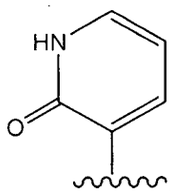
13. El compuesto de la reivindicación 4, donde R^2 es $-C(O)NHSO_2$-metilo, $-C(O)NHSO_2$-etilo, $-C(O)NHSO_2$-isopropilo, $-C(O)NHSO_2$-t-butilo, $-C(O)NHSO_2$-fenilo o $-C(O)NHSO_2$-ciclopropilo.

14. El compuesto de la reivindicación 4, donde R^2 es –C(O)OH.

15. El compuesto de la reivindicación 1, donde R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$.

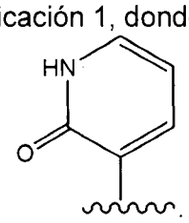
16. El compuesto de la reivindicación 6, donde R^3 es piridilo, o fenilo que está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$ o $-NHC(O)R^8$.

17. El compuesto de la reivindicación 1, donde R^3 es fenilo, piridilo o



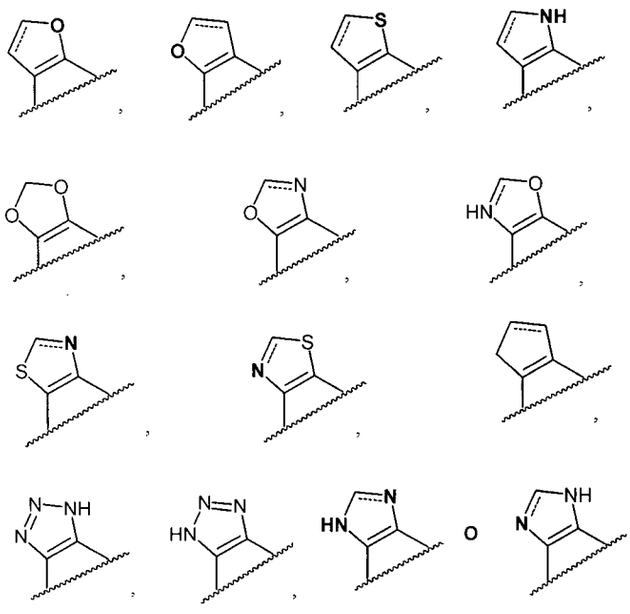
, cada uno de los cuales puede estar opcionalmente sustituido con uno a 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$, -NHalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2$alquilo, $-S(O)_2$-alquilo o $-SO_2$NHalquilo.

18. El compuesto de la reivindicación 1, donde R^3 es:



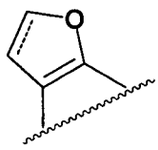
19. El compuesto de la reivindicación 1, donde el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros.

20. El compuesto de la reivindicación 8, donde el anillo Z es:



donde una línea de puntos representa un enlace opcional y adicional y donde los grupos Z del anillo anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1.

21. El compuesto de la reivindicación 8, donde el anillo Z es:



22. El compuesto de la reivindicación 1, donde cada R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo.

23. El compuesto de la reivindicación 2, donde el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros.

R^2 es -C(O)OH, heteroarilo o $-C(O)NHSO_2R^{11}$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

cada R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es fenilo, piridilo o pirimidinilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -OH, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

24. El compuesto de la reivindicación 2, donde el anillo Z es un heterocicloalquenilo de 5 miembros o heteroarilo de 5 miembros;

R^2 es -C(O)OH, heteroarilo o $-C(O)NHSO_2R^{11}$;

R^3 es arilo, heteroarilo o heterocicloalquenilo, cada uno de los cuales está no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, cicloalquilo, heterocicloalquilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, -C(O)alquilo, $-C(O)N(R^9)_2$, $-N(R^9)_2$, -O-haloalquilo, $-NHC(O)NH_2$, -NHC(O)NH-alquilo, $-NHSO_2R^{11}$, $-S(O)_2R^{11}$ o $-SO_2NHR^{11}$;

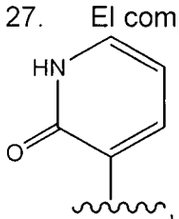
cada R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ o $-NHSO_2$-alquilo; y

R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, $-C(O)N(R^9)_2$, -alquilen-OR^9, $-OR^9$, $-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$.

25. El compuesto de la reivindicación 11, donde R^2 es -C(O)OH.

26. El compuesto de la reivindicación 11, donde R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es alquilo, arilo o cicloalquilo.

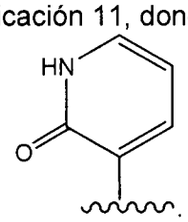
27. El compuesto de la reivindicación 11, donde R^3 es fenilo, piridilo o



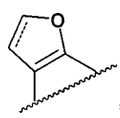
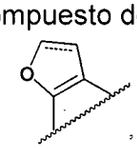
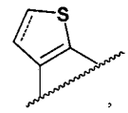
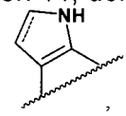
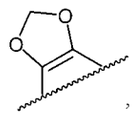
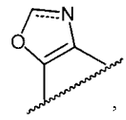
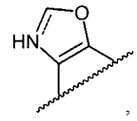
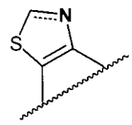
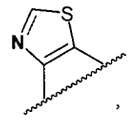
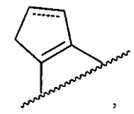
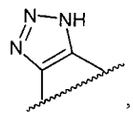
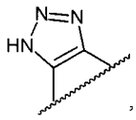
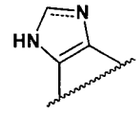
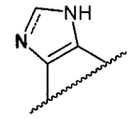
, cada uno de los cuales puede estar opcionalmente sustituido con uno a 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, $-CF_3$, -CN, -C(O)alquilo, $-C(O)NH_2$, -C(O)NHalquilo, F, Cl, -OH, $-OCF_3$, $-NH_2$,

-NHalquilo, -NHC(O)NH_2, -NHC(O)NH-alquilo, -$NHSO_2$alquilo, -$S(O)_2$-alquilo o -SO_2NHalquilo.

28. El compuesto de la reivindicación 11, donde R^3 es:



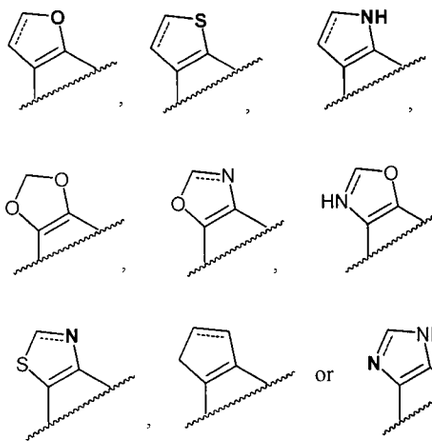
29. El compuesto de la reivindicación 11, donde el anillo Z es:














o


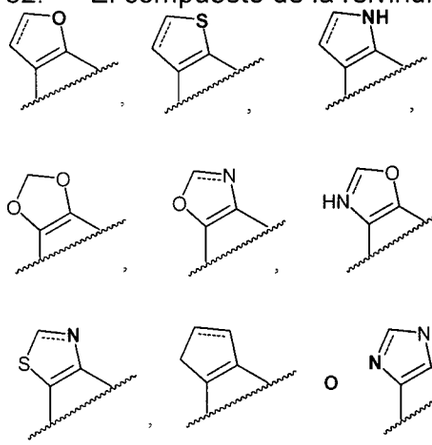
donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1.

30. El compuesto de la reivindicación 14, donde el anillo Z puede estar sustituido con hasta 3 sustituyentes opcionales de carbono del anillo, que son iguales o diferentes, y que se seleccionan de H, alquilo, -OH, F, Cl, -O-alquilo, -CF_3, –OCF_3 y cicloalquilo.

31. El compuesto de la reivindicación 15, donde el anillo Z es:

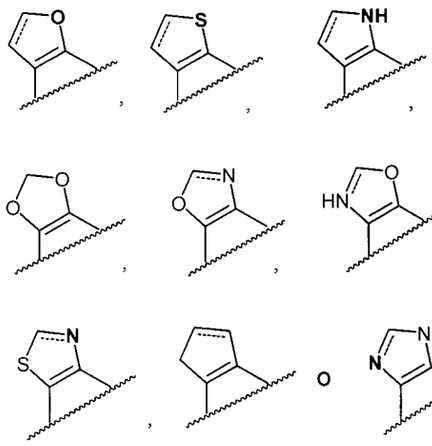


32. El compuesto de la reivindicación 11, donde el anillo Z es



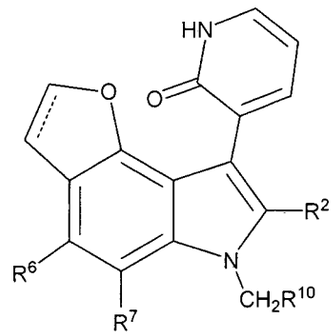
donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1.

33. El compuesto de la reivindicación 11A, donde el anillo Z es



donde una línea punteada representa un enlace opcional y adicional, y donde los grupos del anillo Z anterior pueden estar opcionalmente sustituidos como se expuso anteriormente en la reivindicación 1.

34. Un compuesto que tiene la fórmula:



(Ia)

o una sal, solvato, éster o profármaco aceptable para uso farmacéutico del mismo, donde la línea punteada indica un enlace opcional y adicional y donde:

R^2 es $-C(O)OR^9$ o $-C(O)NHSO_2R^{11}$;

cada R^6 y R^7 se selecciona independientemente de H, alquilo, F, Cl, $-CF_3$, -OH, -O-alquilo, $-OCF_3$, $-NH_2$ y $-NHSO_2$-alquilo;

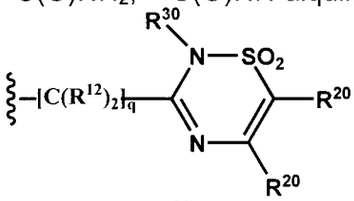
R^9 es H o alquilo;

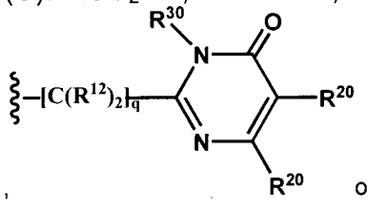
R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo, donde un grupo cicloalquilo,

cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar opcionalmente sustituido con hasta 4 sustituyentes, cada uno de los cuales se selecciona en forma independiente de H, alquilo, alquenilo, alquinilo, arilo, $-[C(R^{12})_2]_q$-cicloalquilo, $-[C(R^{12})_2]_q$-cicloalquenilo, $-[C(R^{12})_2]_q$-heterocicloalquilo, $-[C(R^{12})_2]_q$-heterocicloalquenilo, $-[C(R^{12})_2]_q$-heteroarilo, $-[C(R^{12})_2]_q$-haloalquilo, $-[C(R^{12})_2]_q$-hidroxialquilo, halo, -OH, $-OR^9$, -CN, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ y $-SO_2N(R^9)C(O)N(R^9)_2$; y

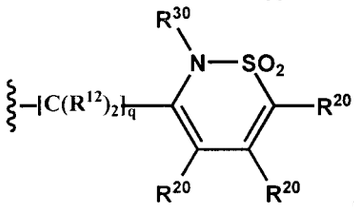
R^{11} es alquilo, arilo o cicloalquilo.

35. El compuesto de la reivindicación 34, donde R^2 es -C(O)OH, -C(O)Oalquilo, $-C(O)NH_2$, -C(O)NH-alquilo, -C(O)NH-cicloalquilo, $-C(O)NHSO_2R^{11}$, heteroarilo,





o



donde el grupo heteroarilo, ariltiazin-il- o ariltiadiazol-il- puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, hidroxialquilo, -OH, -CN, $-C(O)R^8$, $-C(O)OR^9$, $-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-OR^9$, $-[C(R^{12})_2]_q-N(R^9)_2$, $-NHC(O)R^8$, $-NHSO_2R^{11}$, $-S(O)_pR^{11}$ o $-SO_2N(R^9)_2$; de modo que si Z es tiofenilo, R^2 es diferente de –C(O)O-alquilo.

36. El compuesto de la reivindicación 35, donde R^2 es $-C(O)NHSO_2$-alquilo, $-C(O)NHSO_2$-arilo, $-C(O)NHSO_2$-cicloalquilo o $-C(O)NHSO_2$-alquilen-cicloalquilo.

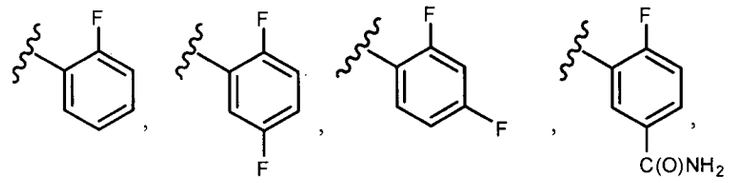
37. El compuesto de la reivindicación 36, donde R^2 es -C(O)$NHSO_2$-metilo, -C(O)$NHSO_2$-etilo, -C(O)$NHSO_2$-isopropilo, -C(O)$NHSO_2$-t-butilo, -C(O)$NHSO_2$-fenilo o -C(O)$NHSO_2$-ciclopropilo.

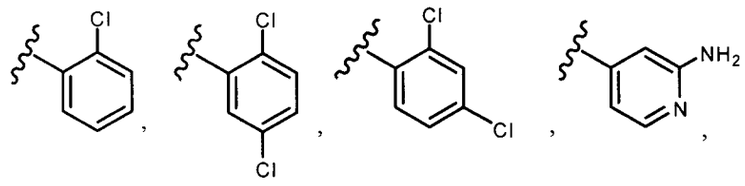
38. El compuesto de la reivindicación 35, donde R^2 es –C(O)OH.

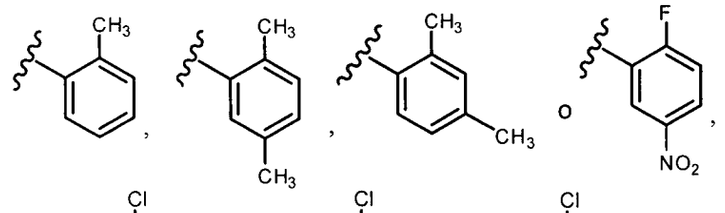
39. El compuesto de la reivindicación 34, donde R^{10} es arilo bicíclico o heteroarilo bicíclico, cada uno de los cuales puede estar no sustituido u opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, arilo, heteroarilo, halo, haloalquilo, heterocicloalquilo, heterocicloalquenilo, hidroxialquilo, -CN, -C(O)alquilo, -C(O)Oalquilo, -C(O)$N(R^9)_2$, -alquilen-OR^9, -OR^9, -$N(R^9)_2$, -$NHC(O)R^8$, -$NHSO_2R^{11}$, -$S(O)_pR^{11}$ o -$SO_2N(R^9)_2$.

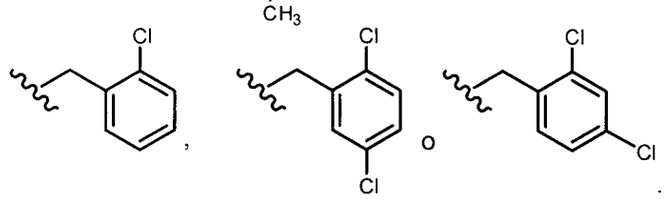
40. El compuesto de la reivindicación 34, donde R^{10} es fenilo, piridilo, benzoimidazol, benzoimidazolona, quinolina, quinolinona, quinoxalina, quinoxalinona, quinazolina, quinazolinona, naftiridina, naftiridinona, pteridina, pteridinona, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, -NH_2, -NH-alquilo, -N(alquilo)$_2$ o –$NHSO_2$-alquilo.

41. El compuesto de la reivindicación 34, donde R^{10} es:

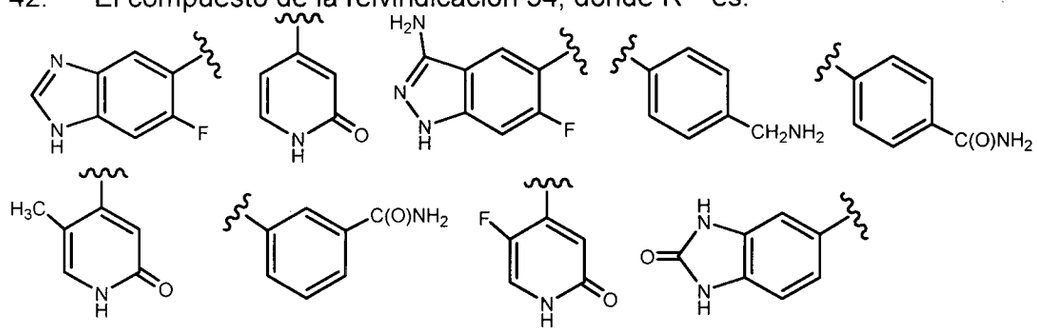


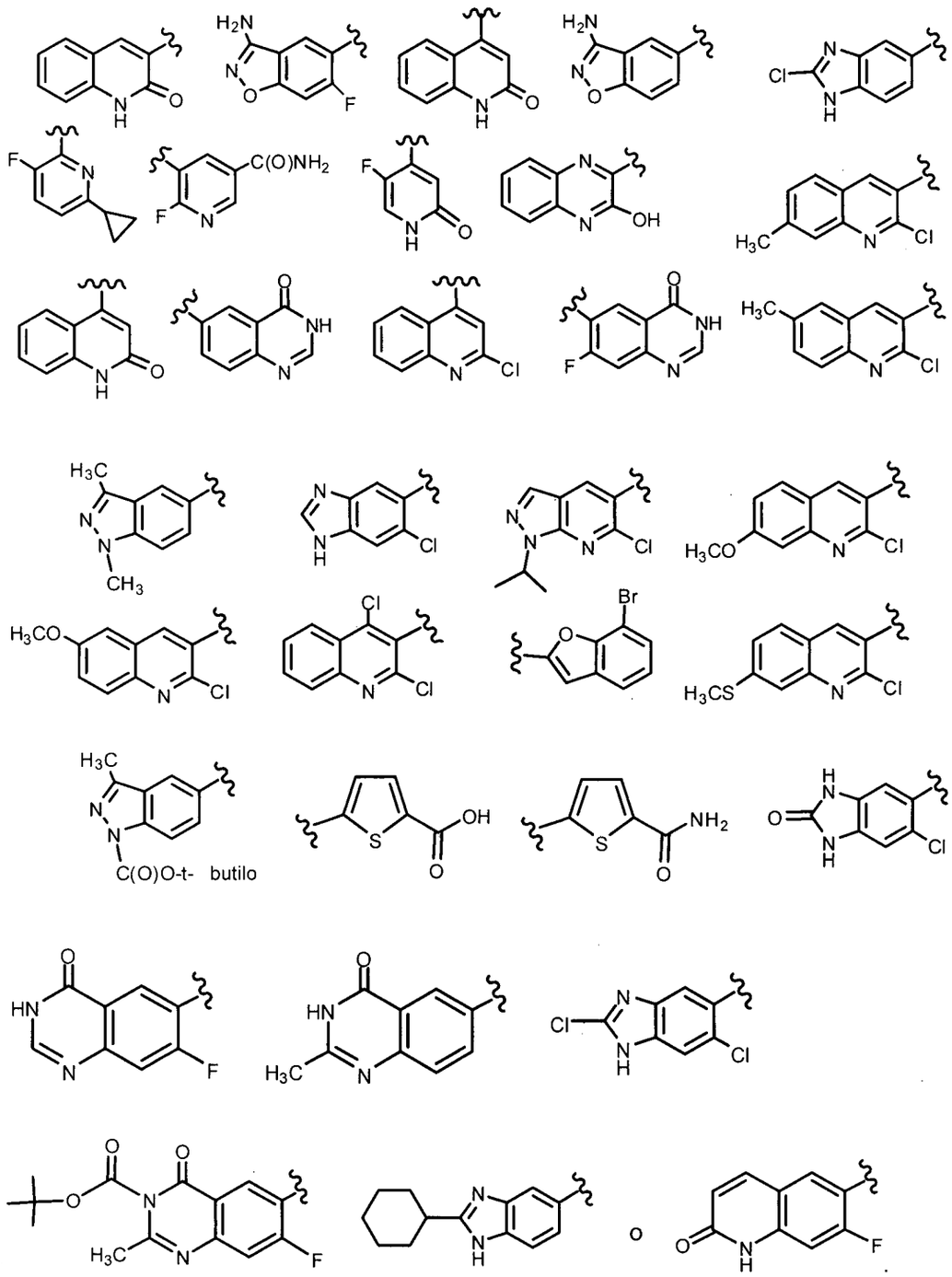




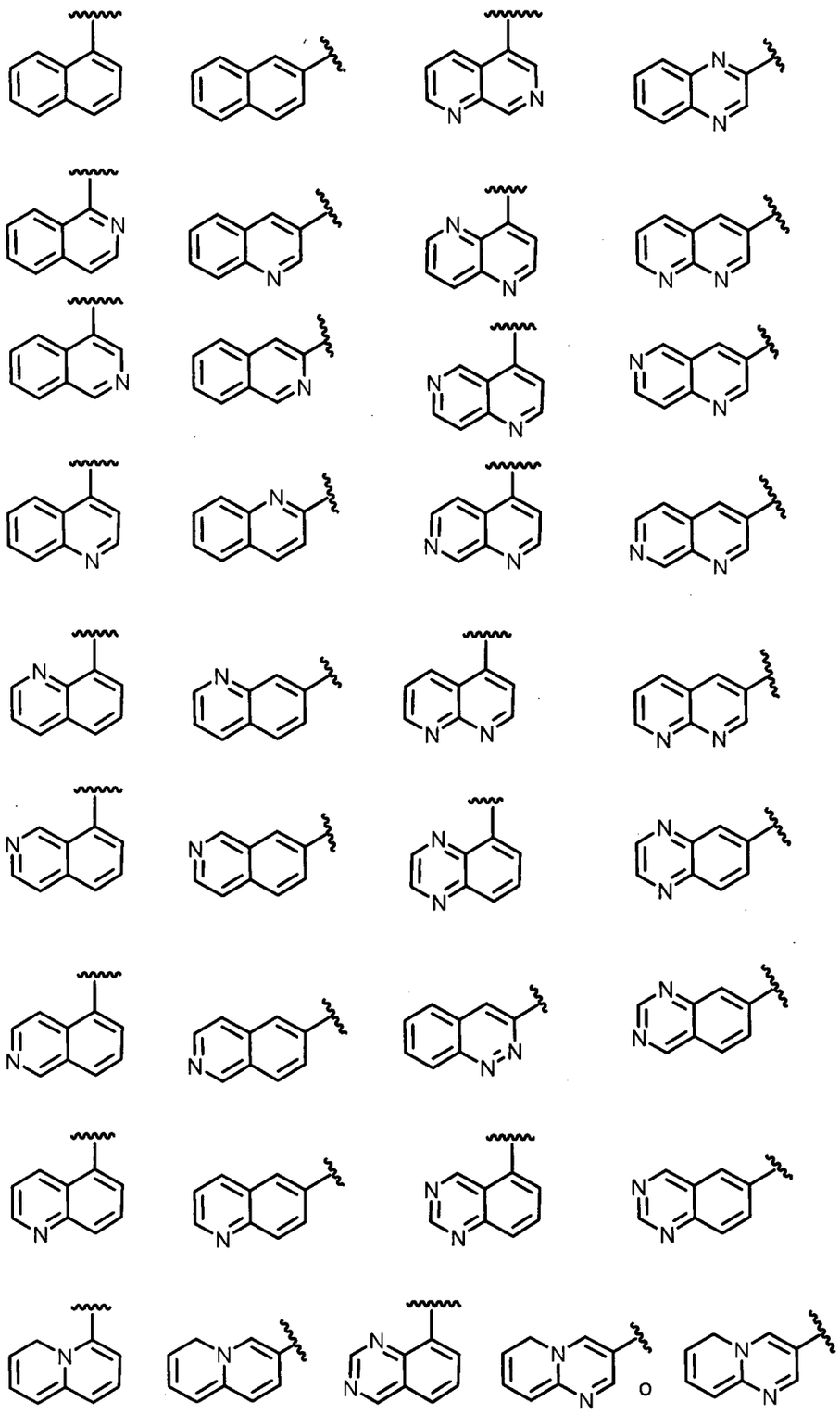


42. El compuesto de la reivindicación 34, donde R^{10} es:



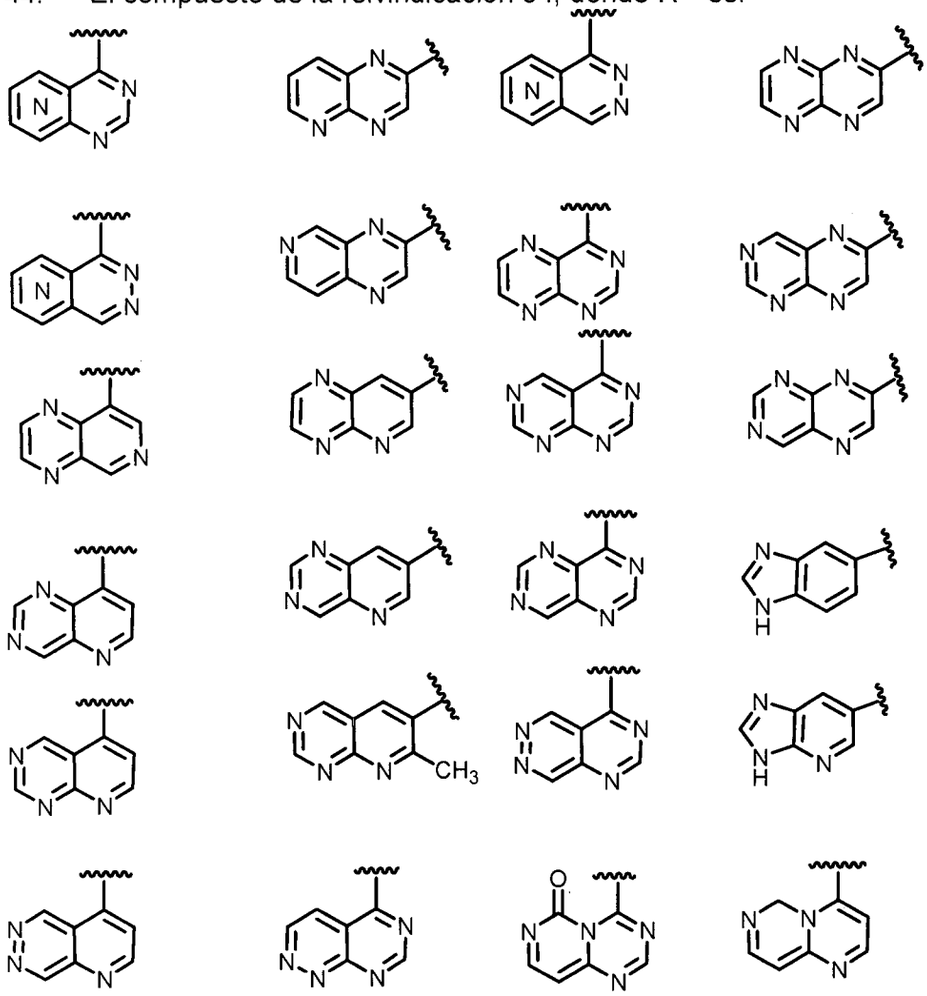


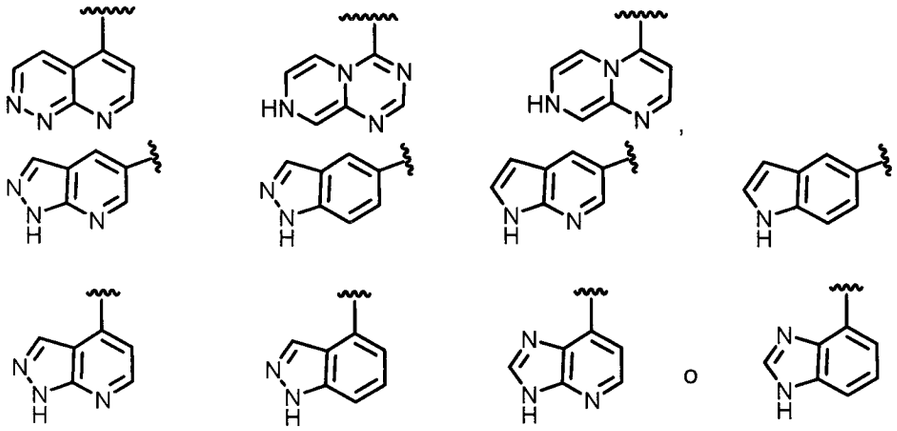
43. El compuesto de la reivindicación 34, donde R^{10} es:



cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo.

44. El compuesto de la reivindicación 34, donde R^{10} es:





, cada uno de los cuales puede estar opcionalmente sustituido con hasta 3 sustituyentes, que son iguales o diferentes, y se seleccionan de alquilo, cicloalquilo, heterocicloalquilo, heterocicloalquenilo, halo, haloalquilo, -O-haloalquilo, -OH, -CN, $-NH_2$, -NH-alquilo, $-N(alquilo)_2$ o $-NHSO_2$-alquilo; donde la letra "N" dentro de un anillo indica que el anillo tiene 1 o 2 átomos de nitrógeno.

45. El compuesto de la reivindicación 34, donde cada R^6 y R^7 es H.

46. El compuesto de la reivindicación 39, donde R^2 es $-C(O)OH$.

47. El compuesto de la reivindicación 40, donde R^2 es $-C(O)OH$.

48. El compuesto de la reivindicación 41, donde R^2 es $-C(O)OH$.

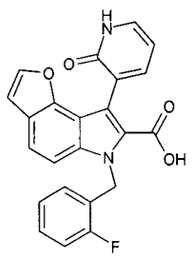
49. El compuesto de la reivindicación 42, donde R^2 es $-C(O)OH$.

50. El compuesto de la reivindicación 43, donde R^2 es $-C(O)OH$.

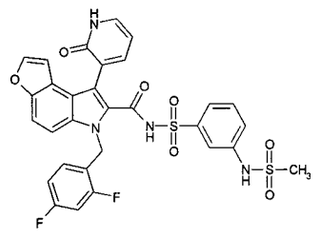
51. El compuesto de la reivindicación 44, donde R^2 es $-C(O)OH$.

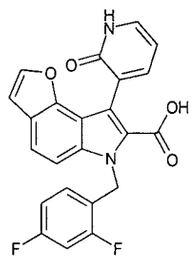
52. Un compuesto que tiene la estructura:

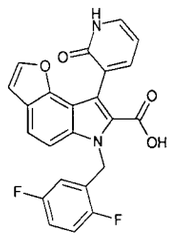
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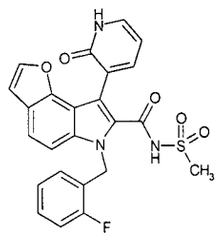


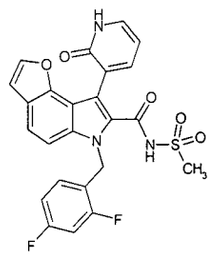
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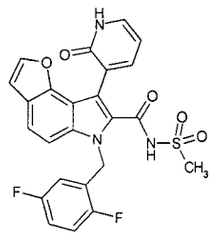


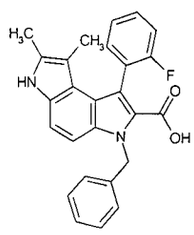
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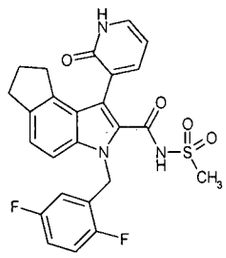
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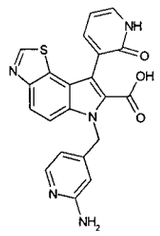
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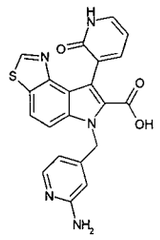
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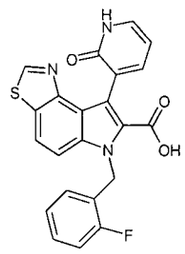
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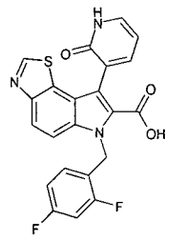
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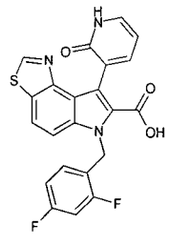
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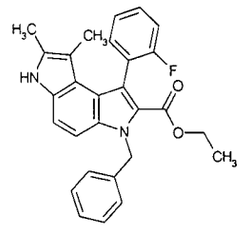
13 

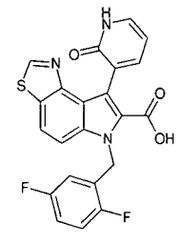
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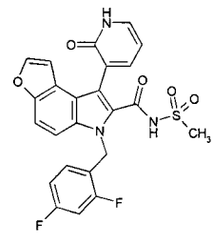
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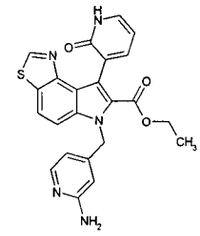
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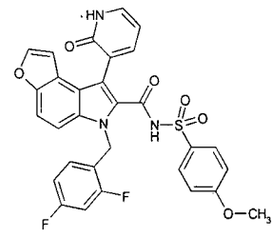
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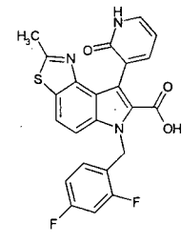
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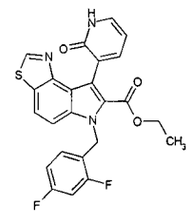
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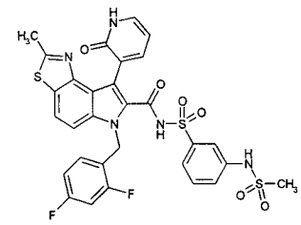
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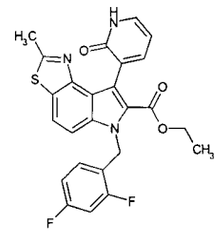
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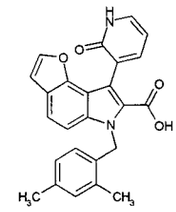
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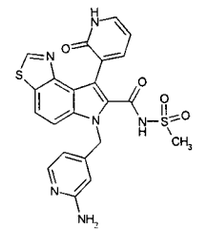
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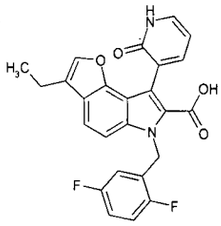
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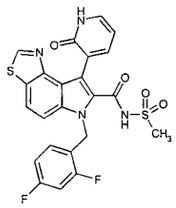
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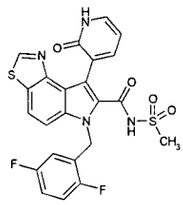
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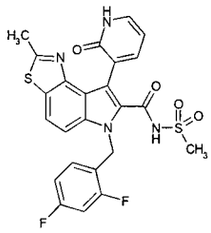
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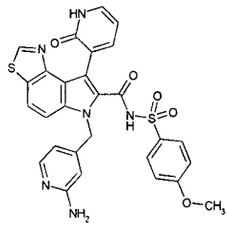
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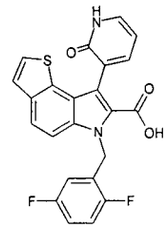
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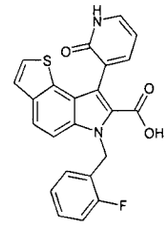
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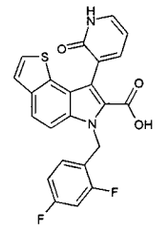
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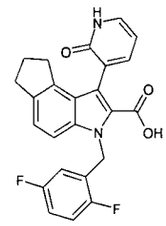
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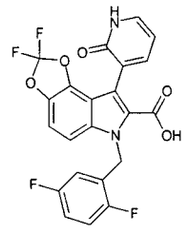
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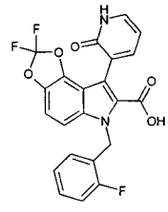
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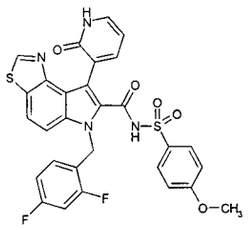
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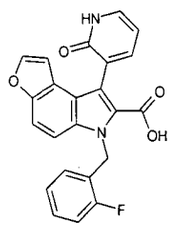
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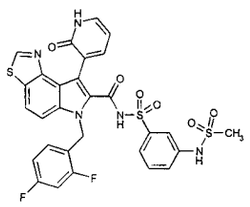
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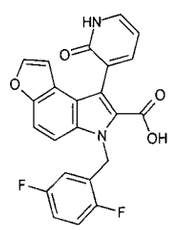
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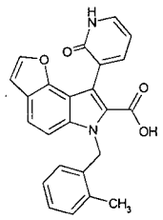
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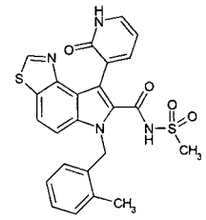
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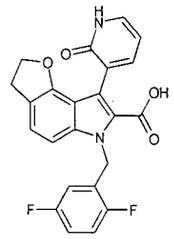
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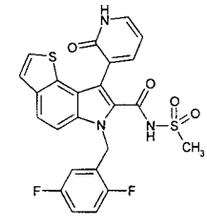
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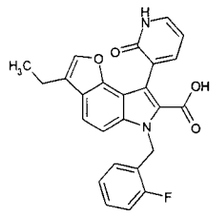
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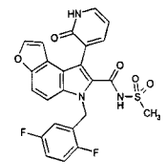
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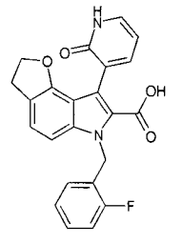
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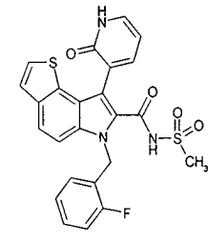
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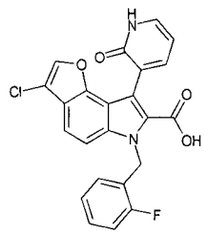
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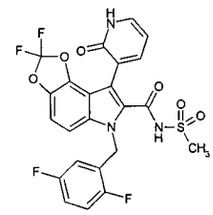
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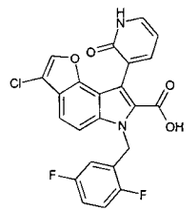
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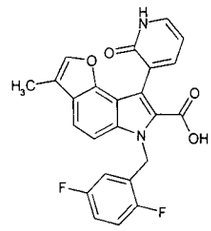
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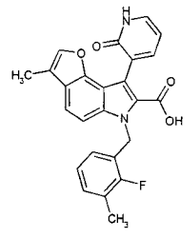
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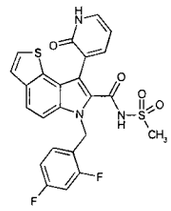
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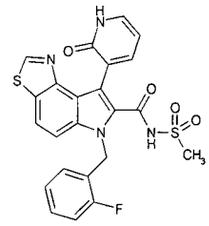
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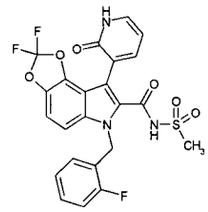
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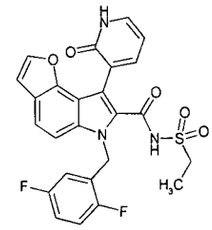
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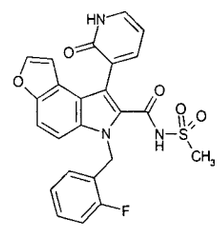
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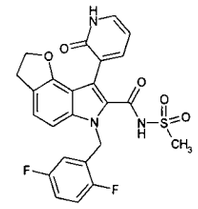
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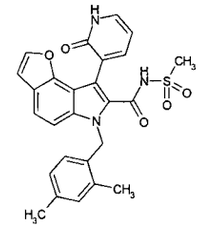
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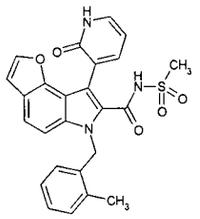
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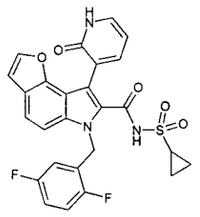
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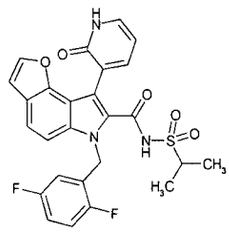
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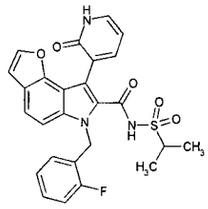
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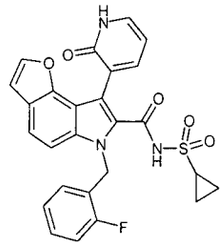
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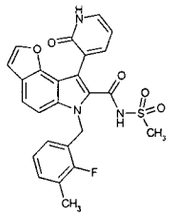
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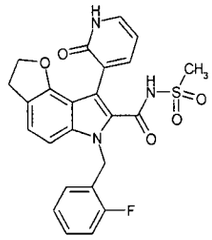
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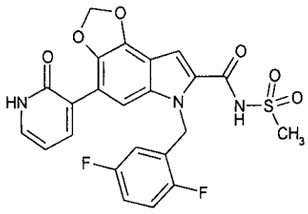
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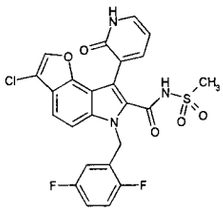
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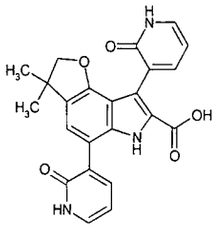
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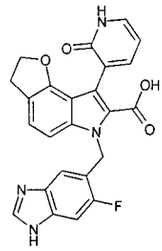
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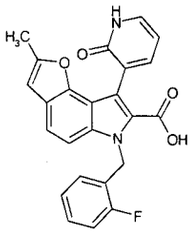
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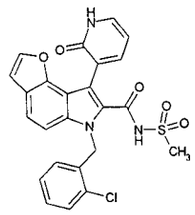
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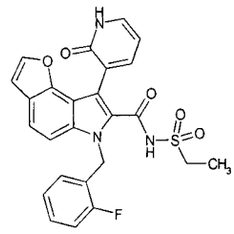
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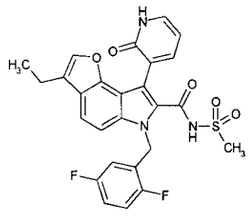
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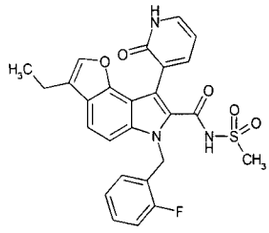
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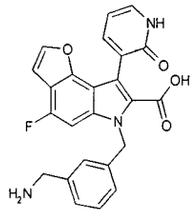
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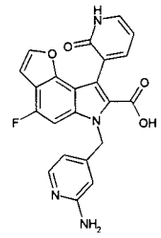
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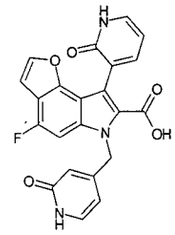
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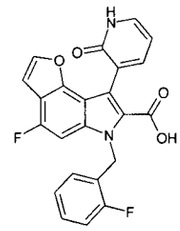
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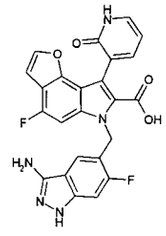
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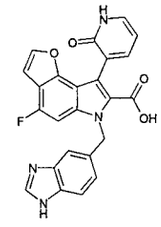
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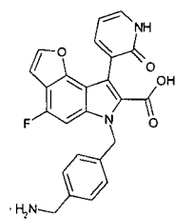
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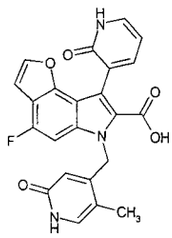
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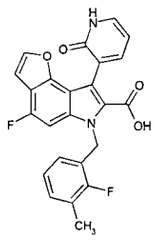
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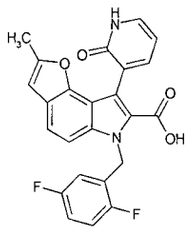
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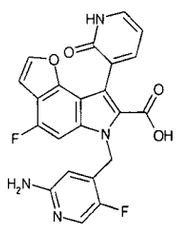
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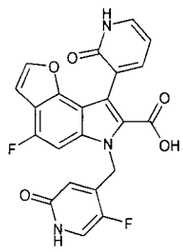
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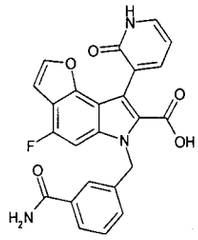
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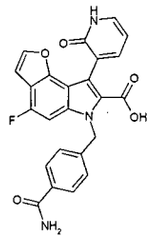
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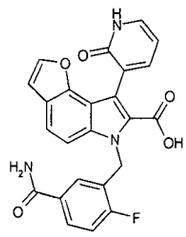
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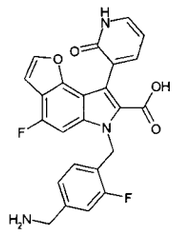
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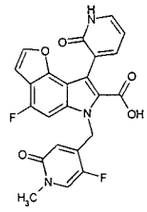
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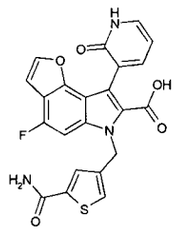
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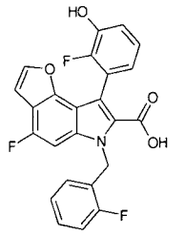
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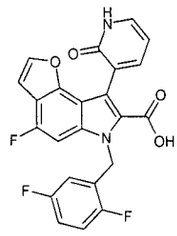
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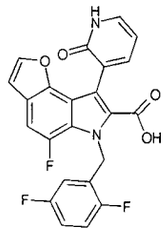
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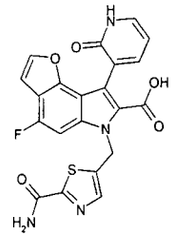
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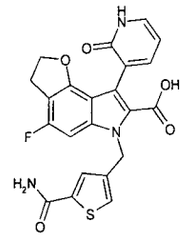
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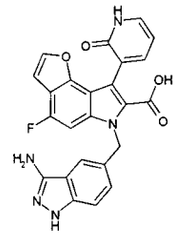
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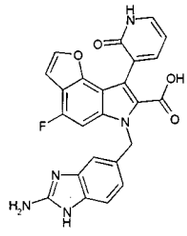
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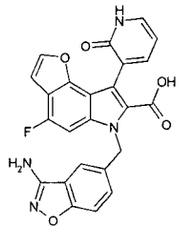
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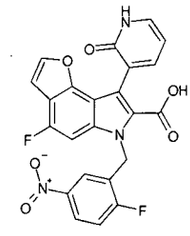
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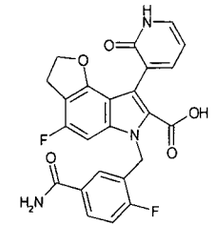
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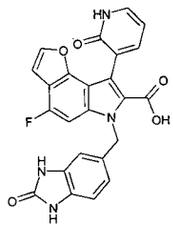


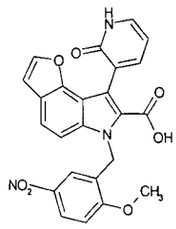
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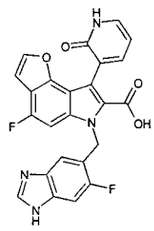


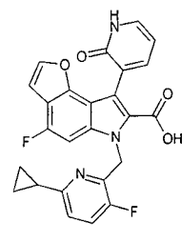
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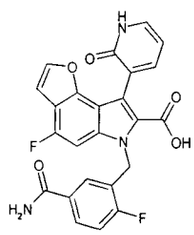


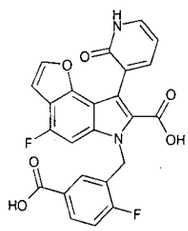
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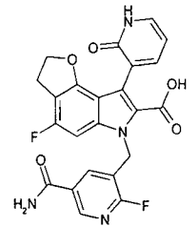
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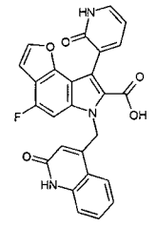
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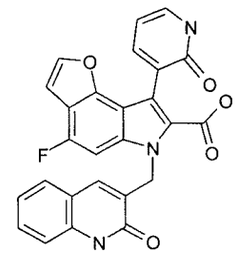
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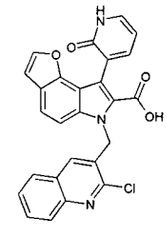
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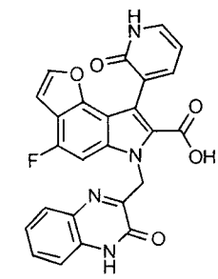
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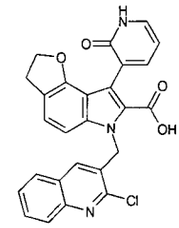
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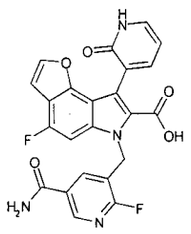
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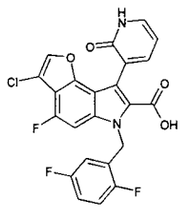
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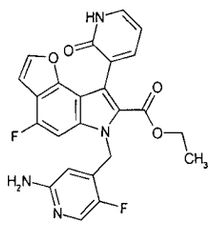
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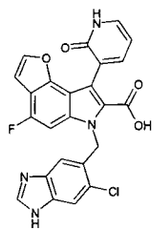
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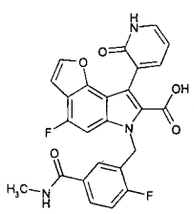
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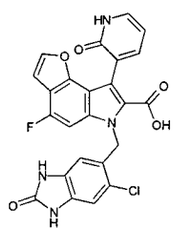
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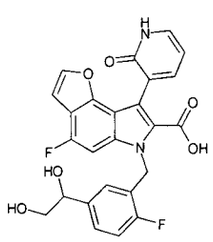
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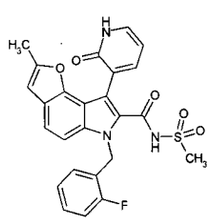
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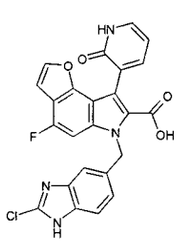
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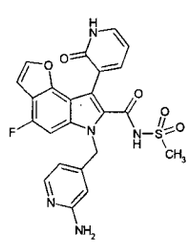
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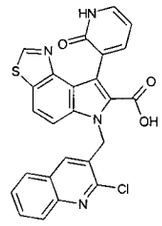
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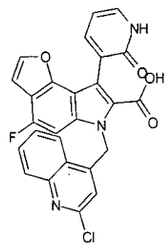
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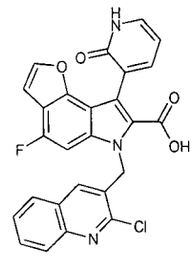
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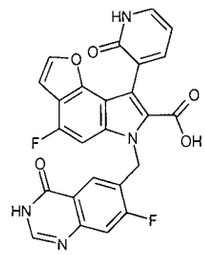
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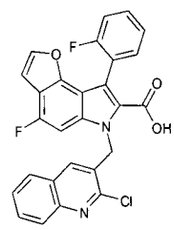
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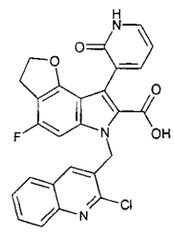
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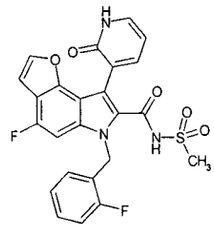
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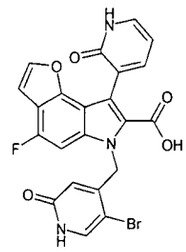
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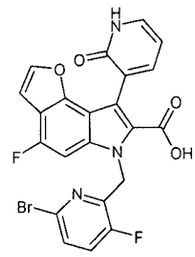
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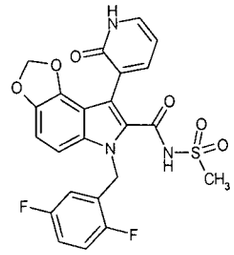
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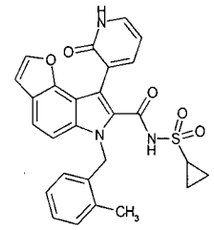
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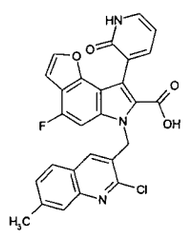
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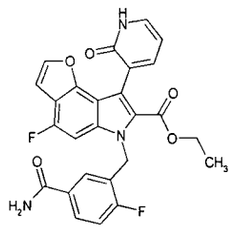
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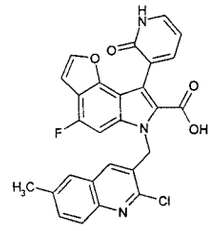
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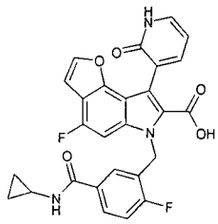
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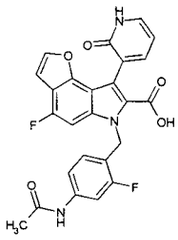
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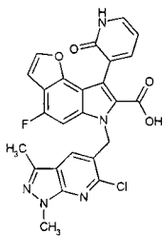


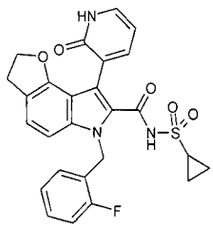
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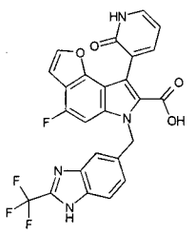


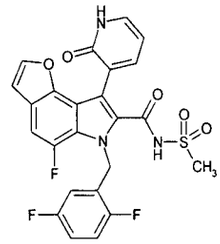
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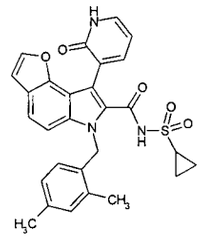
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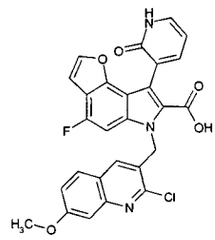
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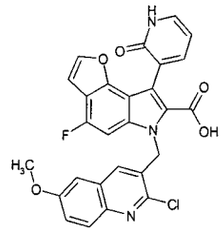
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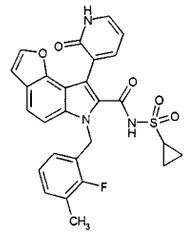
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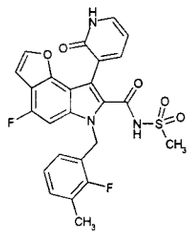
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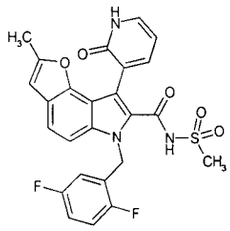
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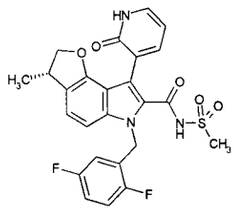
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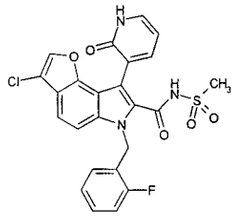
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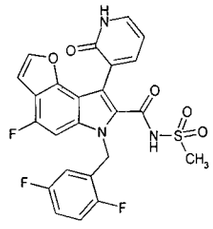
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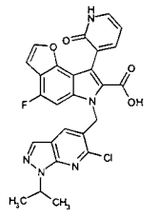
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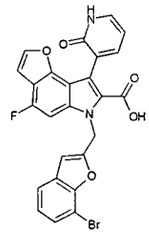
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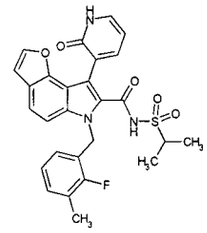
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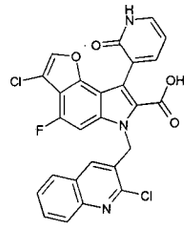
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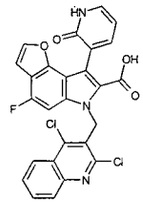
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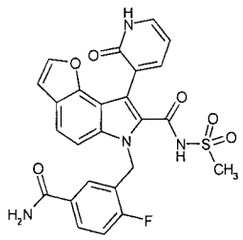


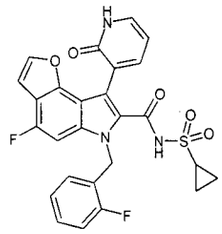
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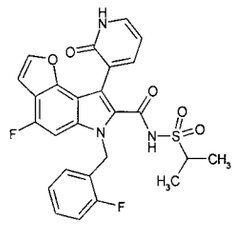


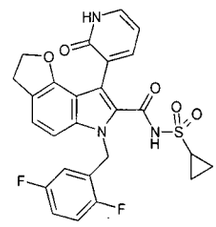
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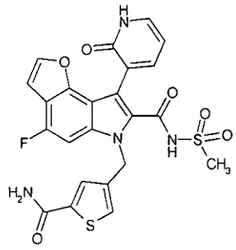


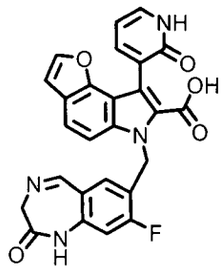
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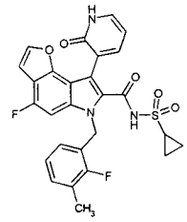
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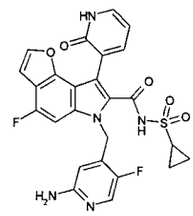
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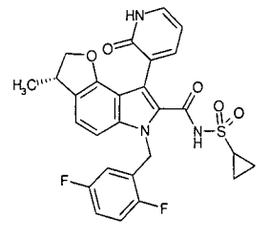
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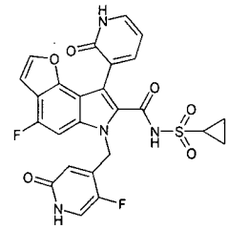
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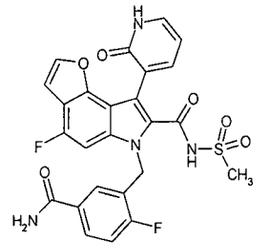
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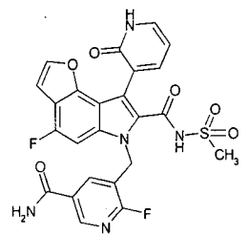
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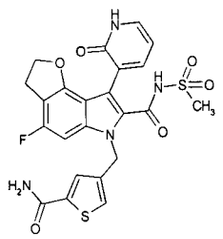
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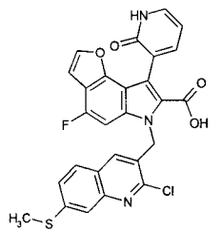
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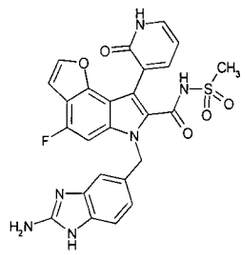
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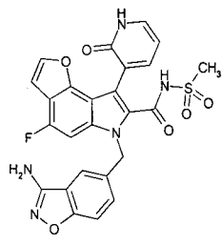
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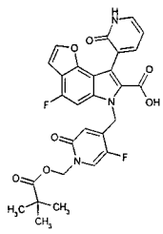
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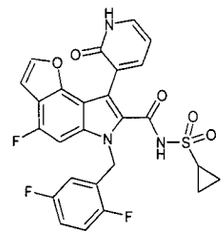
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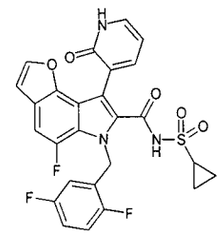
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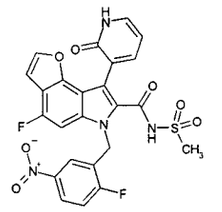
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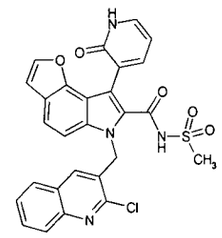
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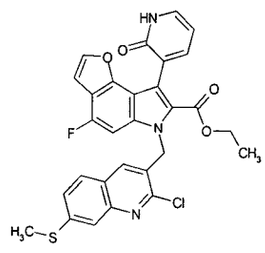
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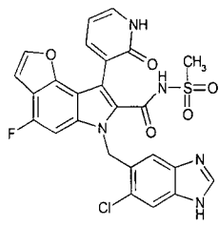
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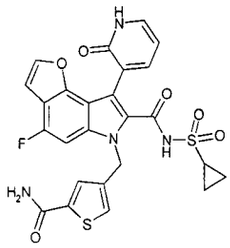
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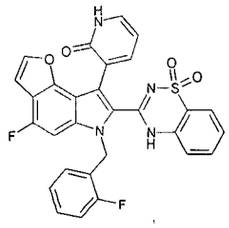
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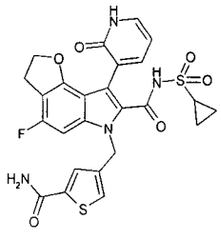
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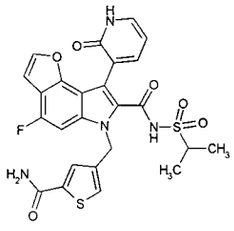
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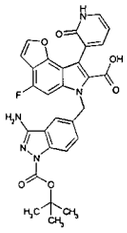
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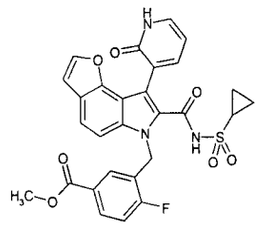
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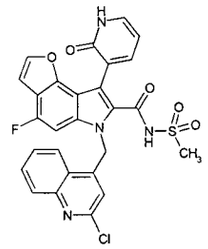
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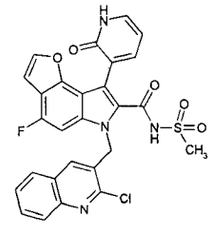
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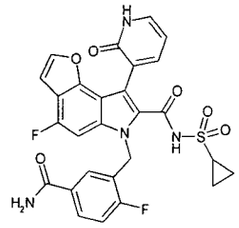
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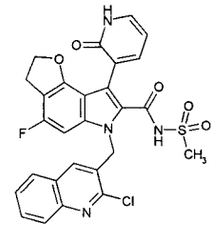
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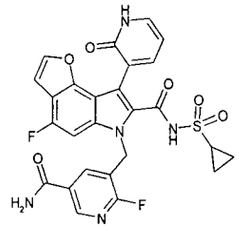
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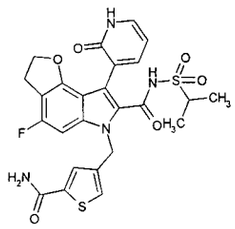
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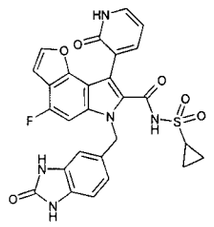
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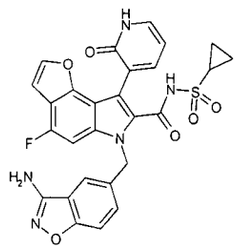
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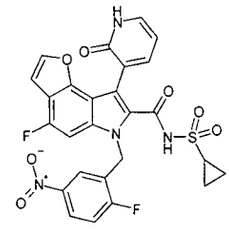
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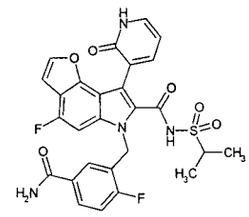
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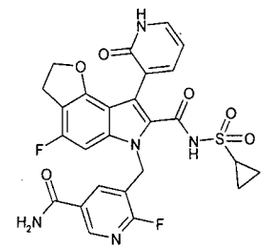
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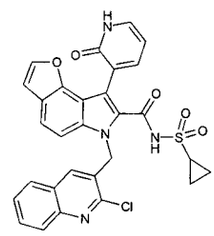
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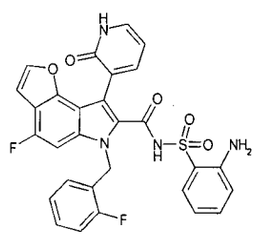
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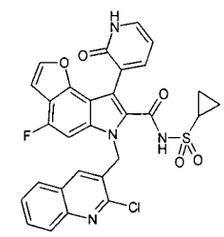
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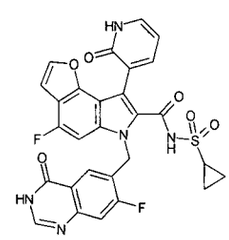
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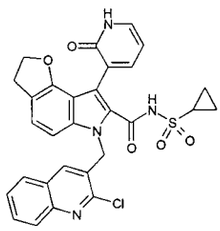
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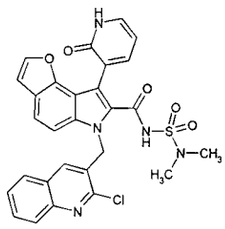
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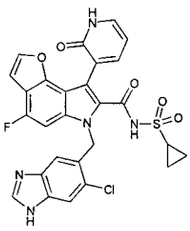
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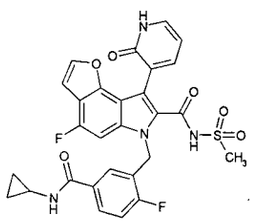
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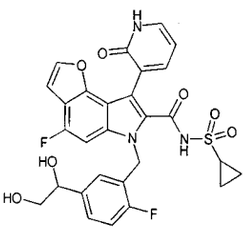
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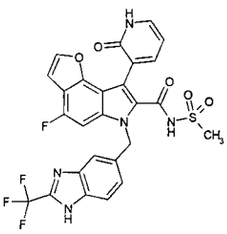
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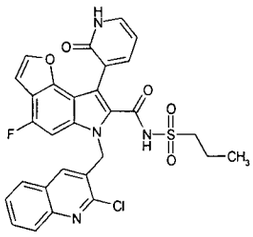
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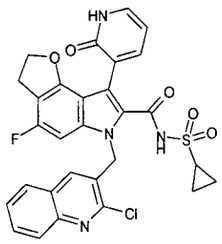
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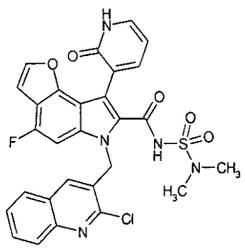
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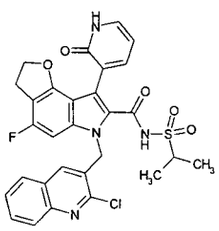
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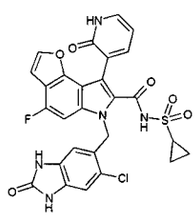
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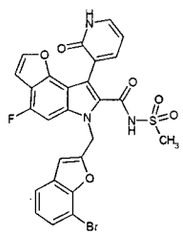
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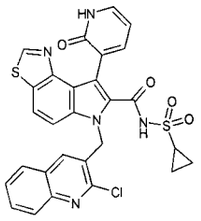


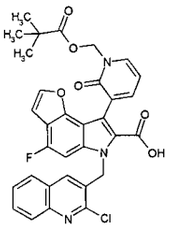
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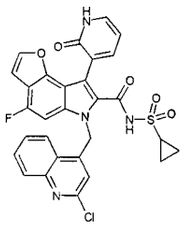


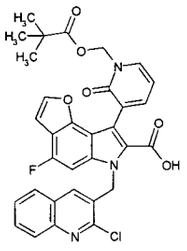
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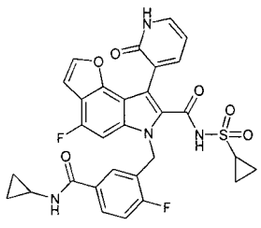


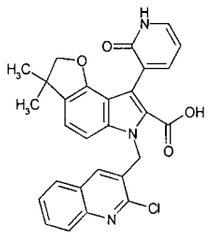
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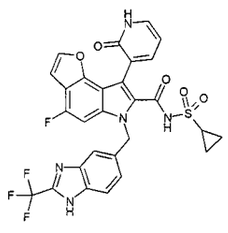
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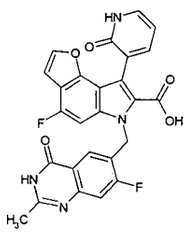
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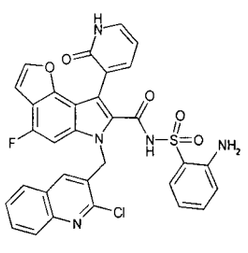
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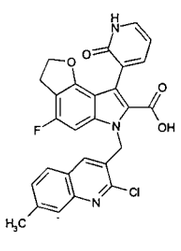
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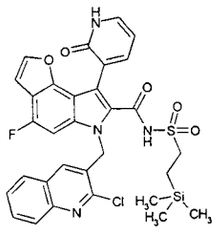
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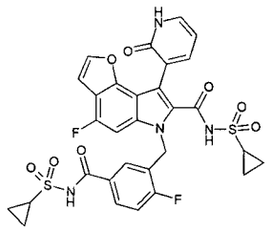
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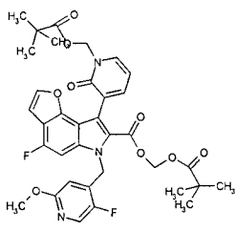
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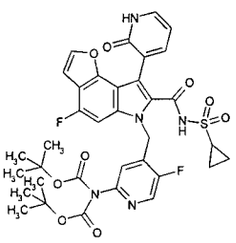
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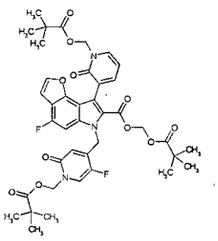
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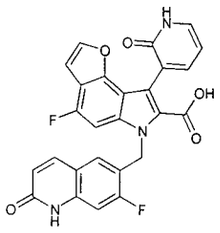
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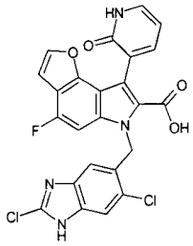
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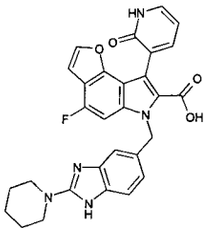
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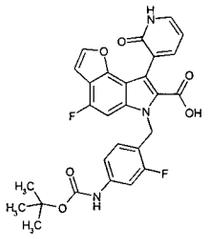
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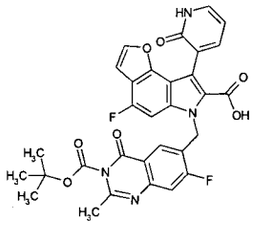
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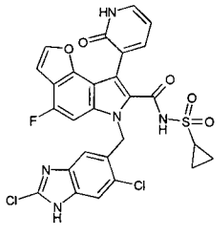
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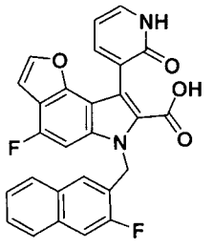
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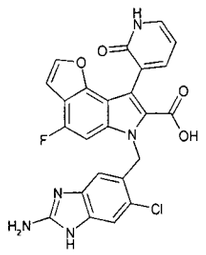
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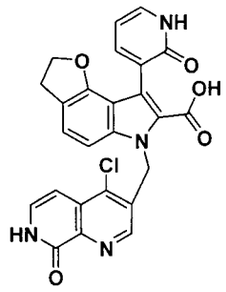
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o una sal, solvato, éster o profármaco aceptable para uso farmacéutico de los mismos.

53. Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 1 o una sal o solvato del mismo aceptable para uso farmacéutico y por lo menos un vehículo aceptable para uso farmacéutico.

54. Una composición farmacéutica que comprende por lo menos un compuesto de la reivindicación 52 o una sal o solvato del mismo aceptable para uso farmacéutico y por lo menos un vehículo aceptable para uso farmacéutico.

55. La composición farmacéutica de la reivindicación 53, que además comprende por lo menos un agente antiviral adicional, donde el agente adicional no es un compuesto de la reivindicación 1.

56. La composición de la reivindicación 55, donde el agente antiviral adicional se selecciona de: un inhibidor de polimerasa de VHC; un interferón; un inhibidor de la replicación del ARN; un agente antisentido; una vacuna terapéutica; un inhibidor de proteasas; una terapia de anticuerpo (monoclonal o policlonal); y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

57. La composición de la reivindicación 55, donde el agente antiviral adicional es un agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

58. La composición de la reivindicación 55, donde el(los) agente(s) antiviral(es) adicional(es) es(son) interferón.

59. La composición de la reivindicación 58, donde el interferón es interferón alfa-2a, interferón alfa-2b, interferón alfacon-1 o un interferón pegilado.

60. La composición de la reivindicación 55, donde el agente antiviral adicional es un inhibidor de proteasas.

61. La composición de la reivindicación 60, donde el inhibidor de proteasas es un inhibidor de la proteasa de VHC o un inhibidor de la serina proteasa NS-3.

62. La composición de la reivindicación 55, donde el agente antiviral adicional es un inhibidor de la polimerasa de VHC.

63. Un método para tratar una infección viral en un paciente, el método que comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de la reivindicación 1 o una sal o solvato del mismo aceptable para uso farmacéutico.

64. Un método para tratar una infección viral en un paciente, el método que comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de la reivindicación 52 o una sal o solvato del mismo aceptable para uso farmacéutico.

65. El método de la reivindicación 63, que además comprende administrar al paciente por lo menos un agente antiviral adicional, donde el agente adicional no es un compuesto de la reivindicación 1, y donde las cantidades administradas son en conjunto efectivas para tratar una infección viral.

66. El método de la reivindicación 64, que además comprende administrar al paciente por lo menos un agente antiviral adicional, donde el agente adicional no es un compuesto de la reivindicación 1, y donde las cantidades administradas son en conjunto efectivas para tratar una infección viral.

67. El método de la reivindicación 65, donde el agente antiviral adicional se selecciona de: un inhibidor de polimerasa de VHC; un interferón; un inhibidor de la replicación del ARN; un agente antisentido; una vacuna terapéutica; un inhibidor

de proteasas; una terapia de anticuerpo (monoclonal o policlonal); y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

68. El método de la reivindicación 67, donde el agente antiviral adicional es un agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

69. El método de la reivindicación 67, donde el(los) agente(s) antiviral(es) adicional(es) es(son) interferón.

70. El método de la reivindicación 69, donde el interferón es interferón alfa-2a, interferón alfa-2b, interferón alfacon-1 o un interferón pegilado.

71. El método de la reivindicación 67, donde el agente(s) antiviral(es) adicional(es) es(son) un inhibidor(es) de proteasas.

72. El método de la reivindicación 71, donde el inhibidor de proteasas es un inhibidor de la proteasa del VHC o un inhibidor de la serina proteasa NS-3.

73. El método de la reivindicación 67, donde el agente antiviral adicional es un inhibidor de la polimerasa de VHC.

74. El método de la reivindicación 66, donde el agente antiviral adicional se selecciona de: un inhibidor de polimerasa de VHC; un interferón; un inhibidor de la replicación del ARN; un agente antisentido; una vacuna terapéutica; un inhibidor de proteasas; una terapia de anticuerpo (monoclonal o policlonal); y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

75. El método de la reivindicación 74, donde el agente antiviral adicional es un agente útil para tratar un trastorno relacionado con la polimerasa dependiente de ARN.

76. El método de la reivindicación 74, donde el(los) agente(s) antiviral(es) adicional(es) es(son) un interferón.

77. El método de la reivindicación 76, donde el interferón es interferón alfa-2a, interferón alfa-2b, interferón alfacon-1 o un interferón pegilado.

78. El método de la reivindicación 74, donde el agente antiviral adicional es un inhibidor de proteasas.

79. El método de la reivindicación 77, donde el inhibidor de proteasas es un inhibidor de la proteasa del VHC o inhibidor de la serina proteasa NS-3.

80. El método de la reivindicación 74, donde el agente antiviral adicional es un inhibidor de la polimerasa de VHC.

81. El método de la reivindicación 63, donde la infección viral es la infección por VHC.

82. El método de la reivindicación 64, donde la infección viral es la infección por VHC.

RESUMEN

La presente invención se refiere a derivados indólicos con anillo unido en las posiciones 4,5, a composiciones que comprenden por lo menos un derivado indólico con anillo unido en las posiciones 4,5 y a métodos de uso de los derivados indólicos con anillo unido en las posiciones 4,5 para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/025754

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/60 C07D401/06 C07D401/14 C07D403/06 C07D471/04
C07D491/04 A61K31/407 A61P31/12 C07D401/04 C07D487/04
C07D495/04 C07D513/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/068412 A (UNIV LONDON PHARMACY [GB]; SEARCEY MARK [GB]; PATTERSON LAURENCE HYLTO) 6 September 2002 (2002-09-06) example 3, intermediate 3.7; claims	1-3,5, 11,22
A	WO 2004/035571 A (RIGEL PHARMACEUTICALS INC [US]; SINGH RAJINDER [US]; DARWISH IHAB S [U) 29 April 2004 (2004-04-29) claims	1-82
A	WO 2006/020082 A (SQUIBB BRISTOL MYERS CO [US]; HUDYMA THOMAS W [US]; ZHENG XIAOFAN [US]) 23 February 2006 (2006-02-23) claims	1-82

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
2 May 2008	13/05/2008

Name and mailing address of the ISA/	Authorized officer
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	Schuemacher, Anne

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/025754

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/106328 A (GEMIN X BIOTECHNOLOGIES INC [CA]; ATTARDO GIORGIO [CA]; DAIRI KENZA [C) 9 December 2004 (2004-12-09) claims	1-82
X	RAWAL, VIRESH H. ET AL: "Photocyclization of pyrrole analogs of stilbene: an expedient approach to antitumor agent CC-1065" JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS , (22), 1526-7 CODEN: JCCCAT; ISSN: 0022-4936, 1984, XP009097820 compounds 9,10	1-3,5, 11,22

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/025754

Box No. 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. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 63-82 are directed to a method 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 No. 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 allsearchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers 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 and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/025754

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02068412 A	06-09-2002	AT 378328 T	15-11-2007
		JP 2004529887 T	30-09-2004
		US 2004157873 A1	12-08-2004
WO 2004035571 A	29-04-2004	AU 2003287160 A1	04-05-2004
		CA 2501547 A1	29-04-2004
		EP 1554271 A1	20-07-2005
		JP 2006505571 T	16-02-2006
		US 2005215614 A1	29-09-2005
WO 2006020082 A	23-02-2006	AU 2005274959 A1	23-02-2006
		CA 2576421 A1	23-02-2006
		EP 1776368 A1	25-04-2007
		JP 2008509218 T	27-03-2008
		KR 20070049635 A	11-05-2007
		US 2006046983 A1	02-03-2006
		US 2006166964 A1	27-07-2006
WO 2004106328 A	09-12-2004	AU 2004242928 A1	09-12-2004
		BR PI0410870 A	04-07-2006
		CA 2527583 A1	09-12-2004
		CN 1832939 A	13-09-2006
		EP 1644363 A1	12-04-2006
		JP 2007502845 T	15-02-2007
		KR 20060036054 A	27-04-2006
		MX PA05012799 A	22-02-2006

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-063496- -00000-0000

Fecha: 2009-06-18 16:42:47 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 658

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCIÓN [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que 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 [ ]

_____
Firma Responsable

Fecha_____

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING - CORPORATION

REFERENCIA	Radicación No.	9 63496
	Solicitud internacional	PCT/US2007/025754
	Fecha inicio fase nacional	22/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	9259

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se 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 14 AGO. 2009
adpa11

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING - CORPORATION

REFERENCIA	Radicación No.	9 63496
	Solicitud internacional	PCT/US2007/025754
	Fecha inicio fase nacional	22/07/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	9269

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 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 14 AGO. 2009
adpa11