Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 10-354185

54. **TÍTULO** Derivados Indolicos 2,3 sustituidos y Metodos de uso de los Mismos

51. **CLASIFICACIÓN INTERNACIONAL** C07D 209/42

71. **SOLICITANTE** Schering corporation

DOMICILIO

74. **APODERADO** Carlos R Olarte

22. **BOGOTÁ, D.C.,**

(FORMA P-10)

OLARTERAISBECK

OLARTE RAISBECK MOURE &

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-035485- -00000-0000
Fecha: 2010-03-25 17:21:38 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 804

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000024**

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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Cual _____
Número 79.782.747 Btá
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
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(5) **PCT (86)**

Solicitud Internacional No. PCT/US2008/010130 Fecha Agosto 27, 2008

Publicación Internacional No. WO 2009/032116 Fecha Marzo 12, 2009

(6) **Título (54)** **DERIVADOS INDÓLICOS 2,3 SUSTITUIDOS Y MÉTODOS DE USO DE LOS MISMOS**

Clasificación Internacional (51) C07D 209/42, C07D 401/04, C07D 401/14 A61K 31/404, A61P 31/12

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Agosto 29, 2007	60/968,745

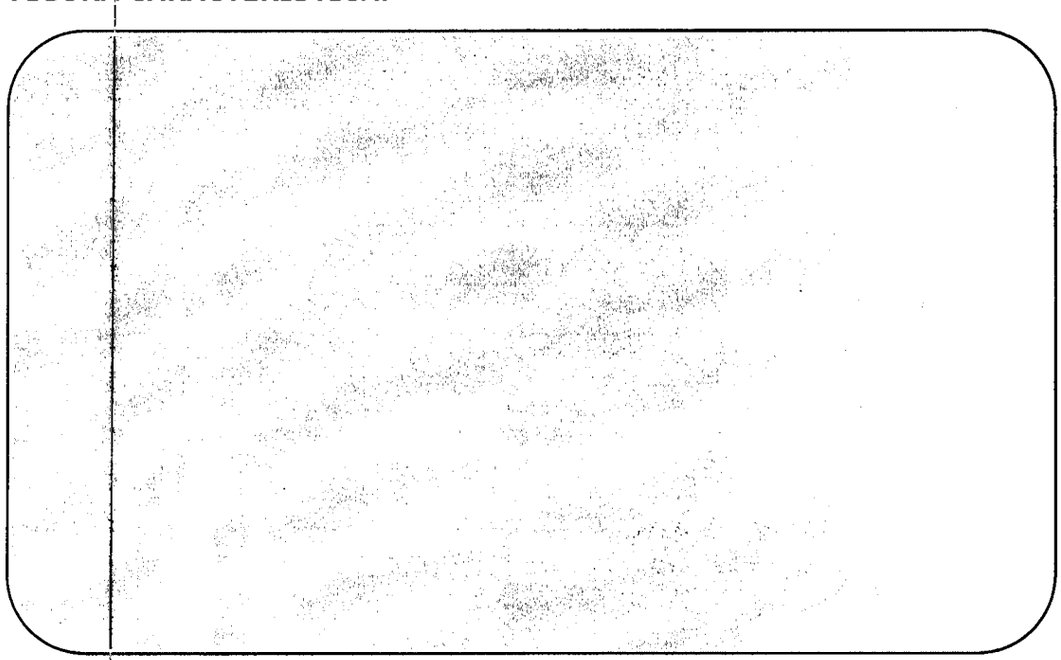
(9) **Comprobante de pago No.** 10- **Fecha** Marzo de 2010

(10) **ANEXOS**

2

- [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 Exp. Nº 07-132.393.
- [ ] 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.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 23,447
FECHA : MARZO 25 DE 2010

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No. 10-035485- -00000-0000
Fecha: 2010-03-25 17:21:38 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 804

***** 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	325578492	25/03/2010	3,794,000.00

***** 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	554,000.00
			TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO 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

8

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

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

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10

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

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

OLARTE RAISBECK & FRIERI, LTDA.
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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):

NOTARY 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
12 March 2009 (12.03.2009)

PCT

(10) International Publication Number
WO 2009/032116 A1

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C07D 209/42 (2006.01) *A61K 31/404* (2006.01)
C07D 401/04 (2006.01) *A61P 31/12* (2006.01)
C07D 401/14 (2006.01)

(21) International Application Number:
PCT/US2008/010130

(22) International Filing Date: 27 August 2008 (27.08.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/968,745 29 August 2007 (29.08.2007) US

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

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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: 2, 3-SUBSTITUTED INDOLE DERIVATIVES FOR TREATING VIRAL INFECTIONS

(57) Abstract: The present invention relates to 2,3-Substituted Indole Derivatives, compositions comprising at least one 2,3-Substituted Indole Derivative, and methods of using the 2,3-Substituted Indole Derivatives for treating or preventing a viral infection or a virus-related disorder in a patient.

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B

2,3-SUBSTITUTED INDOLE DERIVATIVES FOR TREATING VIRAL INFECTIONS

FIELD OF THE INVENTION

The present invention relates to 2,3-Substituted Indole Derivatives, compositions comprising at least one 2,3-Substituted Indole Derivative, and methods of using the 2,3-Substituted 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.

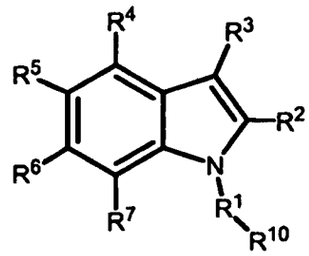
The development of small-molecule inhibitors directed against specific viral targets has become a major focus of anti-HCV research. The determination of crystal structures for NS3 protease, NS3 RNA helicase, and NS5B polymerase has provided important structural insights that should assist in the rational 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 compounds of formula (I):

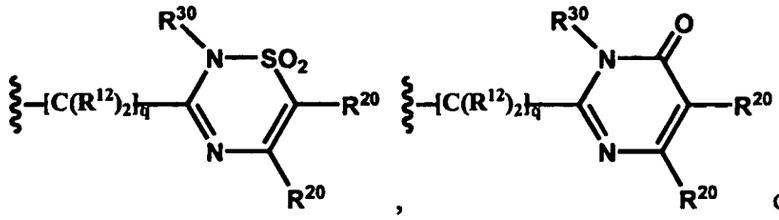


(I)

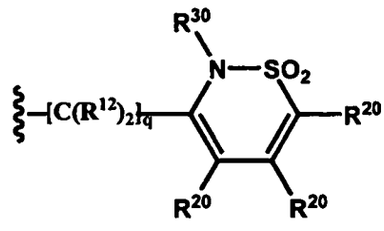
and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein:

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≡C-$[C(R^{12})_2]_q$-, or -$[C(R^{12})_2]_q$-SO_2-$[C(R^{12})_2]_q$-;

R^2 is -$[C(R^{12})_2]_q$-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)$_2$,

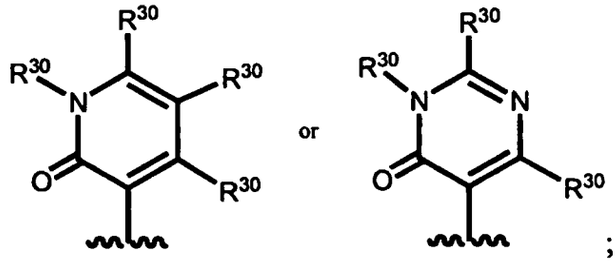


or



;

R^3 is:



;

R^4, R^5, 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, -$[C(R^{12})_2]_q$-O-alkyl, -$[C(R^{12})_2]_q$-N(alkyl)$_2$, -$[C(R^{12})_2]_q$-aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, haloalkyl or hydroxyalkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally and independently 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 and independently 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 and independently 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)NH-alkyl, -$C(O)N(alkyl)_2$, -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 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 -$SO_2N(R^9)C(O)N(R^9)_2$;

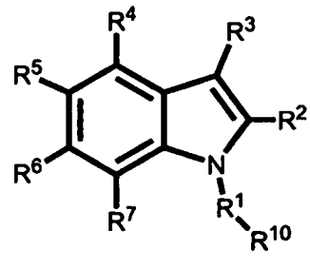
each occurrence of R^{30} is independently H, alkyl, alkenyl, alkynyl, aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, -$[C(R^{12})_2]_q$-haloalkyl, -$[C(R^{12})_2]_q$-hydroxyalkyl, 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.

In another aspect, the present invention provides compounds of formula (II):



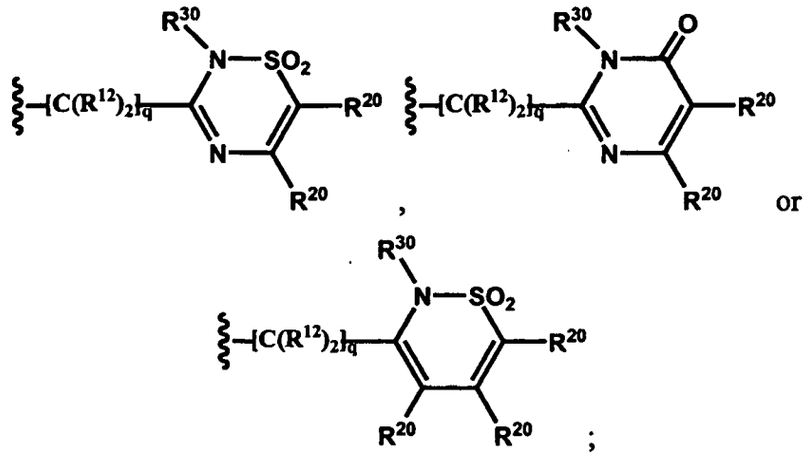
(II)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof,

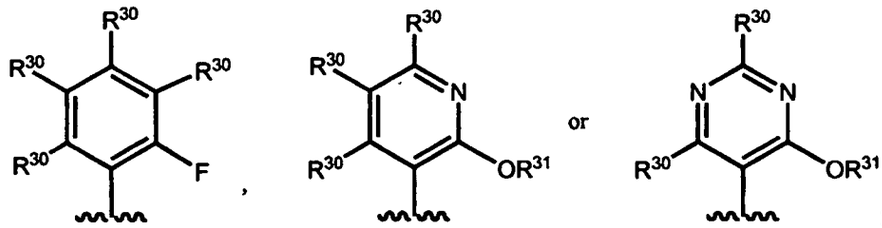
wherein:

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≡C-$[C(R^{12})_2]_q$-, or -$[C(R^{12})_2]_q$-SO_2-$[C(R^{12})_2]_q$-;

R^2 is -$[C(R^{12})_2]_q$-$C(O)N(R^9)SOR^{11}$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)SO_2R^{11}$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)SO_2N(R^9)_2$,



R^3 is



R^4, R^5, 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, -$[C(R^{12})_2]_q$-O-alkyl, -$[C(R^{12})_2]_q$-N(alkyl)$_2$, -$[C(R^{12})_2]_q$-aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, haloalkyl or hydroxyalkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally and independently 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)$_p$$R^{11}$, -[C($R^{12}$)$_2$]$_q$-S$O_2$N($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 and independently 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_2alkyl, -[C(R^{12})$_2$]$_q$-NHSO_2cycloalkyl, -[C(R^{12})$_2$]$_q$-NHSO_2aryl, -[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 and independently 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)NH-alkyl, -C(O)N(alkyl)$_2$, -O-alkyl, -NH_2, -NH(alkyl), -N(alkyl)$_2$, -NHC(O)alkyl, -NHSO_2alkyl, -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 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 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$(R^9)_2$, 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;

R^{31} is 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 or -$[C(R^{12})_2]_q$-hydroxyalkyl;

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 formulas (I) and (II) (herein referred to collectively as the "2,3-Substituted Indole Derivatives") and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof can be useful for treating or preventing a viral infection or 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 2,3-Substituted Indole Derivative.

The present invention further provides pharmaceutical compositions comprising an effective amount of at least one 2,3-Substituted Indole Derivative 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

In an embodiment, the present invention provides 2,3-Substituted Indole Derivatives, pharmaceutical compositions comprising at least one 2,3-Substituted Indole Derivative, and methods of using the 2,3-Substituted Indole Derivatives for treating or preventing a viral infection 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 alkenyl 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 "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 haloalkyl 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.

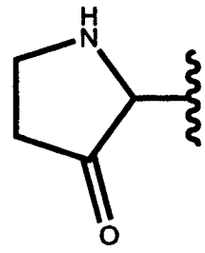
Unless otherwise indicated, the group:



represents a 6-membered heteroaryl group containing 1 or 2 ring nitrogen atoms and no other ring heteroatoms. Examples of such a group include, but are not limited to pyridyl, pyrimidinyl, pyridazinyl and pyrazinyl. In one embodiment, this group has 1 ring nitrogen atom. In another embodiment, this group has 2 ring nitrogen atoms. This group may be optionally and

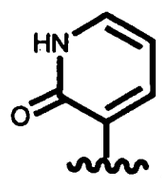
The term "heterocycloalkyl" as used herein, refers to a non-aromatic saturated monocyclic or multicyclic ring system comprising 3 to about 10 ring atoms, wherein from 1 to 4 of the ring atoms are independently O, S or N and the remainder of the ring atoms are carbon atoms. In one embodiment, a heterocycloalkyl 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:



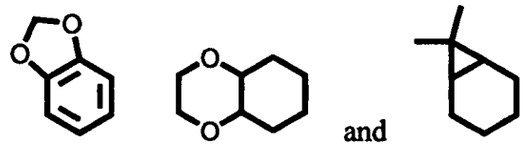
In one embodiment, a heterocycloalkyl group is a 6-membered heterocycloalkyl group. In another embodiment, a heterocycloalkyl group is a 5-membered heterocycloalkyl group.

The term "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, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, 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 "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:


and

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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivatives are contemplated in the present invention.

The 2,3-Substituted Indole Derivatives may form salts, and all such salts are contemplated within the scope of this invention. Reference to a 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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, choline, 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.

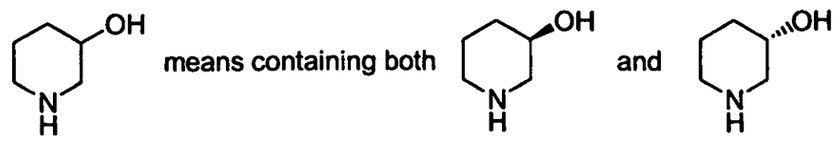
Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (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 2,3-Substituted Indole Derivatives may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative 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.

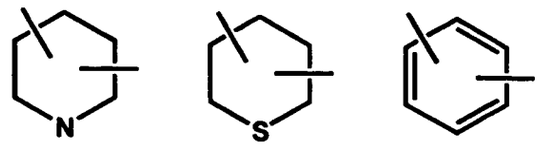
Diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as, for example, by chromatography and/or fractional crystallization. Enantiomers can be separated by converting the 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative 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.

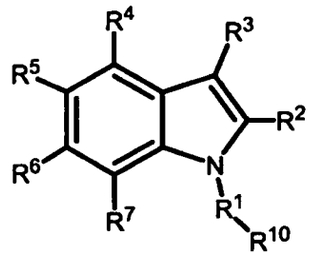
Certain isotopically-labelled 2,3-Substituted Indole Derivatives (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives, and of the salts, solvates, hydrates, esters and prodrugs of the 2,3-Substituted Indole Derivatives, are intended to be included in the present invention.

The following abbreviations are used below and have the following meanings: Bn is benzyl; Bu is butyl; CDI is N,N'-carbonyldiimidazole; DABCO is 1,4-Diazabicyclo[2.2.2]octane; dba is dibenzylideneacetone; DBU is 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM is dichloromethane; DIEA is diethylamine; DIPEA is diisopropylethylamine; DME is dimethoxyethane; DMF is dimethylformamide; DMSO is dimethylsulfoxide; dppf is 1,1'-bis(diphenylphosphino)ferrocene; EDCI is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide; Et is ethyl; Et_3N is triethylamine; EtOAc is ethyl acetate; HATU is N-(diethylamino)-1H-1,2,3-triazolo[4,5-b]pyridine-1-yl-methylene]-N-methylmethanaminium hexafluorophosphate N-oxide; HPLC is high performance liquid chromatography; Me is methyl; MeOH is methanol; MS is mass spectrometry; NBS is N-bromosuccinimide; NIS is N-iodosuccinimide; PPA is polyphosphoric acid; TBAF is tetra-n-butylammonium fluoride; THF is tetrahydrofuran; TLC is thin layer chromatography and TMS is trimethylsilyl.

The 2,3-Substituted Indole Derivatives of Formula (I)

The present invention provides 2,3-Substituted Indole Derivatives having the formula:



(I)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 and R^{10} are defined above for the compounds of formula (I).

In one embodiment, R^1 is bond.

In 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 $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$.

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

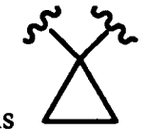
In another embodiment, R^1 is $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$.

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

In one embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or



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

In another embodiment, R^1 is  .

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

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

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

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

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

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

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

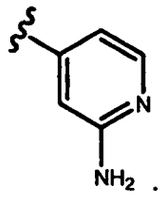
In another embodiment, R^{10} is heterocycloalkyl.

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

In another embodiment, R^{10} is phenyl, which is substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$.

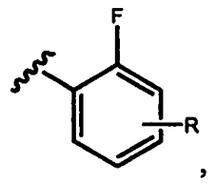
In yet another embodiment, R^{10} is pyridyl.

In a further embodiment, R^{10} is



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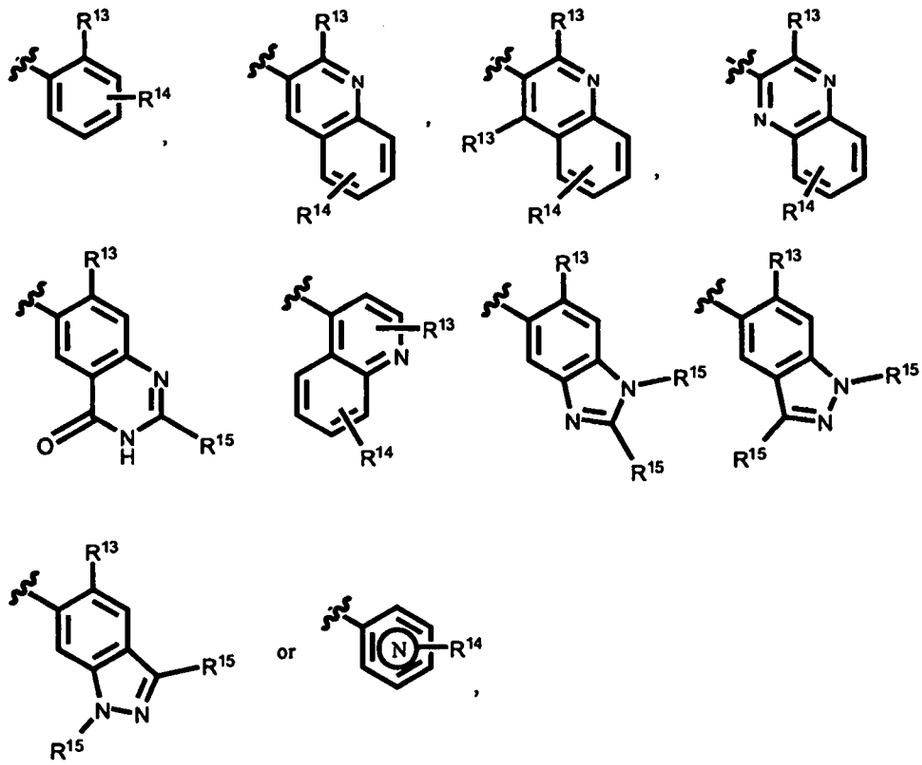
In another embodiment, $-R^{10}$ is:

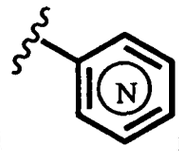


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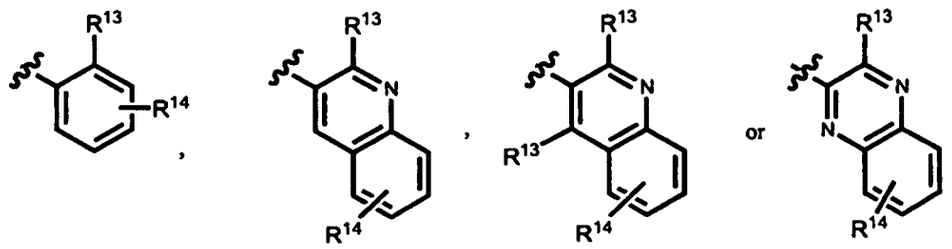
wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, $-NH_2$, $-SO_2$-alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In one embodiment, R^{10} is:



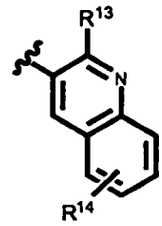
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

In another embodiment, R^{10} is



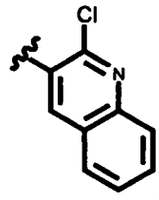
wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

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

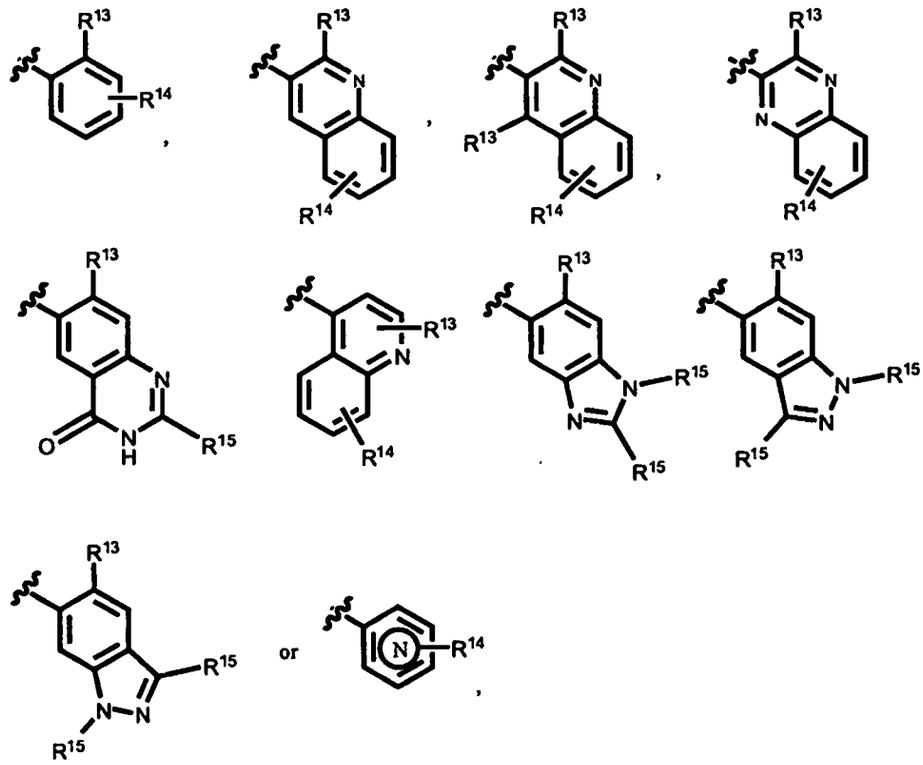


wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

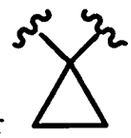
In a further embodiment, R^{10} is :

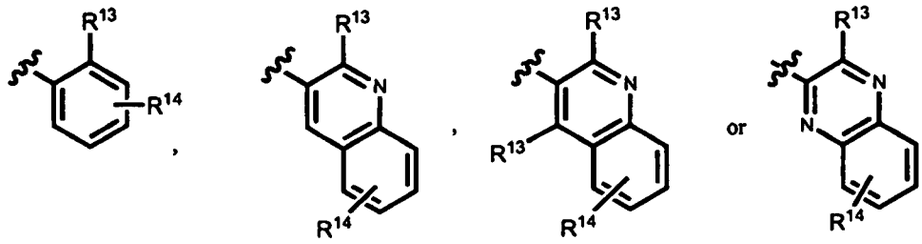


In another embodiment, R^1 is –CH_2- or  and R^{10} is



wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

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



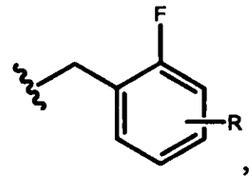
wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2,

$-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2$NH-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

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

In another embodiment, $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$.

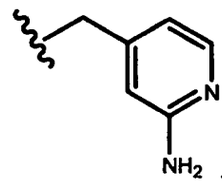
In still another embodiment, $-R^1-R^{10}$ is



,

wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, $-NH_2$, $-SO_2$-alkyl, $-SO_2$NH-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

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



.

In still another embodiment, $-R^1-R^{10}$ is alkyl.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with 1 or 2 fluorine atoms.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with 1 or 2 methyl groups.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with one fluorine atom and one methyl group.

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

In a further embodiment, $-R^1-R^{10}$ is $-CH_2$-cycloalkyl.

In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$.

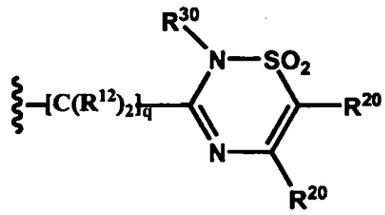
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

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

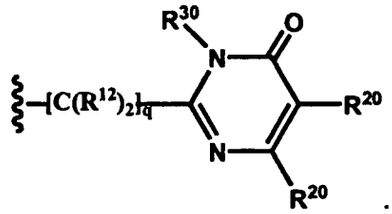
In another embodiment, R^2 is $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$.

In still another embodiment, R^2 is $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^{11})_2$.

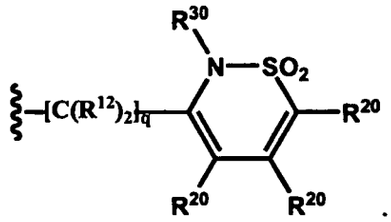
In another embodiment, R^2 is



In another embodiment, R^2 is



In yet another embodiment, R^2 is



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

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

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-alkyl.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-aryl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-cycloalkyl.

In a further embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-heterocycloalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-heteroaryl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-haloalkyl.

In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-hydroxyalkyl.

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

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

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

In a further embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is heterocycloalkyl.

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

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

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

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-phenyl.

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

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

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-NH_2$ or $-N(CH_3)_2$.

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

In another embodiment, R^2 is $-C(O)NHSO_2CH_2CH_3$.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$, and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

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

In one embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is $-[C(R^{12})_2]_q$-O-alkyl or $-[C(R^{12})_2]_q$-N(alkyl)$_2$.

In still another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is $-(CH_2)_2$-$N(CH_3)_2$ or $-(CH_2)_3$-$N(CH_3)_2$.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, alkyl or cycloalkyl.

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

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, methyl, ethyl or cyclopropyl.

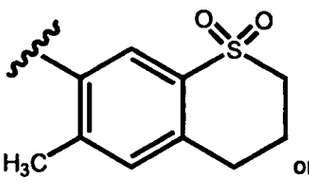
In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is cyclopropyl.

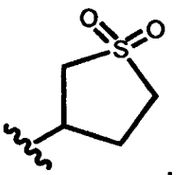
In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H or methyl.

In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q-C(O)O$-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-NHC(O)$-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q-NHSO_2$-alkyl, $-[C(R^{12})_2]$-O-alkyl,or $-[C(R^{12})_2]$-alkyl.

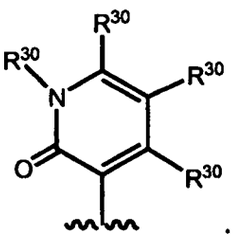
In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is imidazolyl, pyridyl, thienyl, furanyl, benzofuranyl, benzo[1,3]dioxolyl, tetrahydropyranyl,



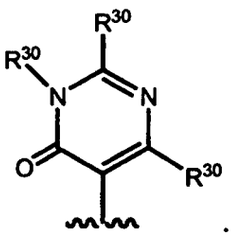
or


In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

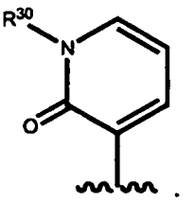
In one embodiment, R^3 is



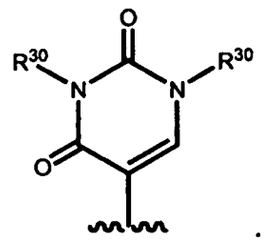
In another embodiment, R^3 is



In another embodiment, R^3 is



In another embodiment, R^3 is



In one embodiment, R^4 is H.

In another embodiment, R^4 is H or F.

In another embodiment, R^4 is F.

In another embodiment, R^5 is H.

In another embodiment, R^6 is H.

In another embodiment, R^6 is H or F.

In another embodiment, R^6 is F.

In still another embodiment, R^7 is H.

In another embodiment, R^4 and R^7 are each H.

In yet another embodiment, R^4, R^6 and R^7 are each H.

In another embodiment, R^4, R^5, R^6 and R^7 are each H.

In a further embodiment, R^4, R^6 and R^7 are each H and R^5 is other than H.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is alkyl.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is halo.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is methyl.

In a further embodiment, R^4, R^6 and R^7 are each H and R^5 is Cl.

In another embodiment, R^4 and R^7 are each H and and R^5 and R^6 are other than H.

In another embodiment, R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

In another embodiment, R^5 is other than H.

In still another embodiment, R^5 is alkyl.

In yet another embodiment, R^5 is halo.

In still another embodiment, R^5 is methyl.

In another embodiment, R^5 is ethyl.

In another embodiment, R^6 is H.

In another embodiment, R^6 is other than H.

In a further embodiment, R^6 is alkyl.

In yet another embodiment, R^6 is halo.

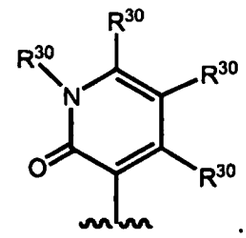
In still another embodiment, R^6 is methyl.

In another embodiment, R^6 is F.

In one embodiment, R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

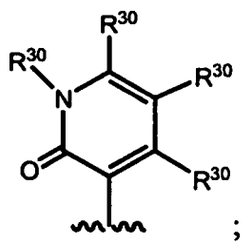
In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$,

and R^3 is :



In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

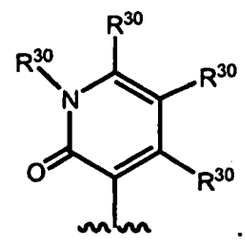
R^3 is :



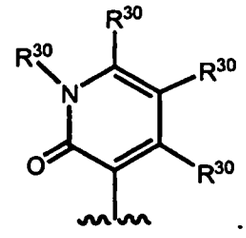
; and two adjacent R^{30} groups and the carbon atoms to which they are attached, join to form a benzene ring.

In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; and

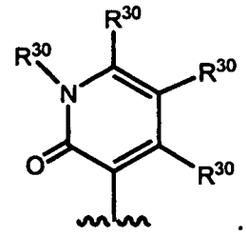
R^3 is



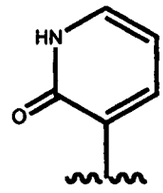
In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^3 is



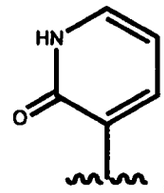
In one embodiment, R^2 is $-C(O)NHSO_2CH_3$, and R^3 is



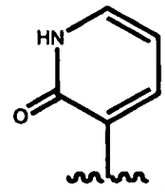
In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$; R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; and R^3 is



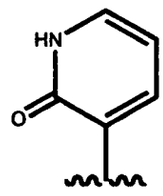
In one embodiment, R^2 is $-C(O)NHSO_2R^1$ and R^3 is



In one embodiment, R^2 is $-C(O)NHSO_2CH_3$, and R^3 is

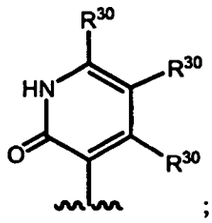


In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; and R^3 is



In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

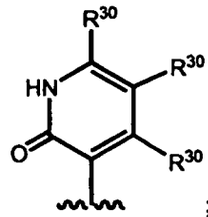
R^3 is :



; and R^4 and R^7 are each independently H, halo or hydroxy.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

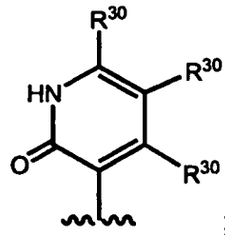
R^3 is :



; and R^5 is H, alkyl, -O-alkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

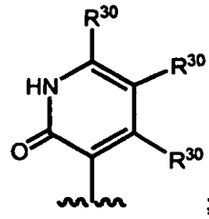
R^3 is



; and R^5 is alkyl, cycloalkyl, halo or hydroxy.

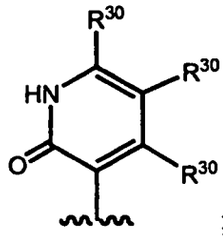
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

R^3 is :



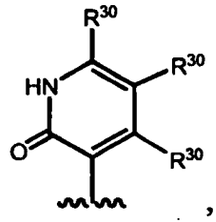
; and R^6 is H, alkyl, -O-alkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is



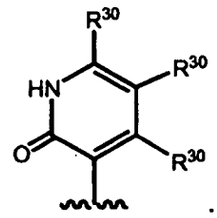
; and R^6 is alkyl, cycloalkyl, halo or hydroxy.

In still another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :

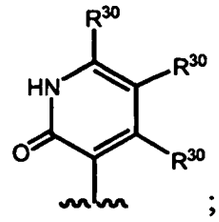


, and R^{10} is aryl or heteroaryl;

In one embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; and R^3 is :

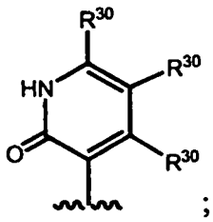


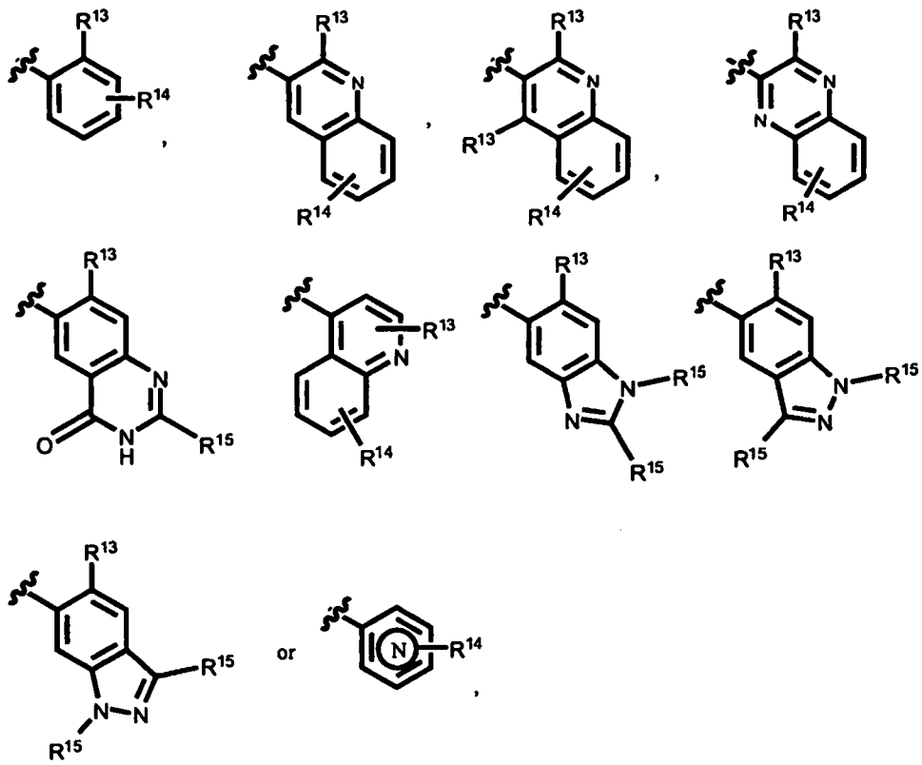
In another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :



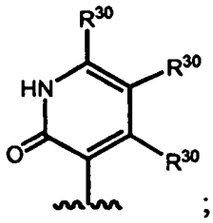
; and R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in claim 1;

In one embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :

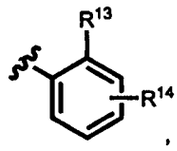
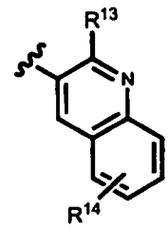
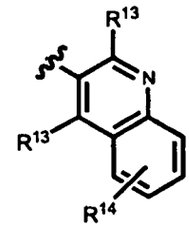
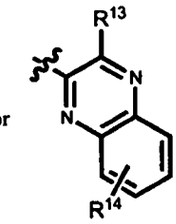

; and R^{10} is:


wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2$NH-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2$NH-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In yet another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :

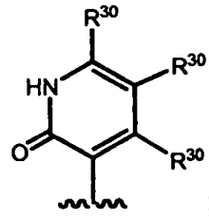


; and R^{10} is:


,

,

or

,

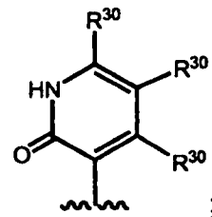
wherein R^{13} is H, F, Br or Cl, and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In another embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is :



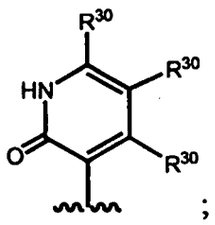
; R^5 is H, alkyl, -O-alkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in claim 1.

In a further embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is :



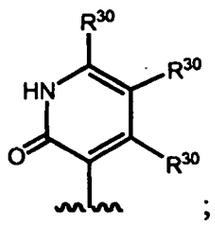
; R^5 is H, methyl, ethyl or cyclopropyl; R^6 is H, F or -OH; and R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in claim 1.

In another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :



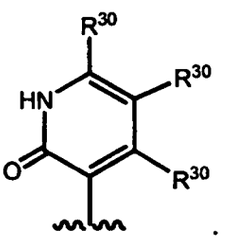
; R^9 is H, methyl or ethyl; R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in claim 1; and R^{11} is methyl, ethyl, cyclopropyl or phenyl.

In one embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :

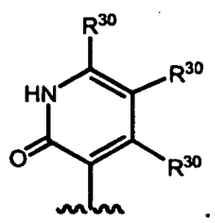


; R^9 is H, methyl or ethyl; R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in claim 1; and R^{11} is methyl, cyclopropyl or phenyl.

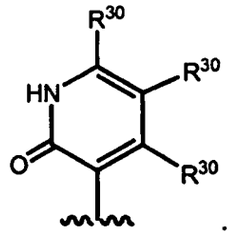
In another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; and R^3 is



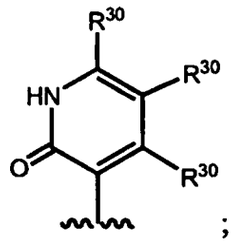
In another embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; and R^3 is :



In another embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; and R^3 is



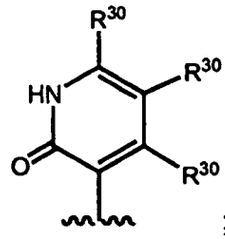
In one embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is



; and

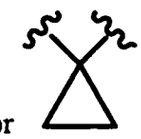
R^{10} is aryl or heteroaryl.

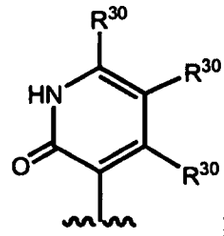
In one embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is



; and

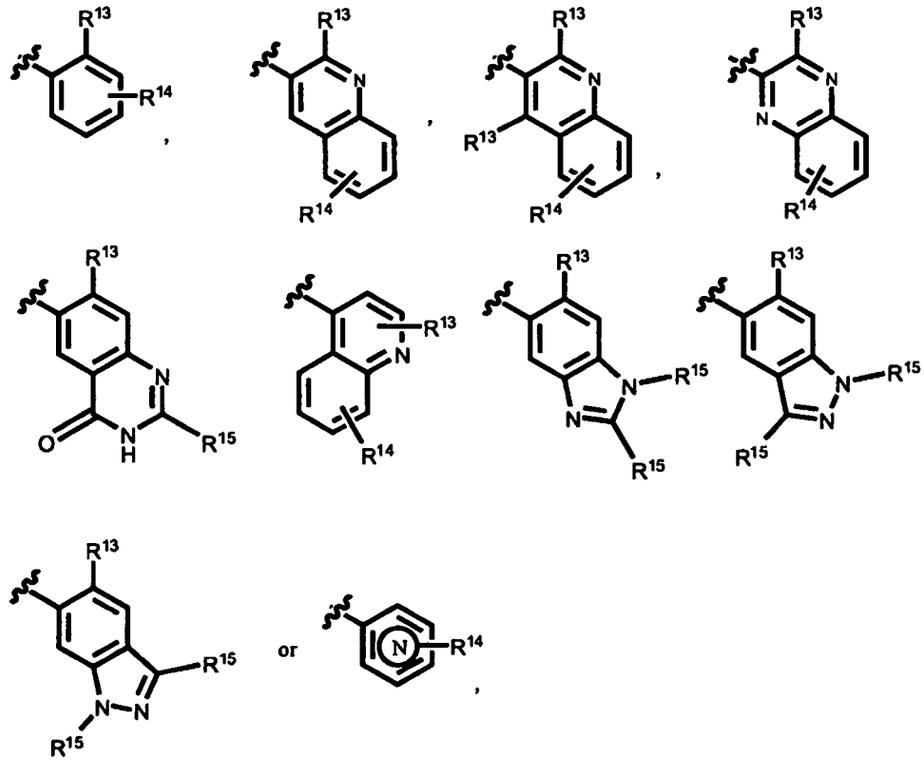
R^{10} is phenyl, naphthyl, pyridyl, quinolinyl or quinoxalinyl, each of which can be optionally substituted as set forth in formula (I).

In one embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is



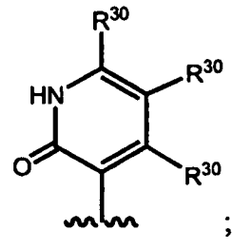
; and

R^{10} is



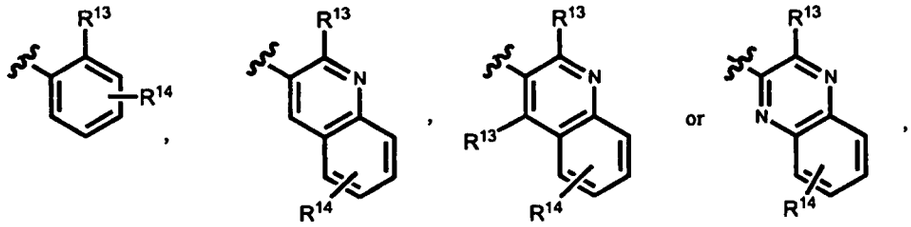
wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is

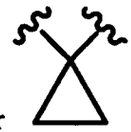


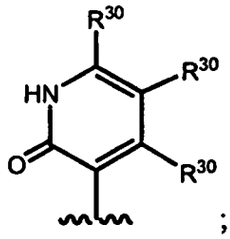
; and

R^{10} is

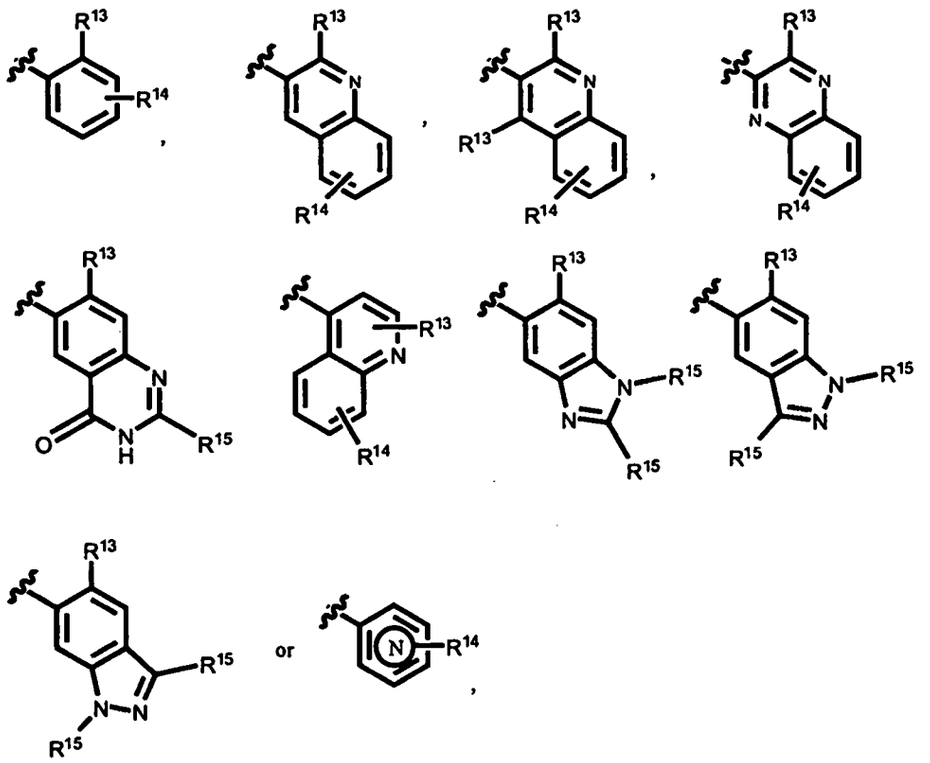


wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

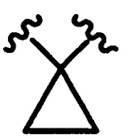
In another embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is

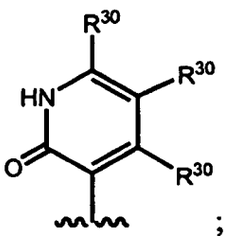


; R^5 is alkyl, cycloalkyl, halo or -OH; R^6 is alkyl, cycloalkyl, halo or -OH; and R^{10} is

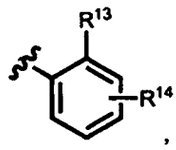
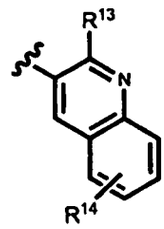
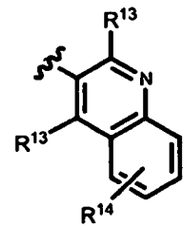
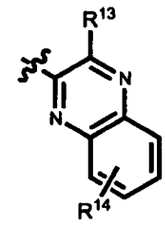


wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is $-CH_2-$ or  ; R^2 is $-C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is

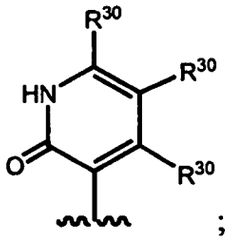


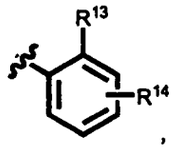
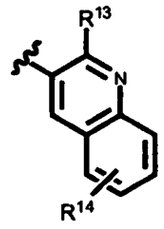
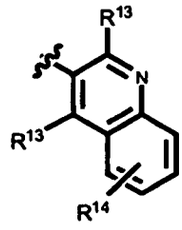
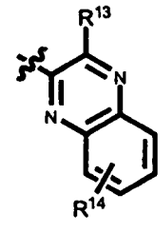
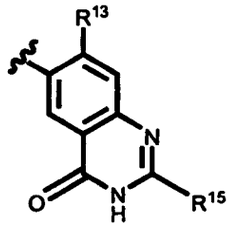
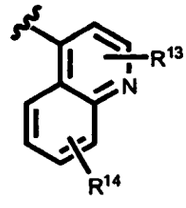
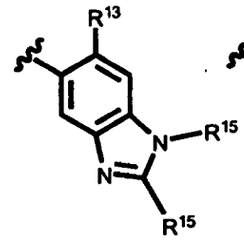
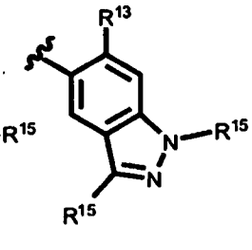
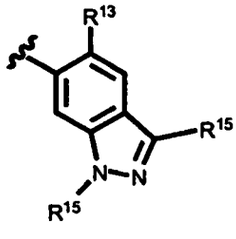
; R^5 is alkyl, cycloalkyl, halo or -OH; R^6 is alkyl, cycloalkyl, halo or -OH; and R^{10} is


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or

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wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In one embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is

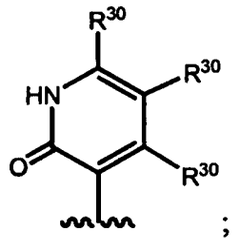

; R^5 is methyl, ethyl or cyclopropyl; R^6 is H, F or -OH; and R^{10} is


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or

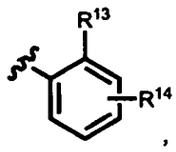
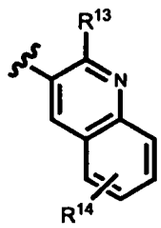
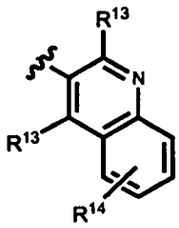
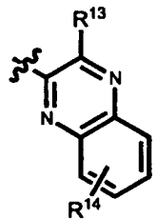
,

wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is

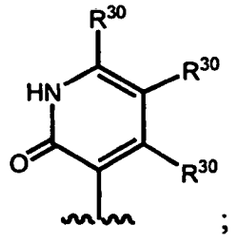


; R^5 is methyl, ethyl or cyclopropyl; R^6 is H, F or -OH; and R^{10} is


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or

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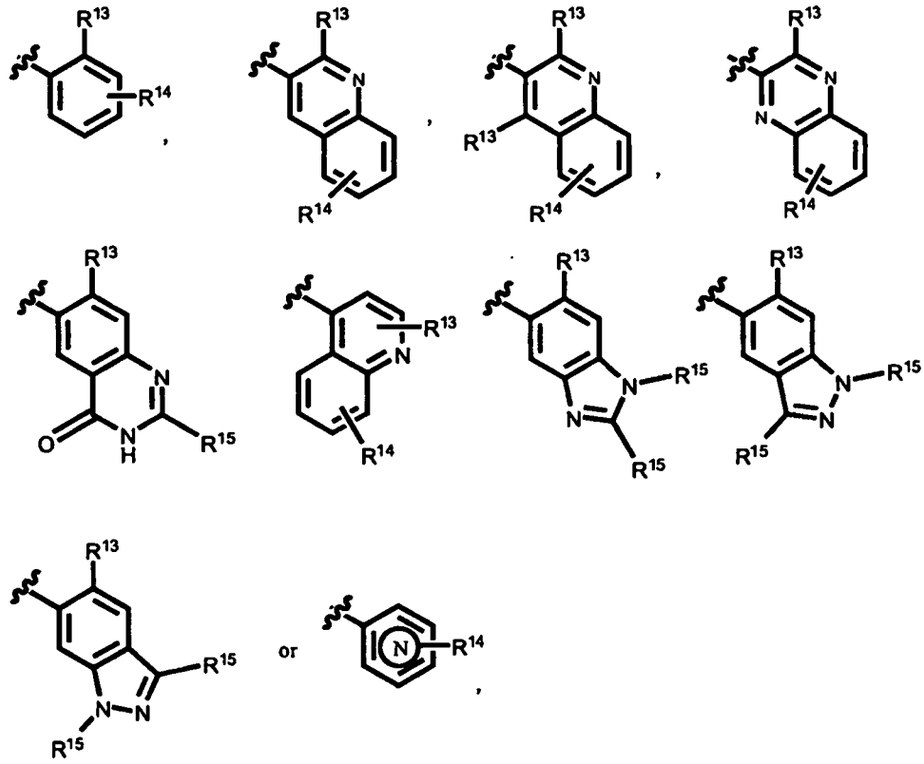
wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In still another embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is



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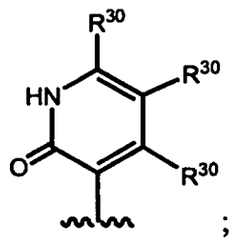
R^9 is H, methyl or ethyl; R^{10} is



wherein R^{11} is methyl, ethyl, cyclopropyl or phenyl; R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

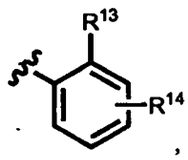
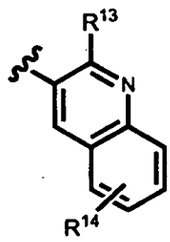
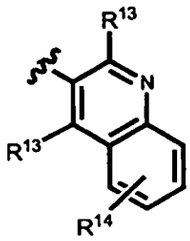
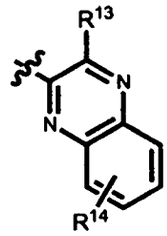
In a further embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is

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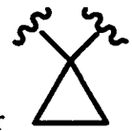


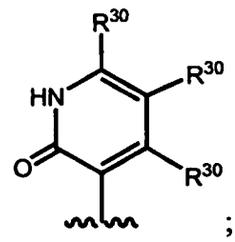
;

R^9 is H, methyl or ethyl; R^{10} is


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or

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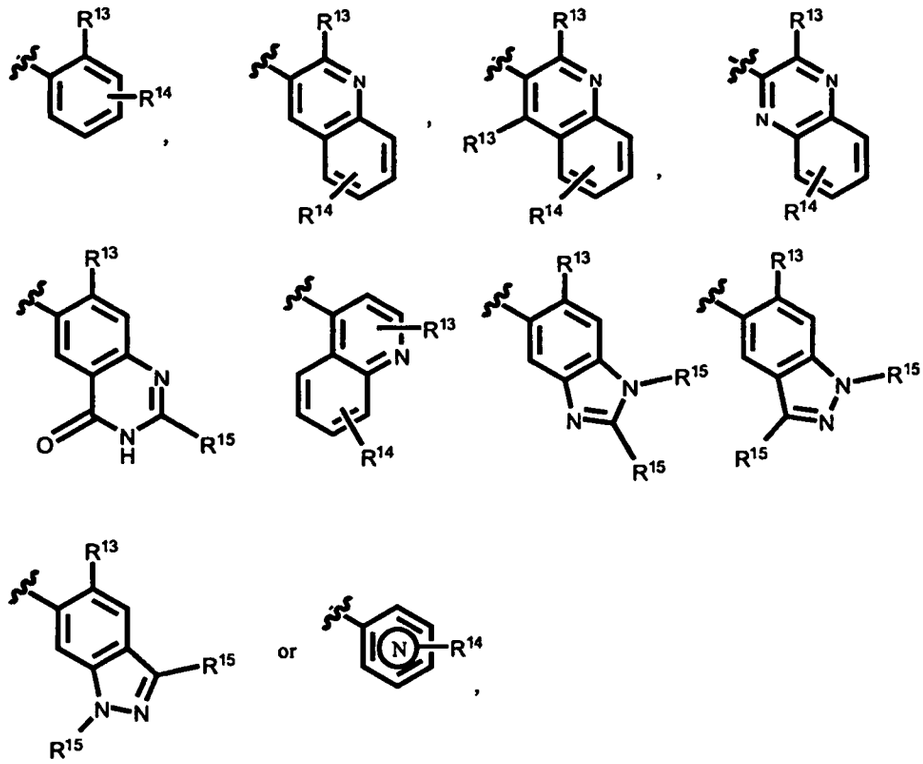
wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and R^{11} is methyl, ethyl, cyclopropyl or phenyl.

In another embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is



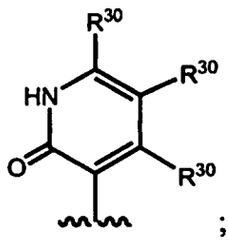
;

R^9 is H, methyl or ethyl; R^{10} is



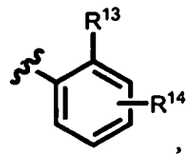
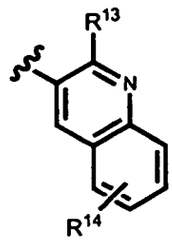
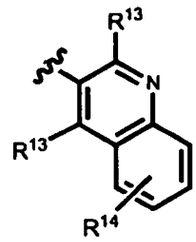
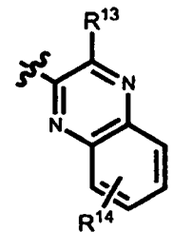
wherein R^{11} is methyl, ethyl or phenyl; R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is –CH_2- or  ; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is



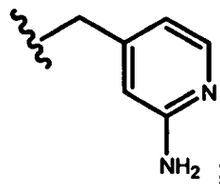
;

R^9 is H, methyl or ethyl; R^{10} is

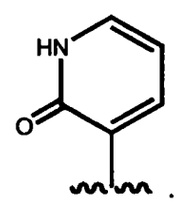

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or

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wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and R^{11} is methyl, ethyl or phenyl.

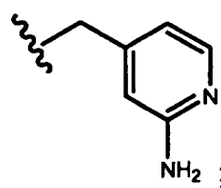
In one embodiment, R^1-R^{10} is


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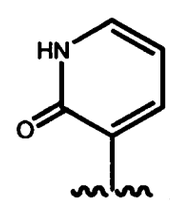
R^2 is $-C(O)NHSO_2R^{11}$; and R^3 is


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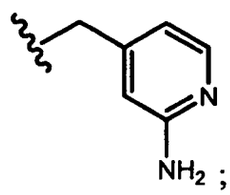
In one embodiment, R^1-R^{10} is


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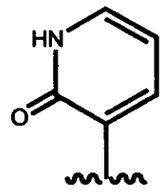
R^2 is $-C(O)NHSO_2CH_3$; and R^3 is


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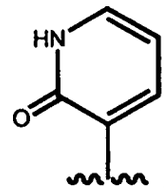
In one embodiment, R^1-R^{10} is



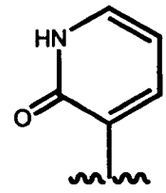
R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; and R^3 is



In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$; and R^3 is

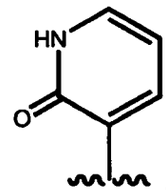


In one embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2CH_3$; and R^3 is



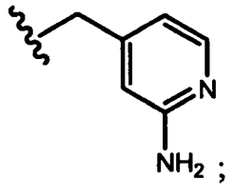
In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally

substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; and R^3 is



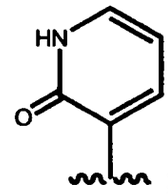
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In one embodiment, R^1-R^{10} is



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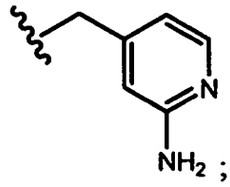
R^2 is $-C(O)NHSO_2R^{11}$; R^3 is



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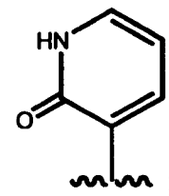
R^4, R^6 and R^7 are each H; and R^5 is other than H.

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



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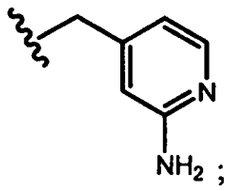
R^2 is $-C(O)NHSO_2CH_3$; R^3 is



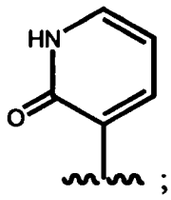
;

R^4, R^6 and R^7 are each H; and R^5 is other than H.

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

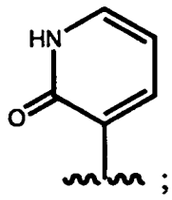


R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; R^3 is



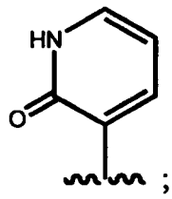
R^4, R^6 and R^7 are each H; and R^5 is other than H.

In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$; R^3 is



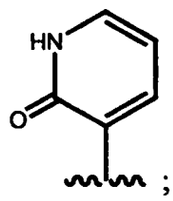
R^4, R^6 and R^7 are each H; and R^5 is other than H.

In another embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2CH_3$; R^3 is



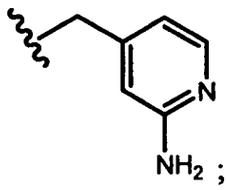
R^4, R^6 and R^7 are each H; and R^5 is other than H.

In another embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; R^3 is

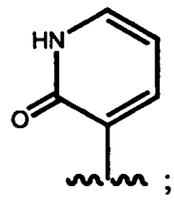


; R^4, R^6 and R^7 are each H; and R^5 is other than H.

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

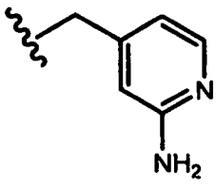


; R^2 is $-C(O)NHSO_2R^{11}$; R^3 is

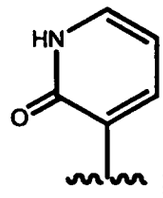


; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

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



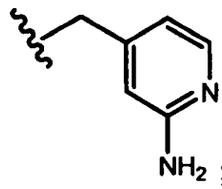
R^2 is $-C(O)NHSO_2CH_3$; R^3 is



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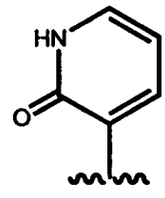
R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

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



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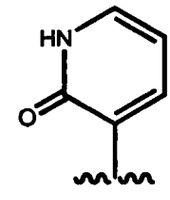
R^2 is -C(O)NHSO$_2$R^{11}, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, -NH$_2$, -NO$_2$, methoxy, -SO$_2$NH$_2$, -COOH, -[C(R^{12})$_2$]$_q$-C(O)O-alkyl, -OH, -NHSO$_2$-alkyl, -[C(R^{12})$_2$]$_q$-SO$_2$-alkyl, -CF$_3$, -CN, thiazolyl, -C(O)NH-alkyl, -NHSO$_2$-phenyl, -NHSO$_2$-cyclopropyl, -NHSO$_2$-alkyl, -[C(R^{12})$_2$]$_q$-NHC(O)-alkyl, pyrazolyl or -OCH$_2$C(O)NH$_2$; R^3 is



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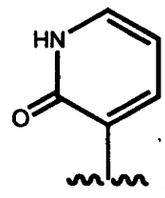
R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, -NH$_2$, -NHSO$_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, -[C(R^{12})$_2$]$_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, -C(O)NH$_2$ or -[C(R^{12})$_2$]$_q$-NH$_2$; R^2 is -C(O)NHSO$_2$R^{11}; R^3 is



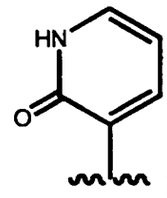
R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In another embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, -NH$_2$, -NHSO$_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, -[C(R^{12})$_2$]$_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, -C(O)NH$_2$ or -[C(R^{12})$_2$]$_q$-NH$_2$; R^2 is -C(O)NHSO$_2$CH$_3$; R^3 is



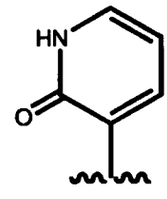
R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In another embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; R^3 is

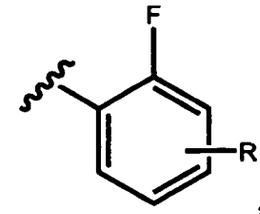


R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In one embodiment, R^1 is $–CH_2$-; R^2 is $–C(O)NHSO_2CH_3$ or $–C(O)NHSO_2$-cyclopropyl; R^3 is



R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; R^7 is H; and $-R^{10}$ is:

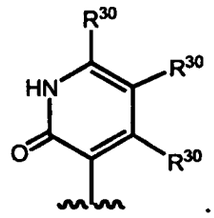


wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, -

NH_2, $-SO_2$-alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

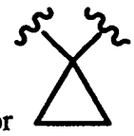
In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^3 is :



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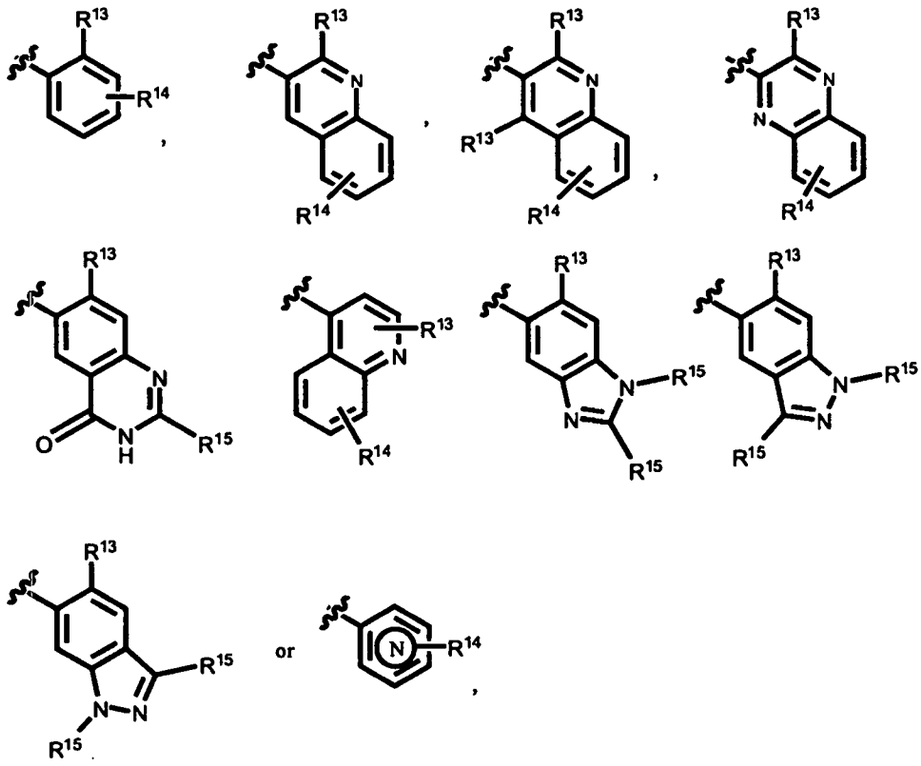
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^1 is $-[C(R^{12})_2]_r-$.

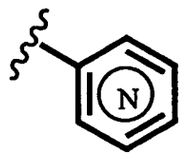
In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^1 is $-CH_2-$, $-CH_2CH_2-$, -$CH(CH_3)$- or  .

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and wherein R^4 and R^7 are each independently H, alkyl, halo or -OH, R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN, and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

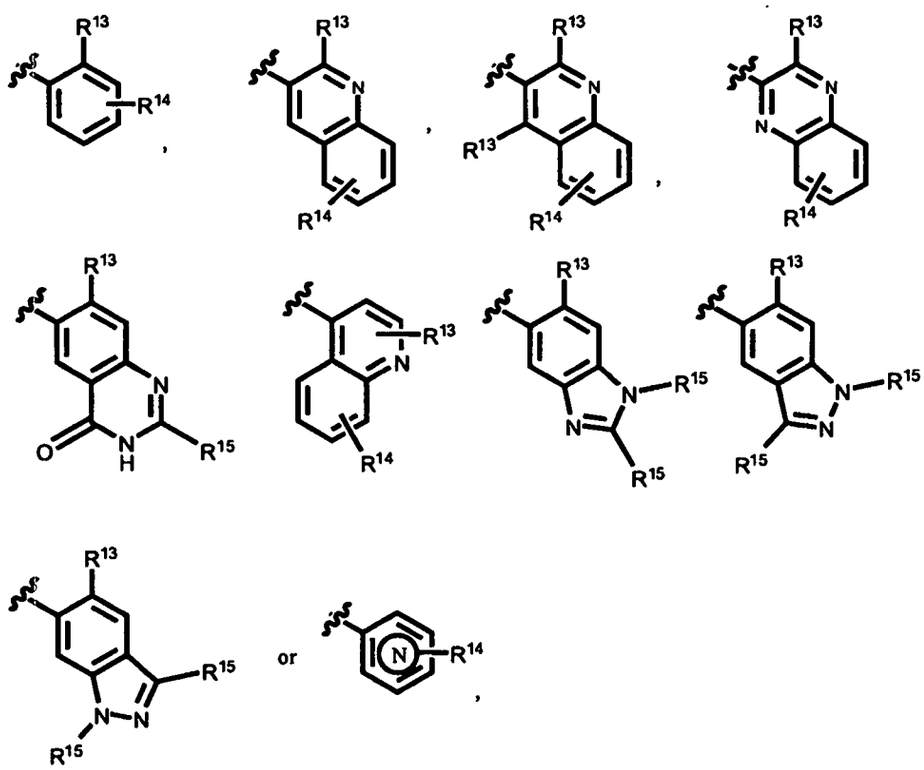
In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^{10} is aryl or heteroaryl.

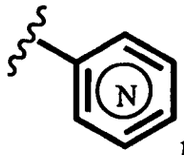
In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^{10} is:



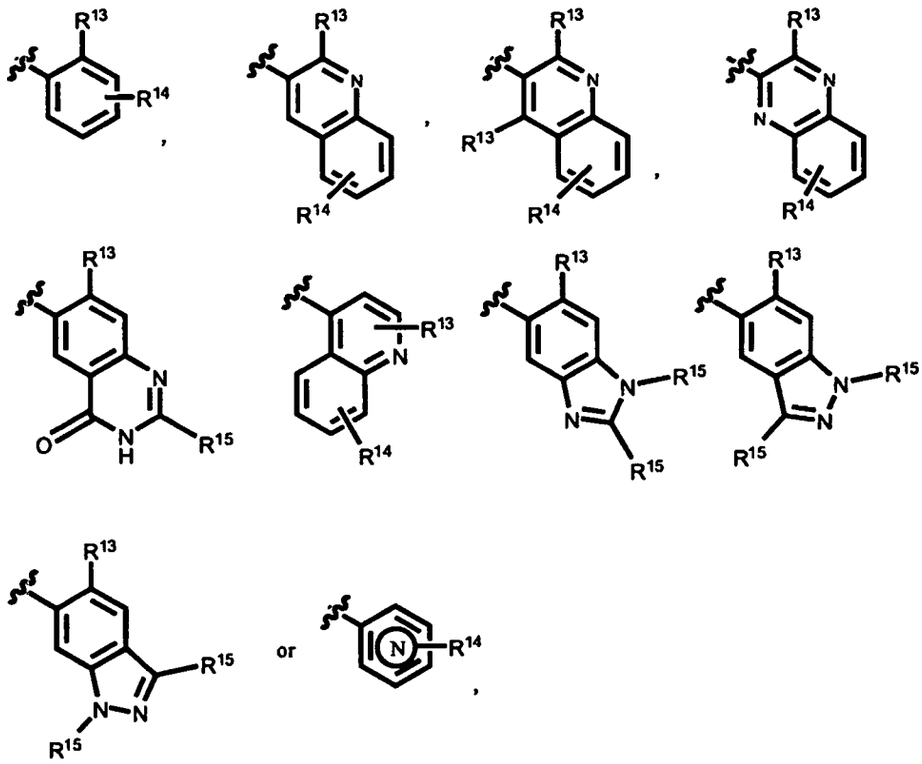
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

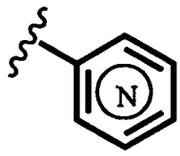
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^{10} is:



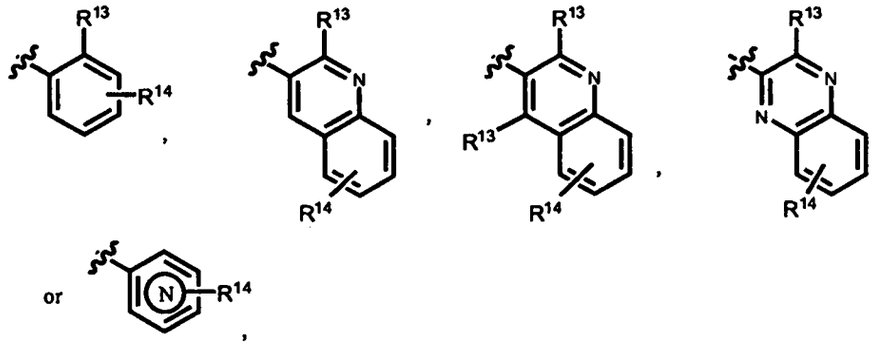
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

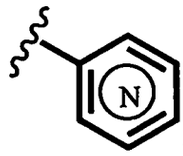
In another embodiment, R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^{10} is:



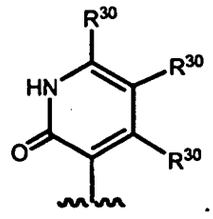
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl;  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions; and R^4 and R^7 are each independently H, halo or -OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN.

In yet another embodiment, R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^{10} is:



wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl;  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions; and R^4 and R^7 are each independently H, halo or -OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN.

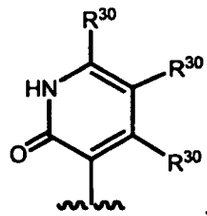
In one embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^3 is :



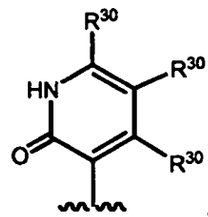
In another embodiment, R^1 is is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or



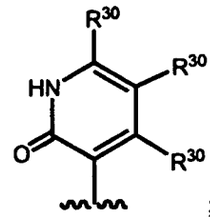
; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^3 is :



In another embodiment, R^1 is is $–CH_2-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^3 is :



In still another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :

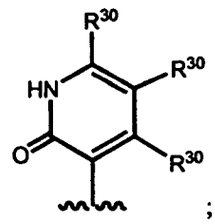


;

R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

In another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or

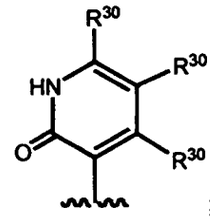
heterocycloalkyl and R^{11} is alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :



;

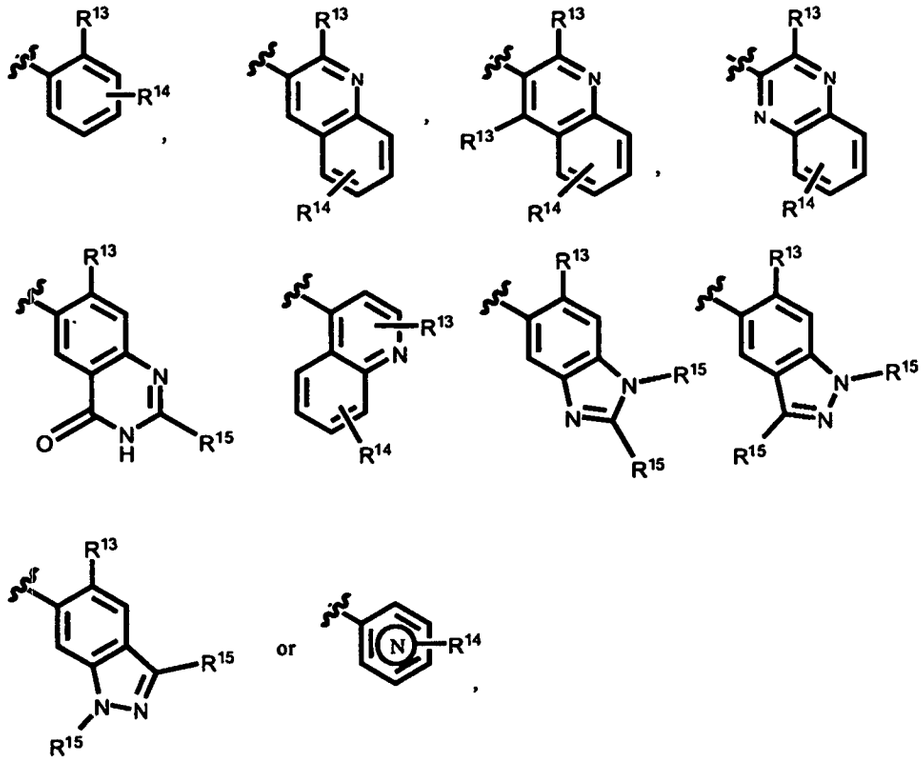
R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^{10} is aryl or heteroaryl.

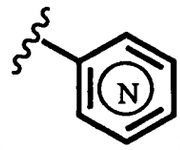
In yet another embodiment, R^1 is -[C(R^{12})$_2$]$_r$-; R^2 is -C(O)NHSO$_2$$R^{11}$ or -C(O)NHSO$_2$N(R^9)$_2$, wherein R^9 is H, alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :



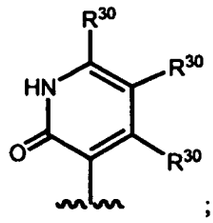
;

R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^{10} is:



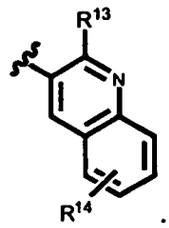
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

In another embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :



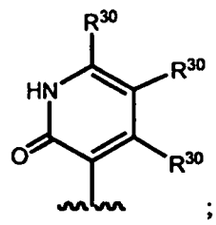
;

R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; and R^{10} is:



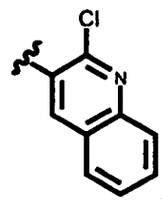
.

In a further embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :



;

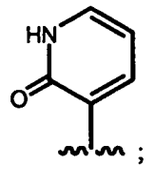
R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; and R^{10} is:



.

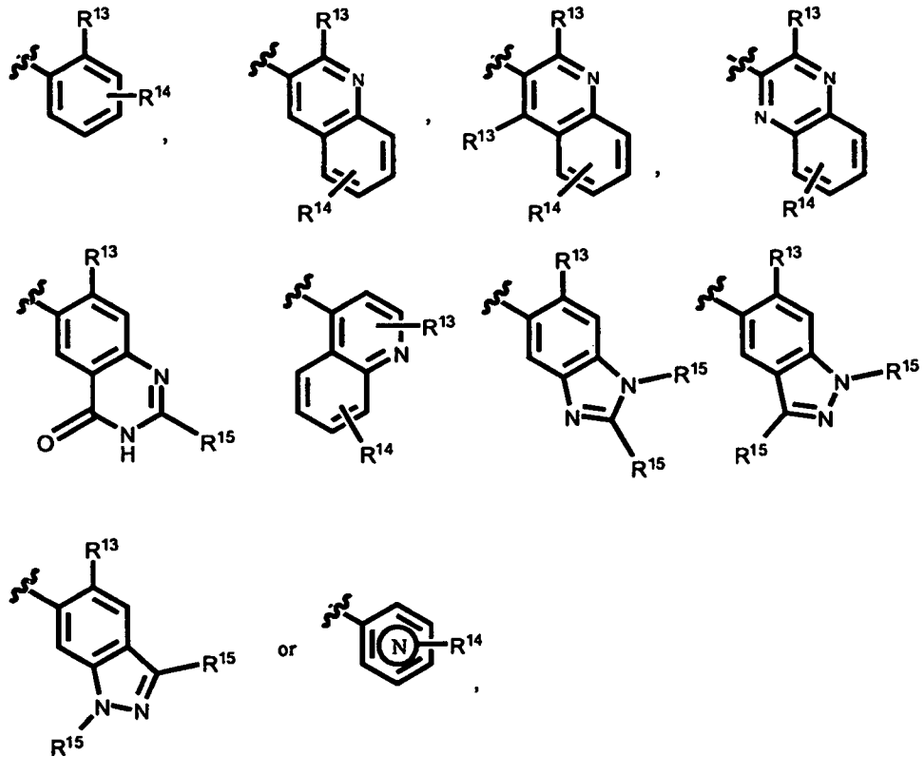
In another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or

heterocycloalkyl and R^{11} is alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^3 is :

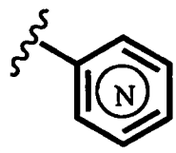


;

R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^{10} is:



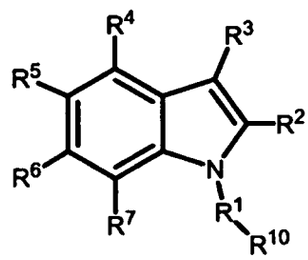
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -C(O)NH_2, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -C(O)NH_2, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-

heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

In one embodiment, for the compounds of formula (I), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 and R^{10} are selected independently of each other.

In another embodiment, the compounds of formula (I) are in purified form.

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



(Ia)

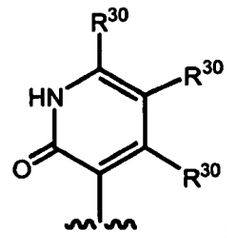
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof,

wherein:

R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ;

R^2 is $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alkyl)SO_2R^{11}$ or $-C(O)N(alkyl)SO_2N(R^9)_2$;

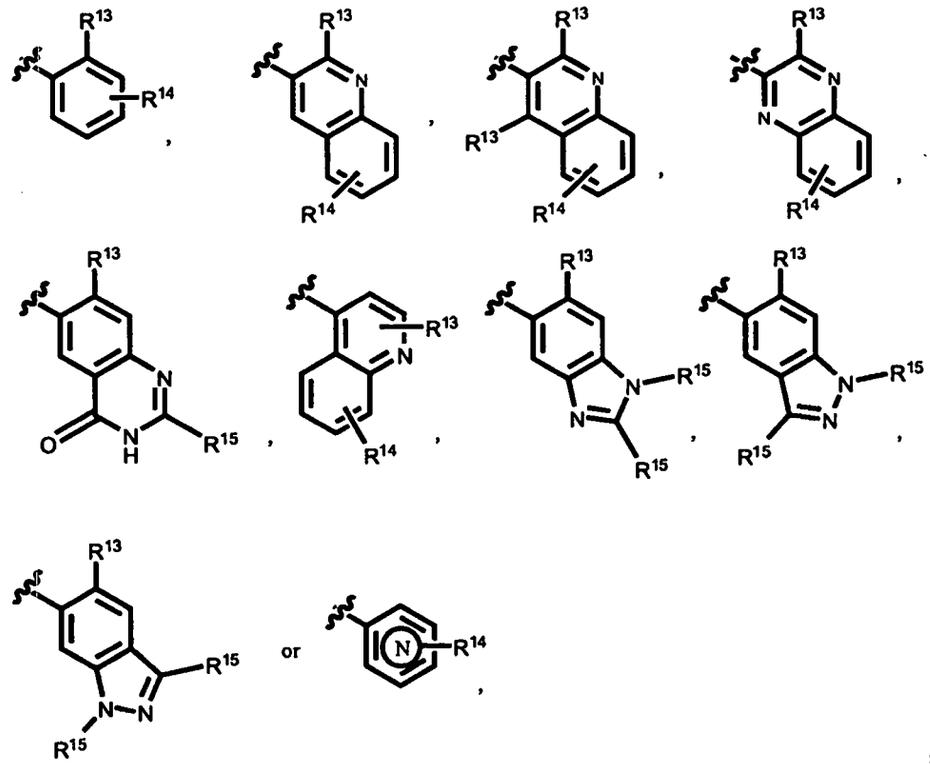
R^3 is:

 ;

R^4, R^5, R^6 and R^7 are each, independently, H, alkyl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, haloalkyl, halo, -OH, $-OR^9$ or $-N(R^9)_2$;

each occurrence of R^9 is independently H, alkyl, -alkyl-$N(alkyl)_2$, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl;

R^{10} is:



such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl;

each occurrence of R^{12} is independently H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, alkyl, cycloalkyl or heterocycloalkyl, 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;

R^{13} is H, F, Br or Cl;

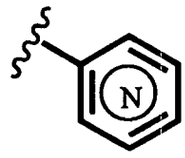
R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -NHSO$_2$-alkyl, -NO$_2$, -C(O)NH$_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH$_2$, -SO$_2$alkyl, -SO$_2$NH-alkyl, -S-alkyl, -CH$_2$NH$_2$, -CH$_2$OH, -SO$_2$NH$_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl;

each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -NHSO$_2$-alkyl, -NO$_2$, -C(O)NH$_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH$_2$, -SO$_2$alkyl, -SO$_2$NH-alkyl, -S-alkyl, -CH$_2$NH$_2$, -CH$_2$OH, -SO$_2$NH$_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl;

each occurrence of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, 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 q is independently an integer ranging from 0 to 4;

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



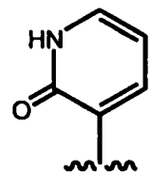
represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

In one embodiment, for the compounds of formula (Ia),

R^1 is –CH_2-;

R^2 is -C(O)NHSO$_2$R^{11} or -C(O)NHSO$_2$N(R^9)$_2$;

R^3 is:



;

R^4, R^5, R^6 and R^7 are each independently H, alkyl, haloalkyl or halo;

each occurrence of R^9 is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl; and

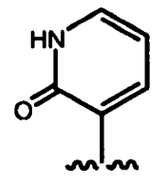
each occurrence of R^{11} is independently alkyl, aryl or cycloalkyl.

In another embodiment, for the compounds of formula (Ia),

R^1 is –CH_2-;

R^2 is -C(O)NHSO$_2$R^{11} or -C(O)NHSO$_2$N(R^9)$_2$;

R^3 is:

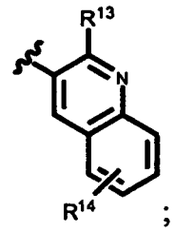


;

R^4, R^5, R^6 and R^7 are each independently H, alkyl, or halo;

each occurrence of R^9 is independently H, alkyl or cycloalkyl;

R^{10} is:



; and

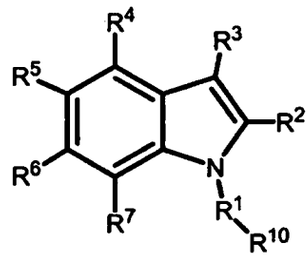
each occurrence of R^{11} is independently alkyl, aryl or cycloalkyl.

In one embodiment, for the compounds of formula (Ia), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 and R^{10} are selected independently of each other.

In another embodiment, the compounds of formula (Ia) are in purified form.

The 2,3-Substituted Indole Derivatives of Formula (II)

The present invention also provides 2,3-Substituted Indole Derivatives having the formula:



(II)

and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof, wherein R^1, R^2, R^4, R^5, R^6, R^7 and R^{10} are defined above for the compounds of formula (II).

In one embodiment, R^1 is bond.

In 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 $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$.

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

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

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

In one embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  .

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

In another embodiment, R^1 is  .

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

In another embodiment, R^{10} is –H.

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

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

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

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

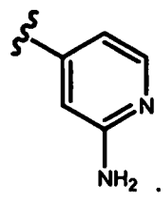
In another embodiment, R^{10} is heterocycloalkyl.

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

In another embodiment, R^{10} is phenyl, which is substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$.

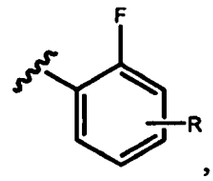
In yet another embodiment, R^{10} is pyridyl.

In a further embodiment, R^{10} is



.

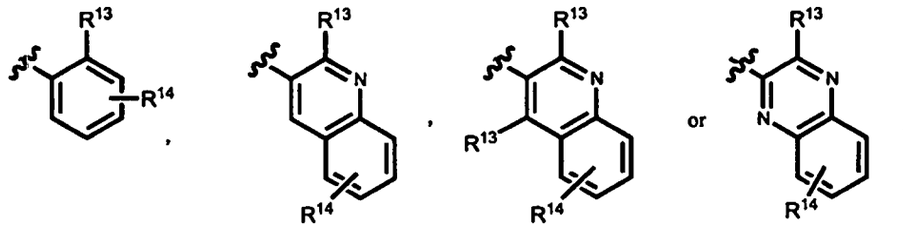
In another embodiment, $-R^{10}$ is:



,

wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, $-NH_2$, $-SO_2$-alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In another embodiment, R^{10} is



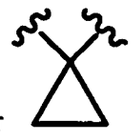
wherein R^{13} is F or Cl and R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

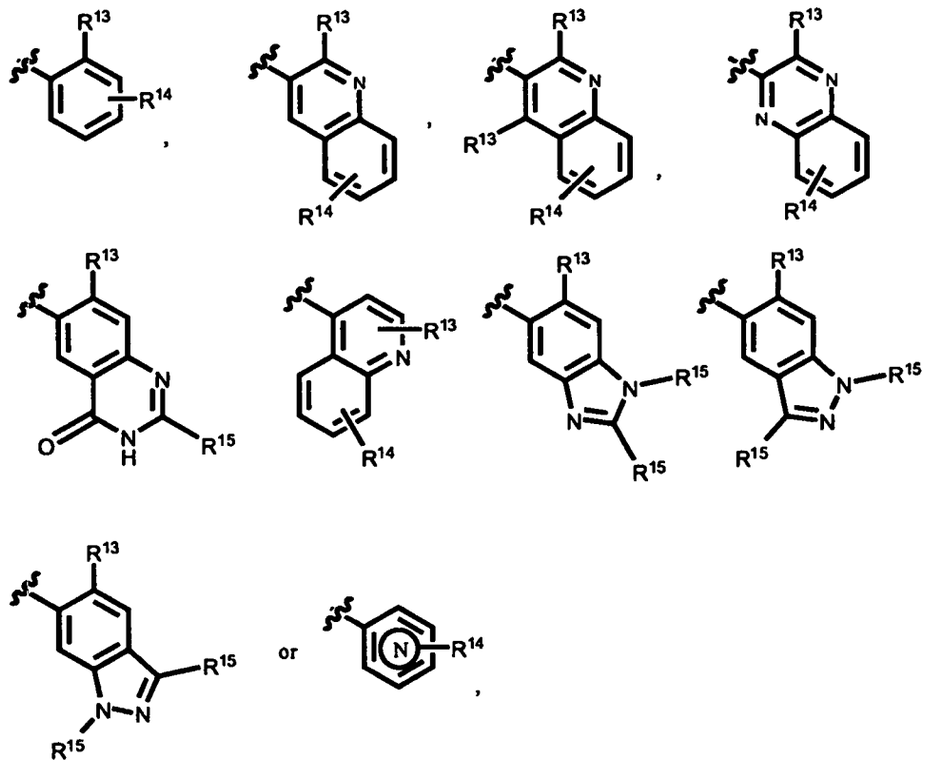
In another embodiment, R^1 is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or  , and R^{10} is aryl or heteroaryl.

In another embodiment, R^1 is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or  , and R^{10} is phenyl.

In another embodiment, R^1 is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or  , and R^{10} is alkyl or cycloalkyl.

In another embodiment, R^1 is –CH_2- and R^{10} is aryl or heteroaryl.

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

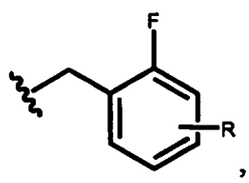


wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

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

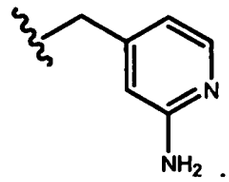
In another embodiment, -R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is substituted with from 1-4 groups independently selected from: halo, -NH_2, -$NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, -$[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, -$C(O)NH_2$ or -$[C(R^{12})_2]_q$-NH_2.

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



wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, $-NH_2$, $-SO_2$-alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

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



In still another embodiment, $-R^1-R^{10}$ is alkyl.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with 1 or 2 fluorine atoms.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with 1 or 2 methyl groups.

In yet another embodiment, $-R^1-R^{10}$ is $-R^1-R^{10}$ is benzyl, wherein the phenyl moiety of the benzyl group is substituted with one fluorine atom and one methyl group.

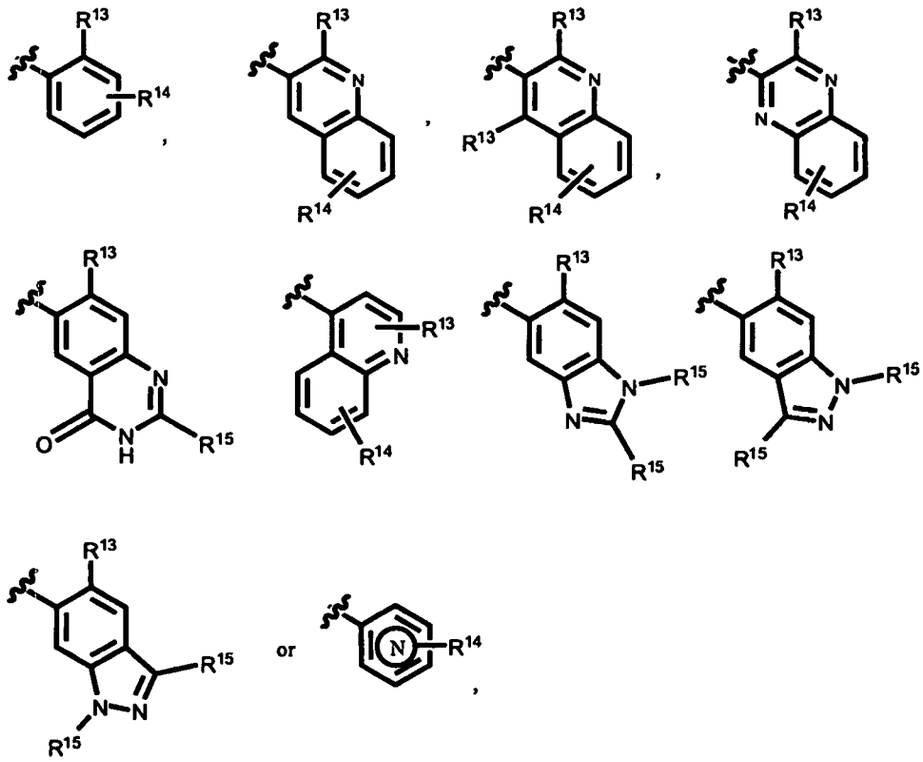
In another embodiment, $-R^1-R^{10}$ is haloalkyl.

In a further embodiment, $-R^1-R^{10}$ is $-CH_2$-cycloalkyl.

In another embodiment, $-R^1-R^{10}$ is other than H.

In another embodiment, R^1 is $-CH_2-$ and R^{10} is alkyl or cycloalkyl.

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



wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

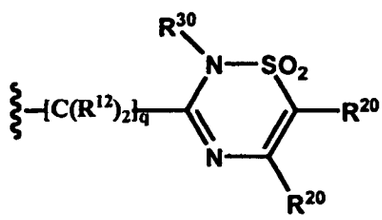
In one embodiment, R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$.

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

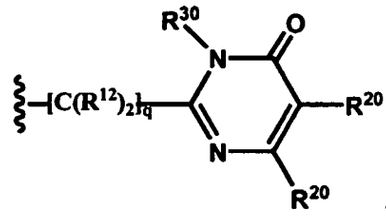
In another embodiment, R^2 is -$[C(R^{12})_2]_q$-$C(O)N(R^9)SOR^{11}$.

In still another embodiment, R^2 is -$[C(R^{12})_2]_q$-$C(O)N(R^9)SO_2N(R^{11})_2$.

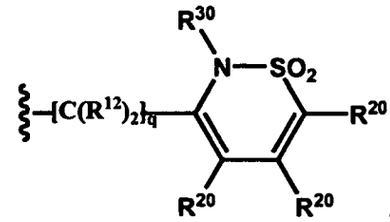
In another embodiment, R^2 is



In another embodiment, R^2 is



In yet another embodiment, R^2 is



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

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

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-alkyl.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-aryl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-cycloalkyl.

In a further embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-heterocycloalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-heteroaryl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-haloalkyl.

In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-hydroxyalkyl.

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

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

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

In a further embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is heterocycloalkyl.

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

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

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

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-phenyl.

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

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

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

$-NH_2$ or $-N(CH_3)_2$.

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

In another embodiment, R^2 is $-C(O)NHSO_2CH_2CH_3$.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$, and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

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

In one embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, alkyl or cycloalkyl.

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

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H, methyl, ethyl or cyclopropyl.

In yet another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is $-[C(R^{12})_2]_q$-O-alkyl or $-[C(R^{12})_2]_q$-N(alkyl)$_2$.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is $-(CH_2)_2$-$N(CH_3)_2$ or $-(CH_2)_3$-$N(CH_3)_2$.

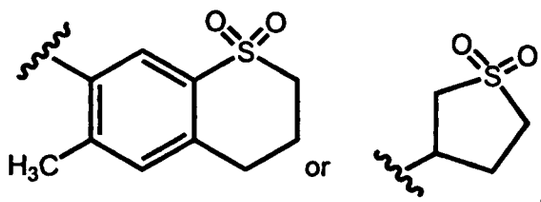
In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is cyclopropyl.

In another embodiment, R^2 is $-C(O)NHSO_2N(R^9)_2$ and R^9 is H or methyl.

In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-SO_2-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$.

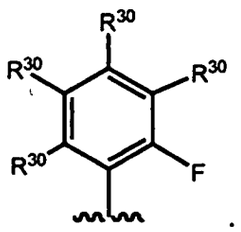
In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is $-[C(R^{12})_2]_q$-$NHSO_2$-alkyl, $-[C(R^{12})_2]$-O-alkyl,or $-[C(R^{12})_2]$-alkyl.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is imidazolyl, pyridyl, thienyl, furanyl, benzofuranyl, benzo[1,3]dioxolyl, tetrahydropyranyl,

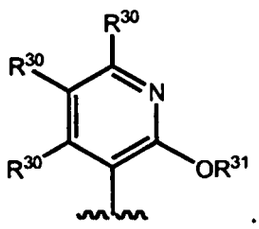


In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ and R^{11} is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

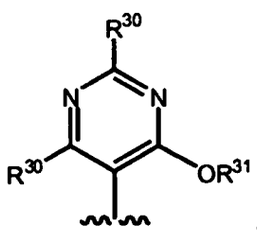
In one embodiment, R^3 is



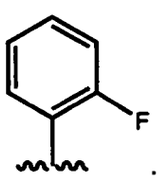
In another embodiment, R^3 is



In another embodiment, R^3 is



In another embodiment, R^3 is



In one embodiment, R^4 is H.

In another embodiment, R^4 is H or F.

In another embodiment, R^4 is F.

In another embodiment, R^5 is H.

In another embodiment, R^5 is other than H.

In yet another embodiment, R^6 is H.

In another embodiment, R^6 is other than H.

In another embodiment, R^6 is H or F.

In a further embodiment, R^6 is F.

In one embodiment, R^9 is H and R^{11} is methyl or ethyl.

In another embodiment, R^9 is H and R^{11} is cyclopropyl.

In still another embodiment, R^7 is H.

In another embodiment, R^4 and R^7 are each independently H, halo or hydroxy.

In another embodiment, R^4 and R^7 are each independently H, F or hydroxy.

In another embodiment, R^4 and R^7 are each H.

In yet another embodiment, R^4, R^6 and R^7 are each H.

In another embodiment, R^4, R^5, R^6 and R^7 are each H.

In a further embodiment, R^4, R^6 and R^7 are each H and R^5 is other than H.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is alkyl.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is halo.

In another embodiment, R^4, R^6 and R^7 are each H and R^5 is methyl.

In a further embodiment, R^4, R^6 and R^7 are each H and R^5 is Cl.

In another embodiment, R^4 and R^7 are each H and and R^5 and R^6 are other than H.

In another embodiment, R^5 is other than H.

In still another embodiment, R^5 is alkyl.

In yet another embodiment, R^5 is halo.

In still another embodiment, R^5 is methyl.

In another embodiment, R^5 is ethyl.

In another embodiment, R^6 is H.

In another embodiment, R^6 is other than H.

In a further embodiment, R^6 is alkyl.

In yet another embodiment, R^6 is halo.

In still another embodiment, R^6 is methyl.

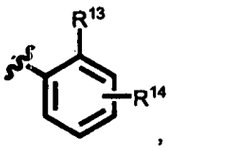
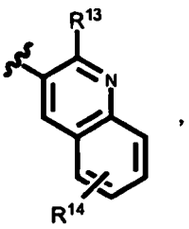
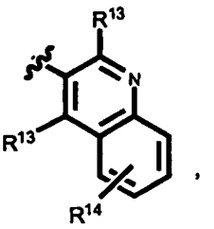
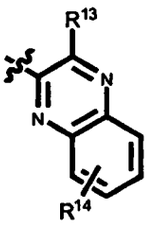
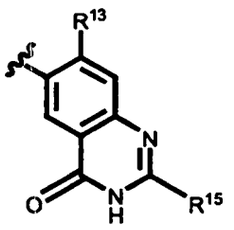
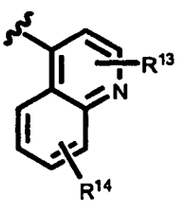
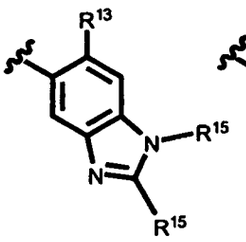
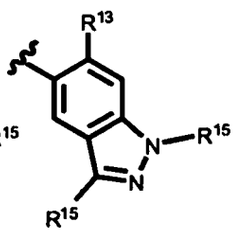
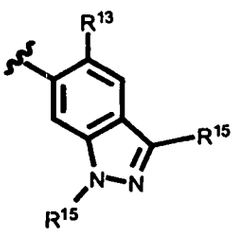
In another embodiment, R^6 is F.

In one embodiment, R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; and R^2 is $-C(O)NHSO_2R^{11}$.

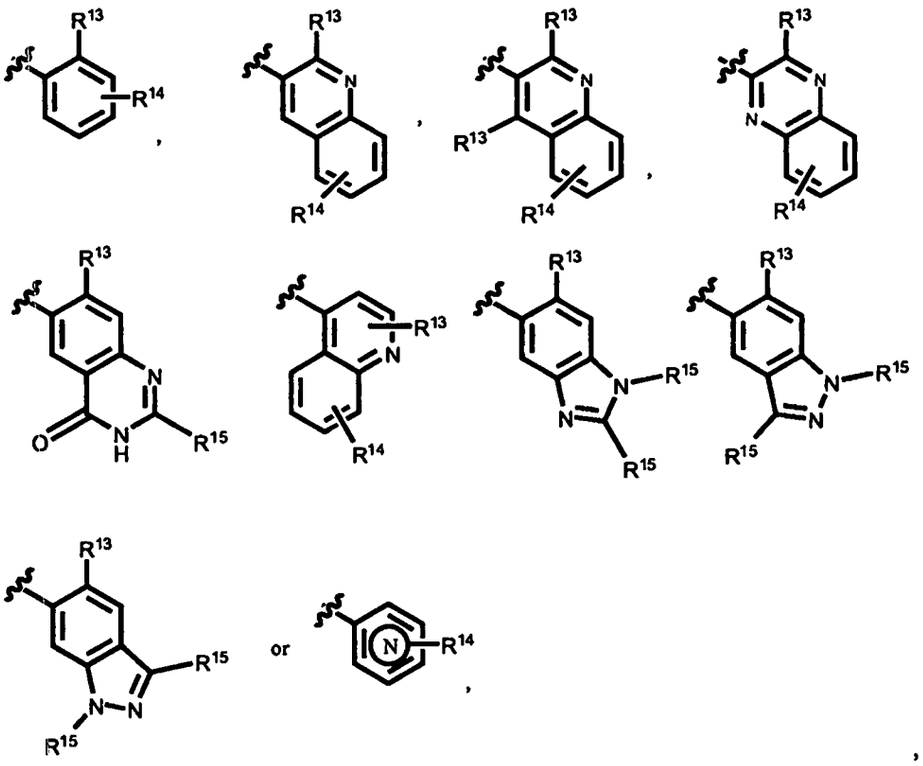
In one embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; and R^2 is $-C(O)NHSO_2CH_3$.

In another embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ; R^2 is $-C(O)N(R^9)SO_2R^{11}$; and R^{10} is:










or

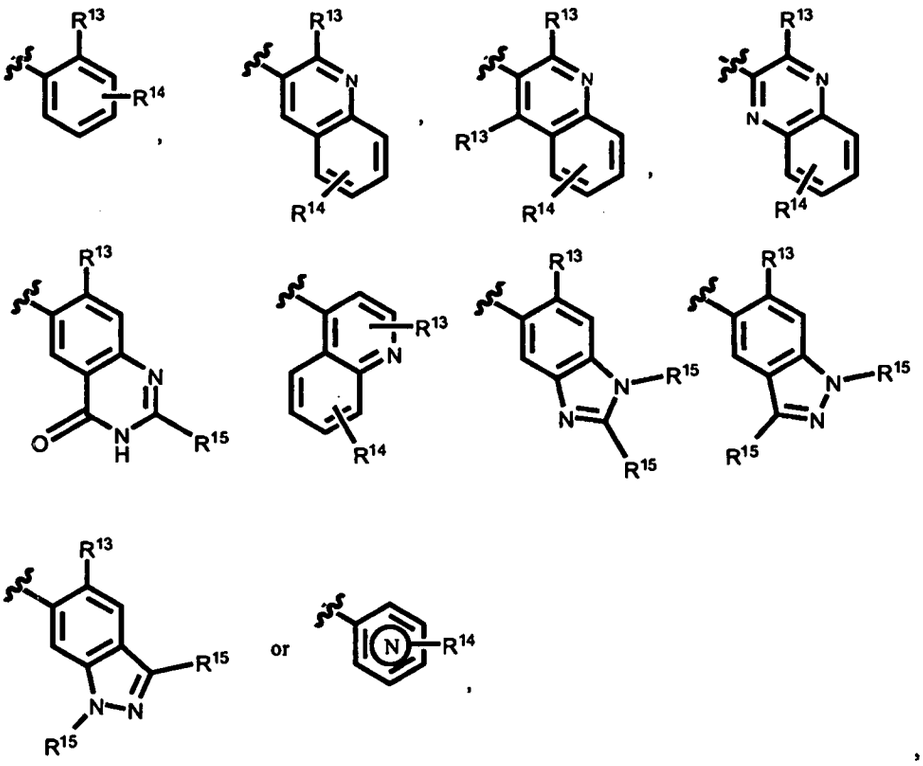

wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ; R^2 is $-C(O)N(R^9)SO_2R^{11}$; R^5 is alkyl, cycloalkyl, halo or -OH; R^6 is H, halo or -OH; and R^{10} is:



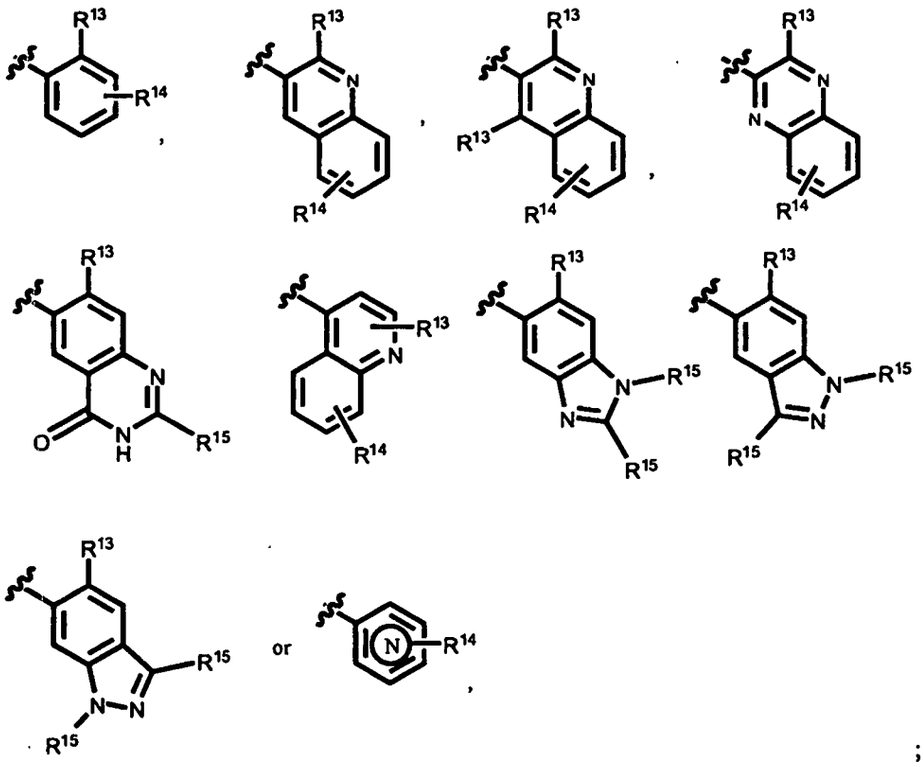
wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ; R^2 is $-C(O)N(R^9)SO_2R^{11}$; R^5 is methyl or ethyl; R^6 is H, F or Cl; and R^{10} is:



wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

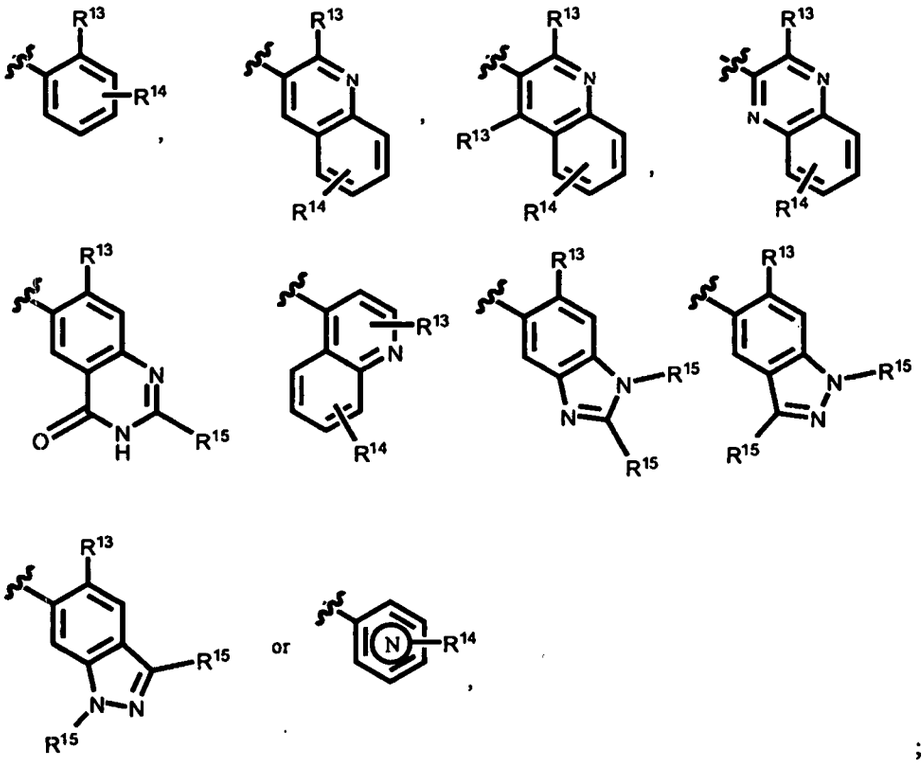
In another embodiment, R^1 is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or  ; R^2 is -$C(O)N(R^9)SO_2R^{11}$; R^5 is methyl or ethyl; R^6 is H, F or Cl; R^9 is H; R^{10} is:



;

R^{11} is methyl; R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

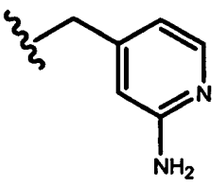
In another embodiment, R^1 is –CH_2-, -CH_2CH_2-, -$CH(CH_3)$- or  ; R^2 is -$C(O)N(R^9)SO_2R^{11}$; R^5 is methyl or ethyl; R^6 is H, F or Cl; R^9 is H;
R^{10} is:



;

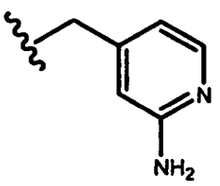
R^{11} is cyclopropyl; R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

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



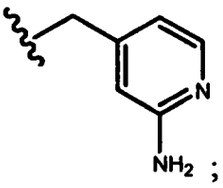
and R^2 is -$C(O)NHSO_2R^1$.

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



and R^2 is $-C(O)NHSO_2CH_3$.

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

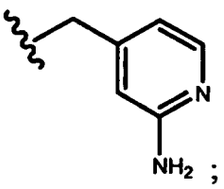


;

R^2 is $-C(O)NHSO_2R^{11}$; and R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$.

In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$; and R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$.

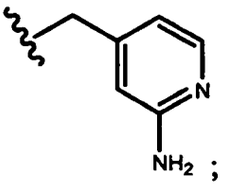
In one embodiment, R^1-R^{10} is



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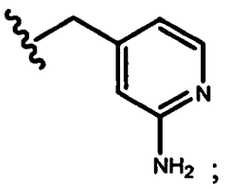
R^2 is $-C(O)NHSO_2R^{11}$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

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



R^2 is $-C(O)NHSO_2CH_3$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

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



R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

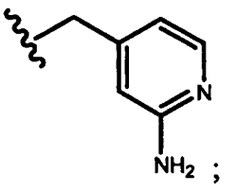
In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

In another embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2CH_3$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

In another embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-

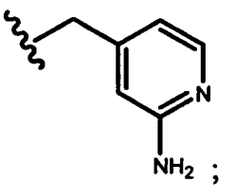
alkyl, -[C(R^{12})$_2$]$_q$-NHC(O)-alkyl, pyrazolyl or -$OCH_2C(O)NH_2$; R^4, R^6 and R^7 are each H; and R^5 is other than H.

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



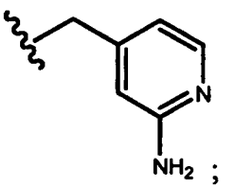
; R^2 is -$C(O)NHSO_2R^{11}$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

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



; R^2 is -$C(O)NHSO_2CH_3$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

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



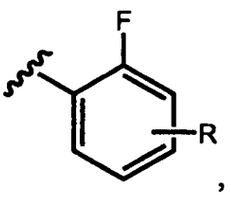
; R^2 is -$C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, -NH_2, -NO_2, methoxy, -SO_2NH_2, -COOH, -[C(R^{12})$_2$]$_q$-C(O)O-alkyl, -OH, -$NHSO_2$-alkyl, -[C(R^{12})$_2$]$_q$-SO_2-alkyl, -CF_3, -CN, thiazolyl, -C(O)NH-alkyl, -$NHSO_2$-phenyl, -$NHSO_2$-cyclopropyl, -$NHSO_2$-alkyl, -[C(R^{12})$_2$]$_q$-NHC(O)-alkyl, pyrazolyl or -$OCH_2C(O)NH_2$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In one embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, -NH_2, -$NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, -[C(R^{12})$_2$]$_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, -$C(O)NH_2$ or -[C(R^{12})$_2$]$_q$-NH_2; R^2 is -$C(O)NHSO_2R^{11}$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In another embodiment, R^1-R^{10} is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2CH_3$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

In another embodiment, R^1-R^{10} is is benzyl, wherein the phenyl moiety of the benzyl group is optionally substituted with from 1-4 groups independently selected from: halo, $-NH_2$, $-NHSO_2$-alkyl, haloalkyl, methoxy, -O-haloalkyl, $-[C(R^{12})_2]_q$-NHC(O)NH-alkyl, alkyl, -OH, -CN, $-C(O)NH_2$ or $-[C(R^{12})_2]_q-NH_2$; R^2 is $-C(O)NHSO_2R^{11}$, R^{11} is phenyl, which is optionally substituted with up to 3 groups independently selected from: alkyl, F, Cl, methyl, $-NH_2$, $-NO_2$, methoxy, $-SO_2NH_2$, -COOH, $-[C(R^{12})_2]_q$-C(O)O-alkyl, -OH, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q-SO_2$-alkyl, $-CF_3$, -CN, thiazolyl, -C(O)NH-alkyl, $-NHSO_2$-phenyl, $-NHSO_2$-cyclopropyl, $-NHSO_2$-alkyl, $-[C(R^{12})_2]_q$-NHC(O)-alkyl, pyrazolyl or $-OCH_2C(O)NH_2$; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; and R^7 is H.

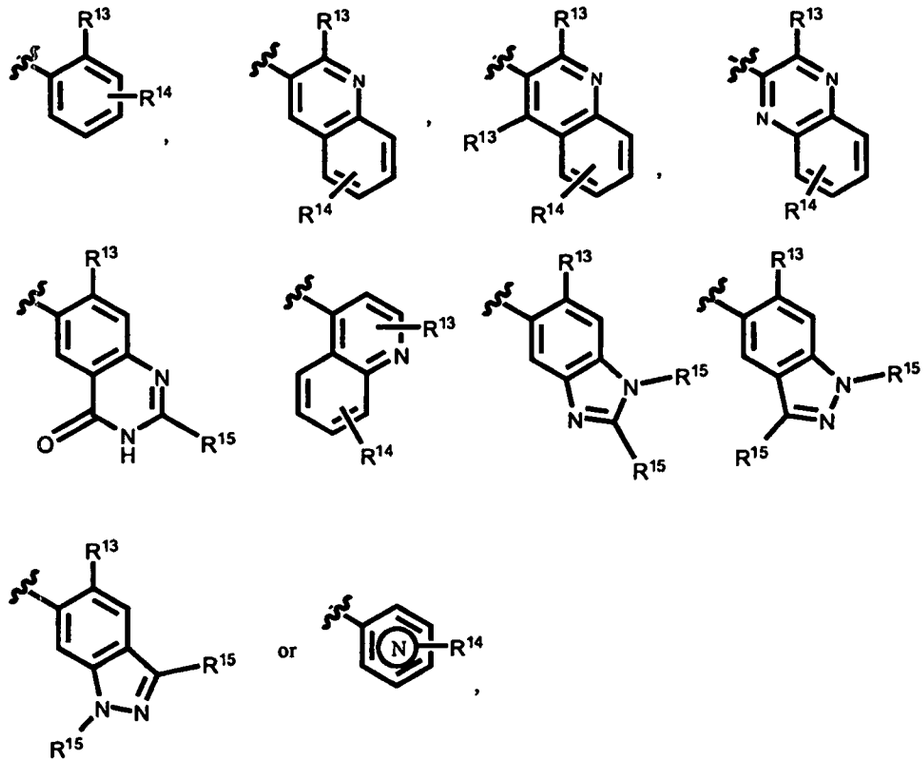
In one embodiment, R^1 is $-CH_2-$; R^2 is $-C(O)NHSO_2CH_3$ or $-C(O)NHSO_2$-cyclopropyl; R^4 is H or F; R^5 is methyl or ethyl; R^6 is H or F; R^7 is H; and $-R^{10}$ is:



,

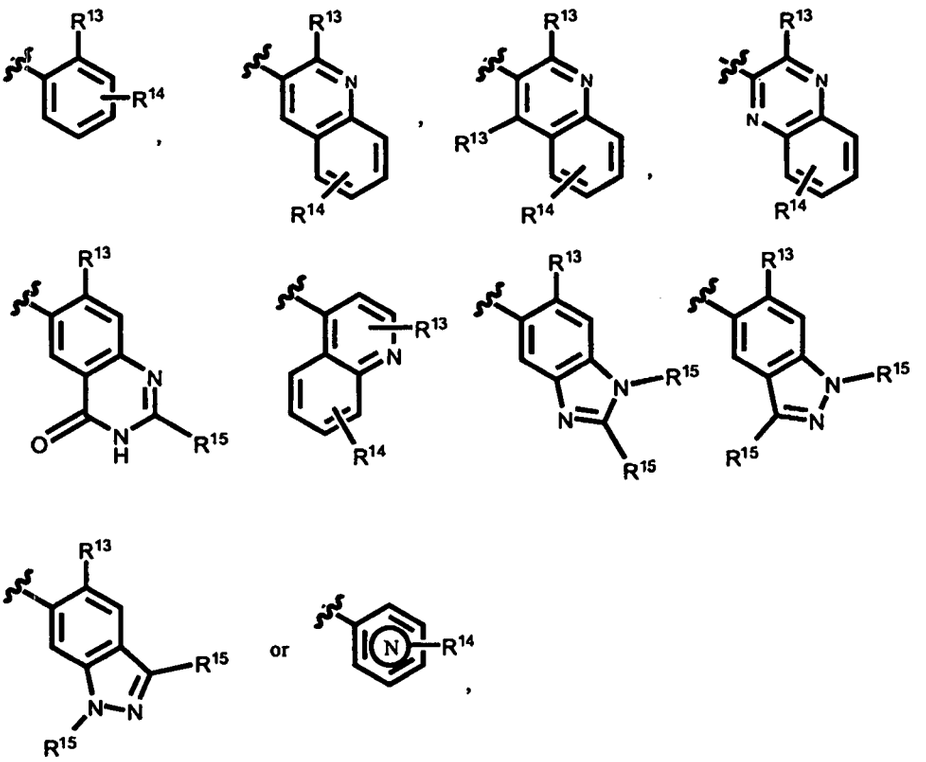
wherein R represents up to 2 optional and additional phenyl substituents, each independently selected from halo, -O-alkyl, alkyl, $-CF_3$, -CN, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)OH, $-NH_2$, $-SO_2$-alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl.

In another embodiment, R^1 is $-CH_2-$; R^5 is alkyl, cycloalkyl, halo or -OH; R^6 is H, halo or -OH; and R^{10} is



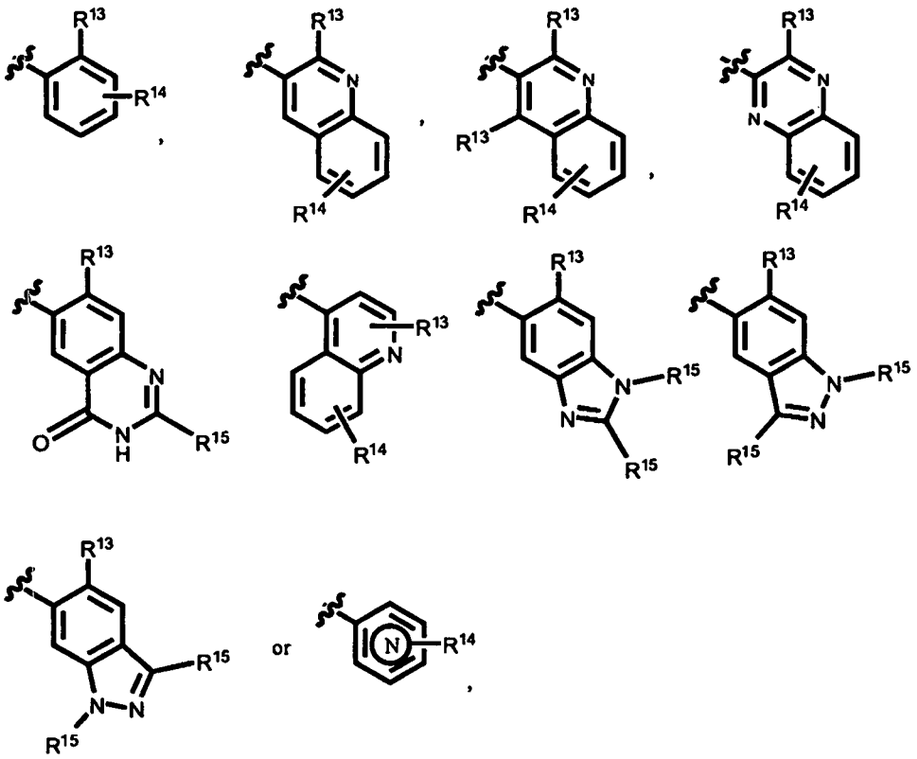
wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

In another embodiment, R^1 is –CH_2-; R^5 is methyl or ethyl; R^6 is H or F; and R^{10} is



wherein R^{13} is F, or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

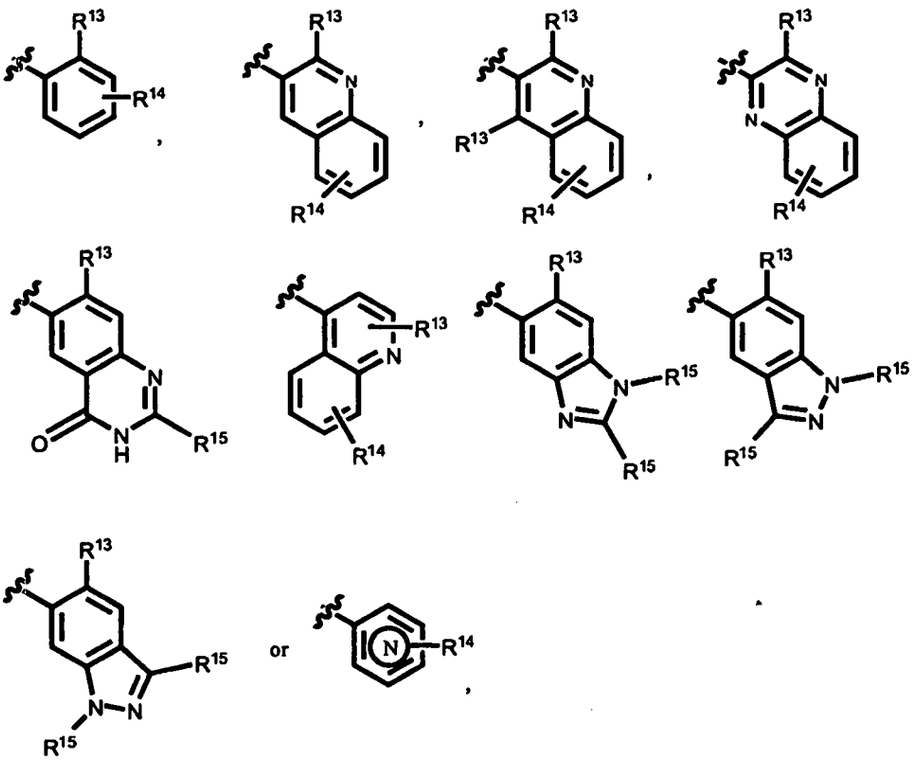
In still another embodiment, R^1 is –CH_2-; R^9 is H; R^{10} is



wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

R^{11} is methyl.

In another embodiment, R^1 is $-CH_2-$; R^9 is H; R^{10} is



wherein R^{13} is F or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, $-NHSO_2$-alkyl, $-NO_2$, $-C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, $-NH_2$, $-SO_2$alkyl, $-SO_2NH$-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl.

R^{11} is cyclopropyl.

In one embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

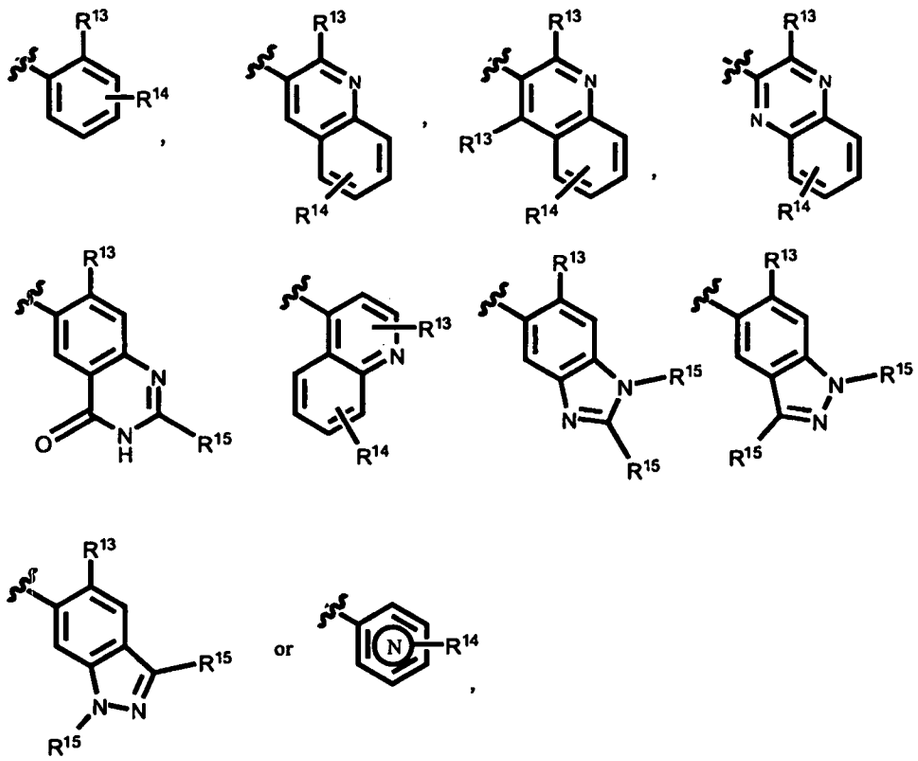
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^1 is $-[C(R^{12})_2]_r-$.

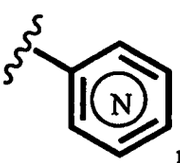
In still another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  .

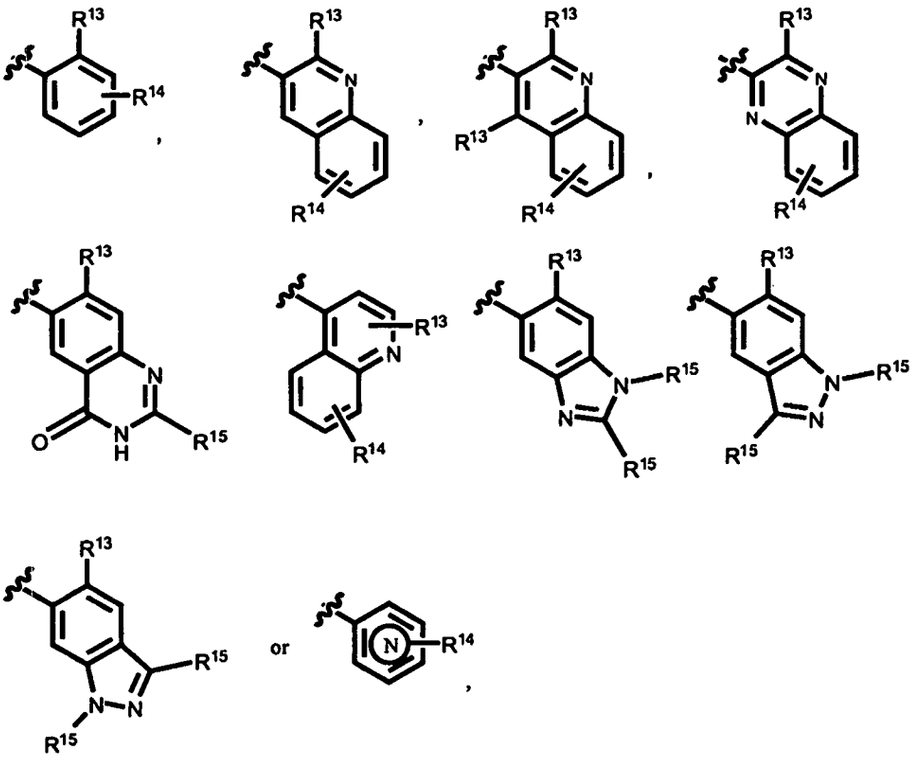
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and wherein R^4 and R^7 are each independently H, alkyl, halo or -OH, R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN, and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

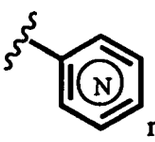
In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^{10} is aryl or heteroaryl.

In yet another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and R^{10} is:



wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.In yet another embodiment, R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; R^{10} is:

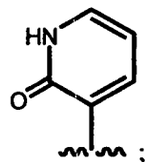


wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl;  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions; and R^4 and R^7 are each independently H, halo or -OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN.

In one embodiment, R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

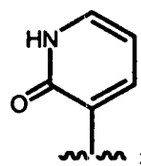
In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

In another embodiment, R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :



; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

In still another embodiment, R^1 is $-[C(R^{12})_2]_r-$; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :

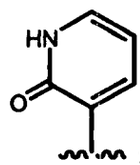


; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

In another embodiment, R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or



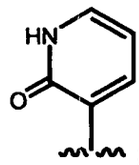
; R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$; R^3 is :



; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence

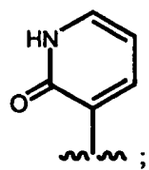
of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

In yet another embodiment, R^1 is –CH_2-; R^2 is -C(O)NHSO$_2$$R^{11}$ or -C(O)NHSO$_2$N(R^9)$_2$; R^3 is :



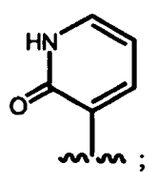
; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

In a further embodiment, R^1 is -[C(R^{12})$_2$]$_r$-; R^2 is -C(O)NHSO$_2$$R^{11}$ or -C(O)NHSO$_2$N(R^9)$_2$; R^3 is :



; R^4 and R^7 are each independently H, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

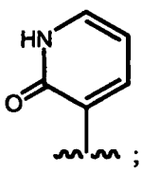
In one embodiment, R^1 is -[C(R^{12})$_2$]$_r$-; R^2 is -C(O)NHSO$_2$$R^{11}$ or -C(O)NHSO$_2$N(R^9)$_2$; R^3 is :



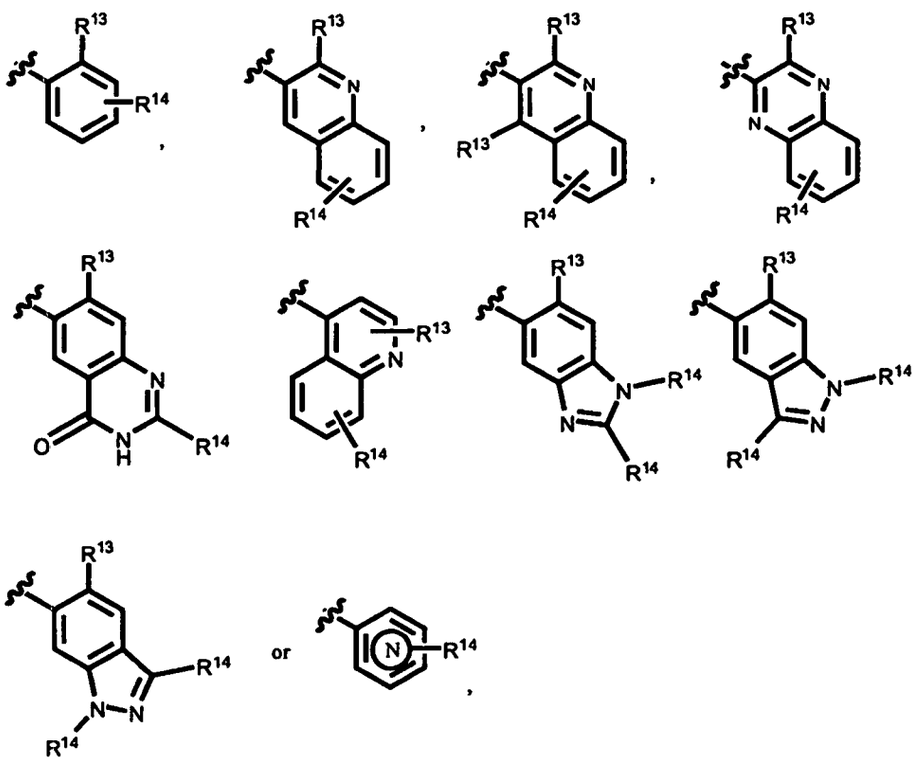
; R^4 and R^7 are each independently H, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^9 is H,

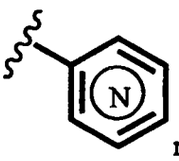
alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group; and R^{10} is aryl or heteroaryl

In another embodiment, R^1 is -[C(R^{12})$_2$]$_r$-; R^2 is -C(O)NHSO$_2$$R^{11}$ or -C(O)NHSO$_2$N(R^9)$_2$; R^3 is :

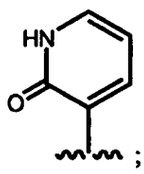


; R^4 and R^7 are each independently H, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH$_2$ or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH$_2$ or –CN; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group; and R^{10} is:

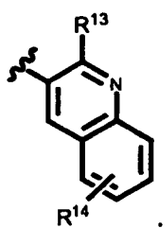


wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2-alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

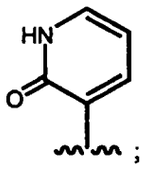
In another embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is :



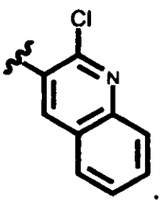
; R^4 and R^7 are each independently H, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, -$N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group; and R^{10} is:



In still another embodiment, R^1 is -$[C(R^{12})_2]_r$-; R^2 is -$C(O)NHSO_2R^{11}$ or -$C(O)NHSO_2N(R^9)_2$; R^3 is :



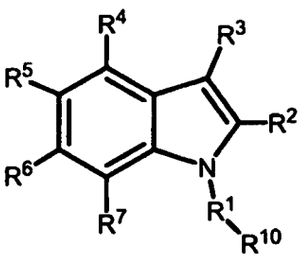
; R^4 and R^7 are each independently H, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN; R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl; R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl; and each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group; and R^{10} is:



In one embodiment, for the compounds of formula (II), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 and R^{10} are selected independently of each other.

In another embodiment, the compounds of formula (II) are in purified form.

In one embodiment, the compounds of formula (II) have the formula (IIa):



(IIa)

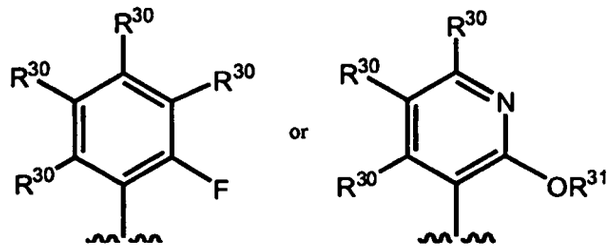
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof,

wherein:

R^1 is $–CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ;

R^2 is $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alkyl)SO_2R^{11}$ or $-C(O)N(alkyl)SO_2N(R^9)_2$;

R^3 is:

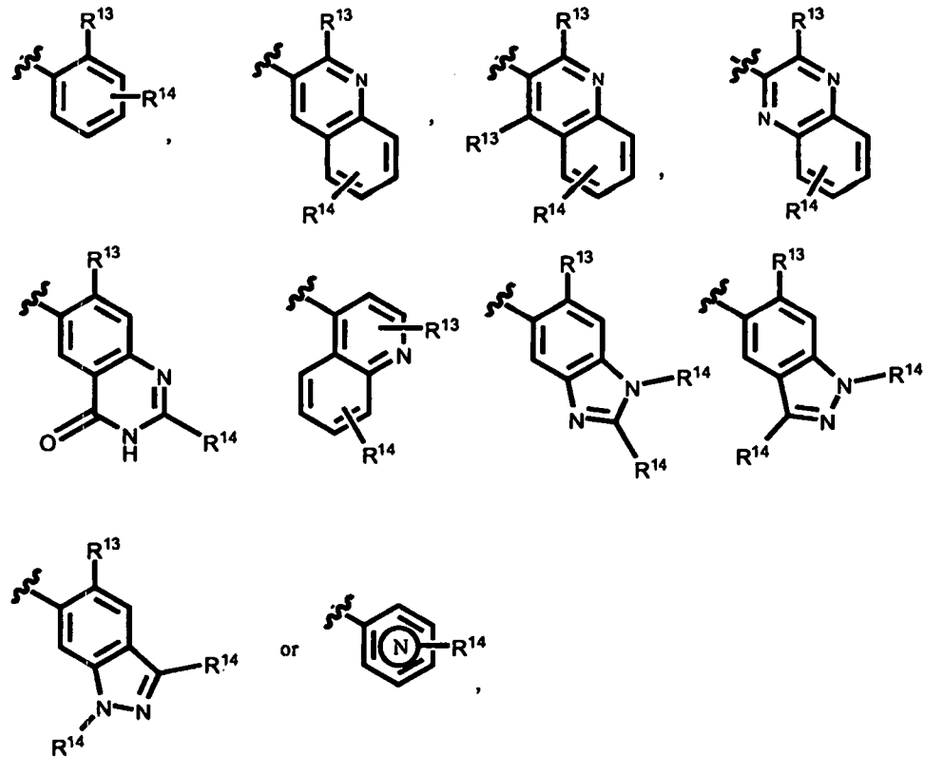


;

R^4, R^5, R^6 and R^7 are each, independently, H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halo, -OH, -OH, -O-alkyl, -O-haloalkyl, $-NH_2$, -NH-alkyl or $-N(alkyl)_2$;

each occurrence of R^9 is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl;

R^{10} is:



such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl;

R^{13} is H, F, Br or Cl;

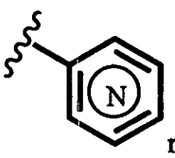
R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl;

each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl;

each occurrence of R^{30} is independently, H, halo, -$N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group;

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

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



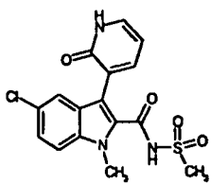
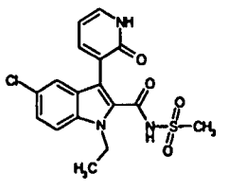
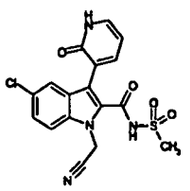
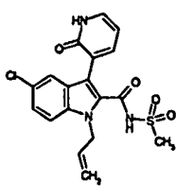
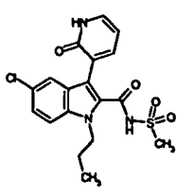
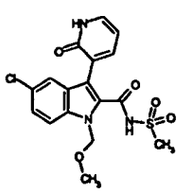
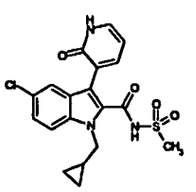
represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

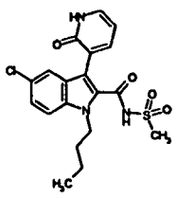
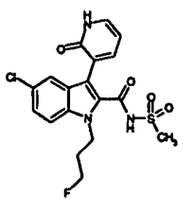
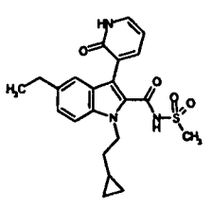
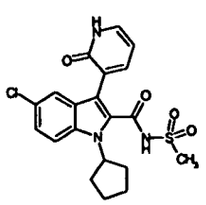
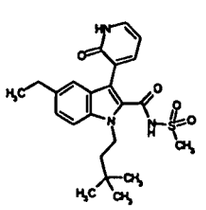
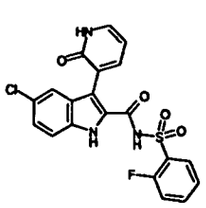
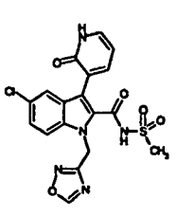
In one embodiment, for the compounds of formula (IIa), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 and R^{10} are selected independently of each other.

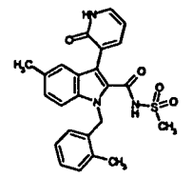
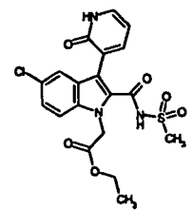
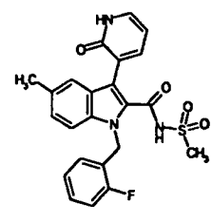
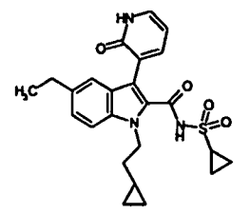
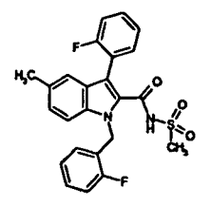
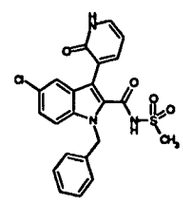
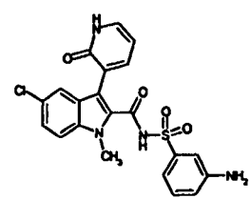
In another embodiment, the compounds of formula (IIa) are in purified form.

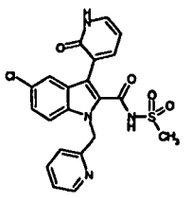
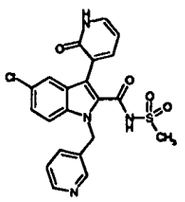
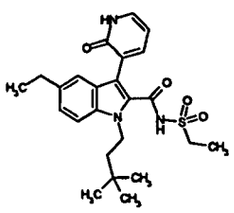
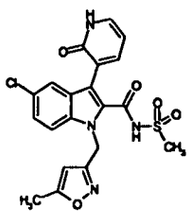
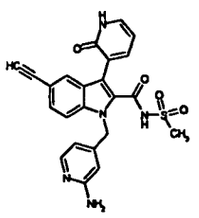
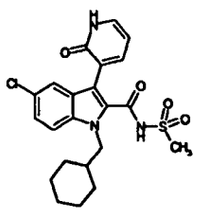
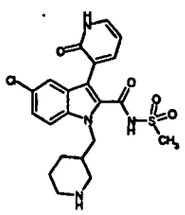
Non-limiting illustrative examples of the 2,3-Substituted Indole Derivatives include compounds 1-641 as set forth in the following table and in the Examples section below.

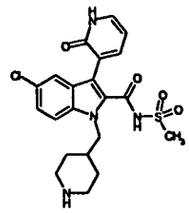
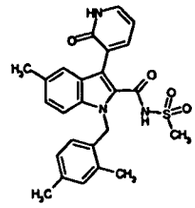
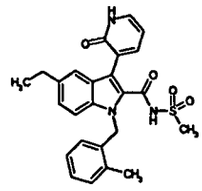
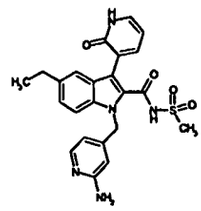
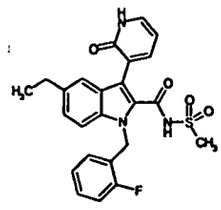
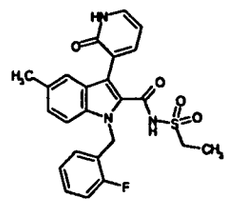
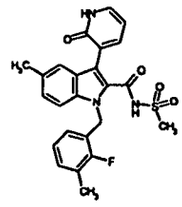
Compound No.	STRUCTURE	M+H

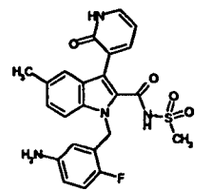
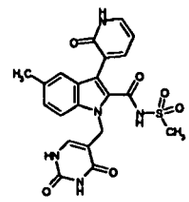
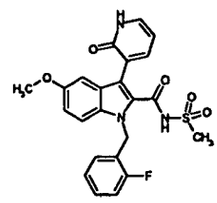
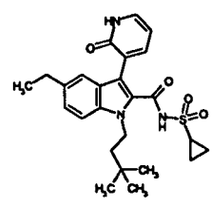
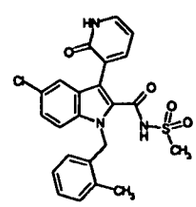
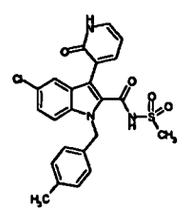
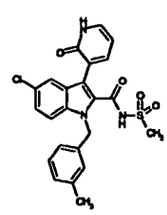
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2		394.9
3		405.8
4		406.9
5		408.9
6		410.9
7		420.9

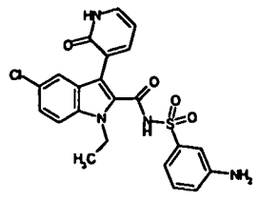
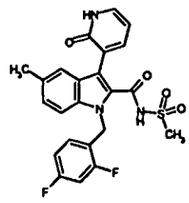
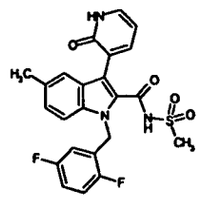
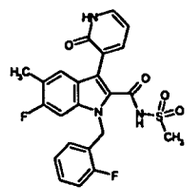
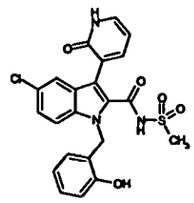
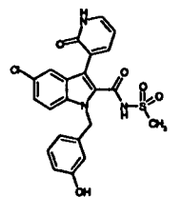
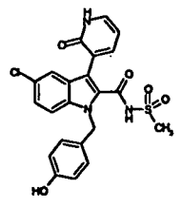
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9		426.9
10		428.5
11		434.9
12		444.6
13		446.9
14		448.9

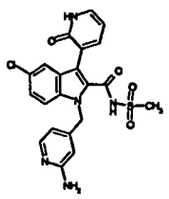
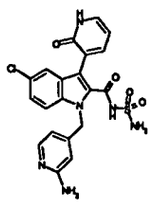
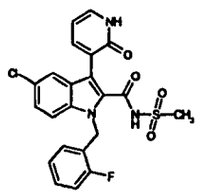
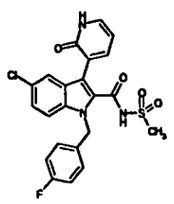
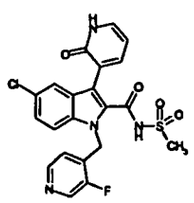
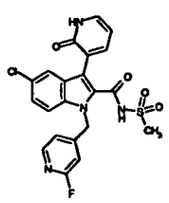
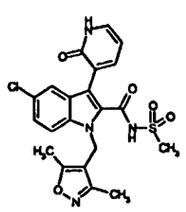
15		450.5
16		452.9
17		454.5
18		454.6
19		455.5
20		456.9
21		457.9

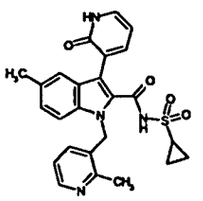
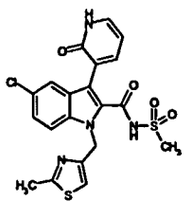
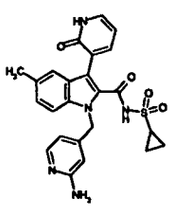
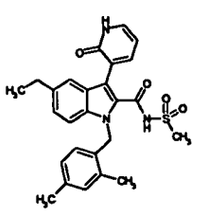
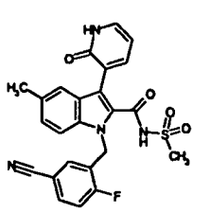
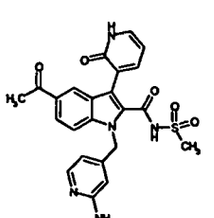
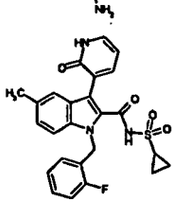
22		457.9
23		457.9
24		458.6
25		461.9
26		462.5
27		463.0
28		464.0

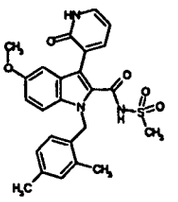
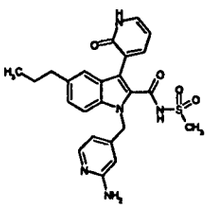
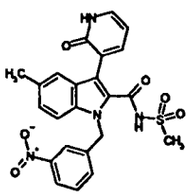
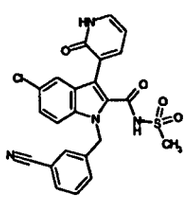
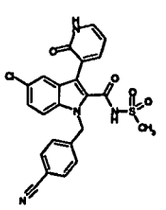
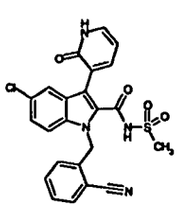
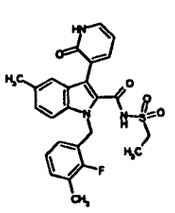
29		464.0
30		464.6
31		464.6
32		466.5
33		468.5
34		468.5
35		468.5

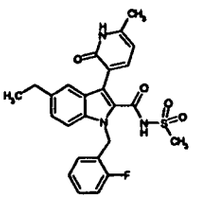
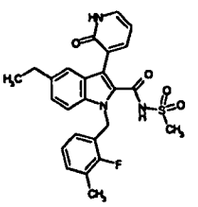
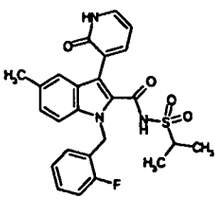
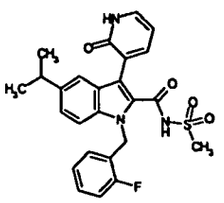
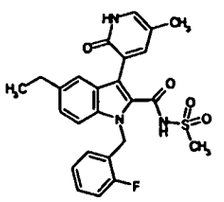
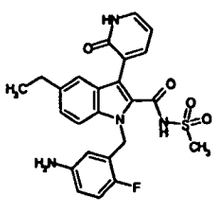
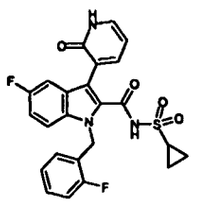
36		469.5
37		470.5
38		470.5
39		470.6
40		471.0
41		471.0
42		471.0

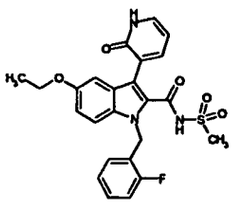
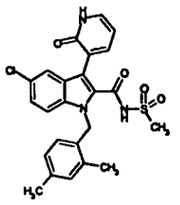
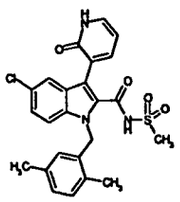
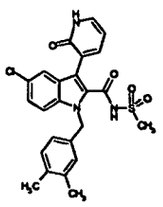
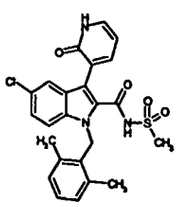
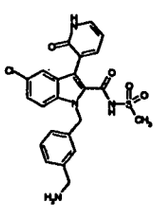
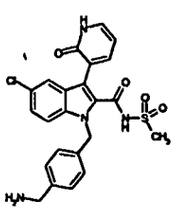
43		471.9
44		472.5
45		472.5
46		472.5
47		472.9
48		472.9
49		472.9

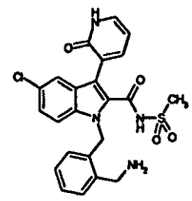
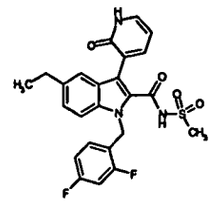
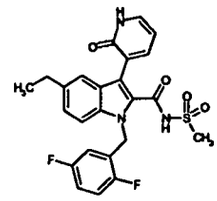
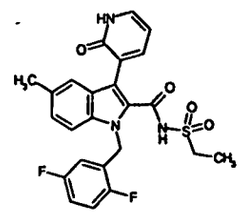
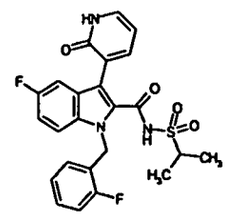
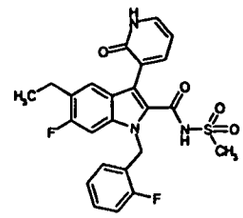
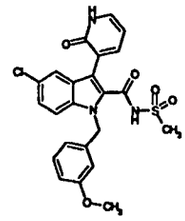
50		472.9
51		473.9
52		474.9
53		474.9
54		475.9
55		475.9
56		475.9

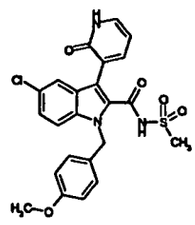
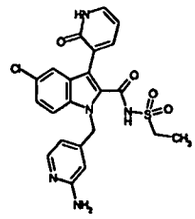
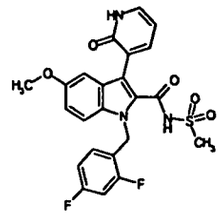
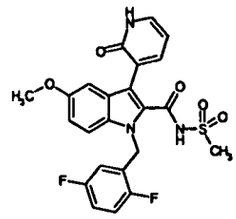
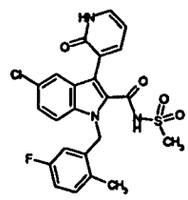
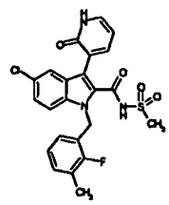
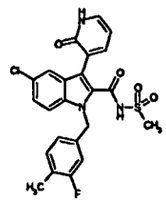
57		477.6
58		478.0
59		478.5
60		478.6
61		479.5
62		480.5
63		480.5

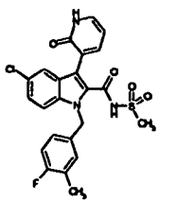
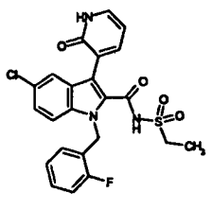
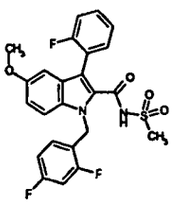
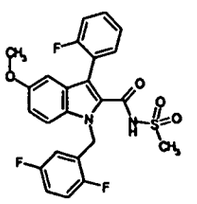
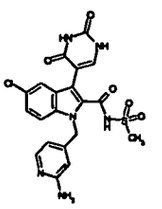
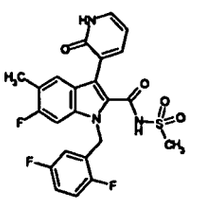
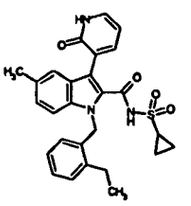
64		480.6
65		480.6
66		481.5
67		481.9
68		481.9
69		481.9
70		482.6

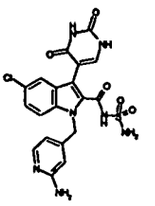
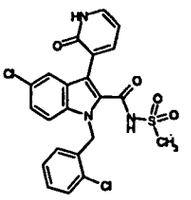
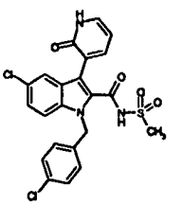
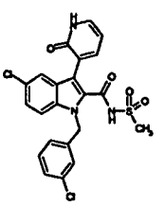
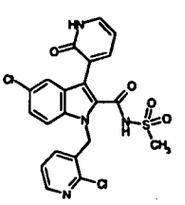
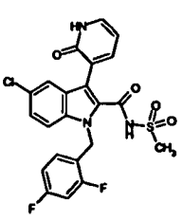
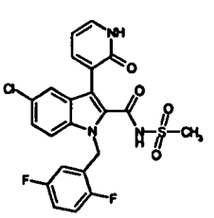
71		482.6
72		482.6
73		482.6
74		482.6
75		482.6
76		483.5
77		484.5

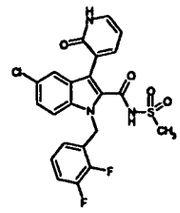
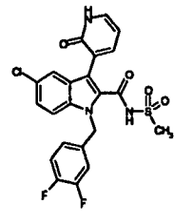
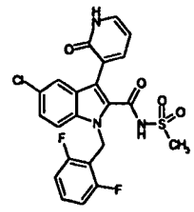
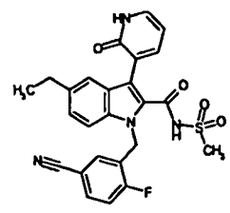
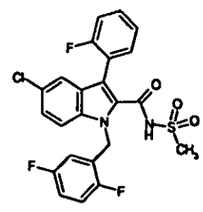
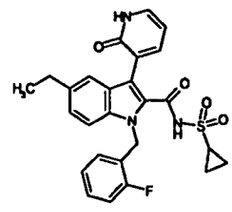
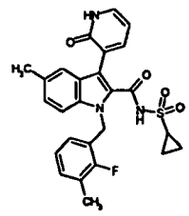
78		484.5
79		485.0
80		485.0
81		485.0
82		485.0
83		486.0
84		486.0

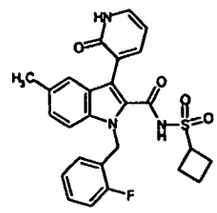
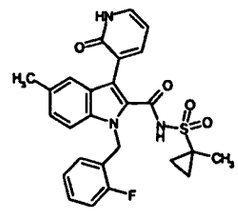
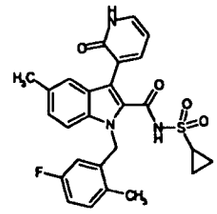
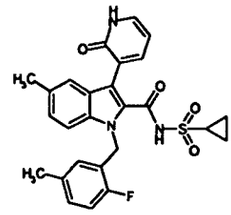
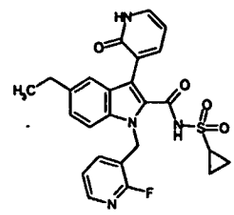
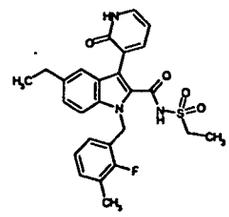
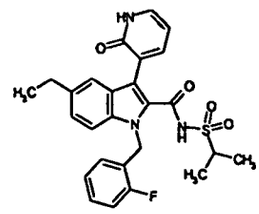
85		486.0
86		486.5
87		486.5
88		486.5
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90		486.5
91		486.9

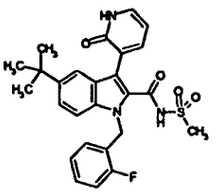
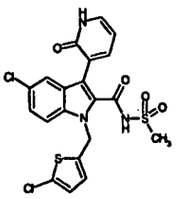
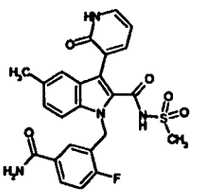
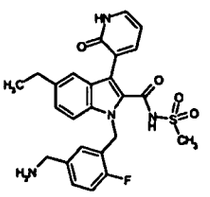
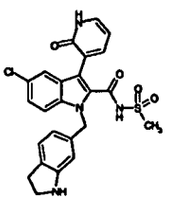
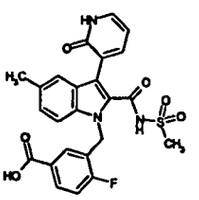
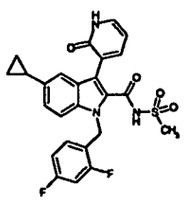
92		486.9
93		487.0
94		488.5
95		488.5
96		488.9
97		488.9
98		488.9

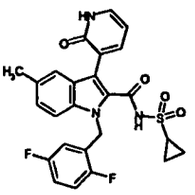
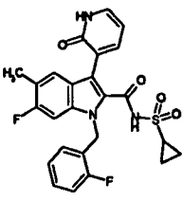
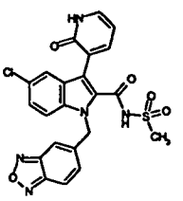
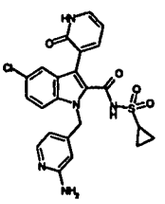
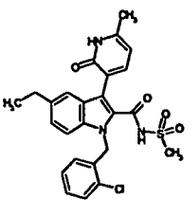
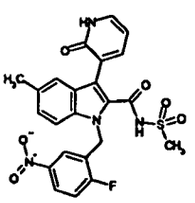
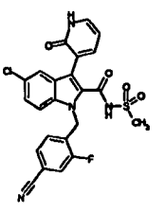
99		488.9
100		488.9
101		489.5
102		489.5
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104		490.5
105		490.6

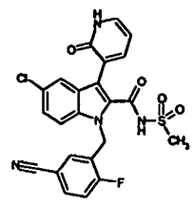
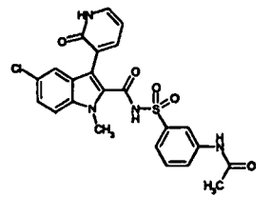
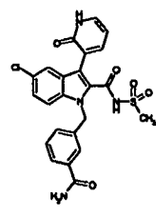
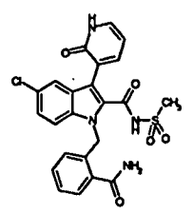
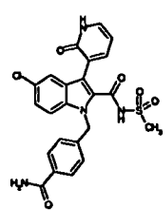
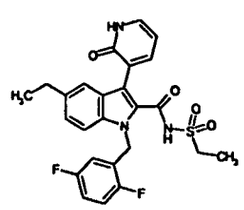
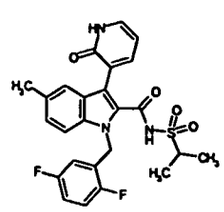
106		490.9
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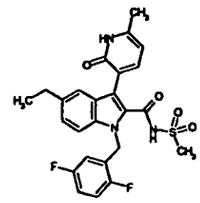
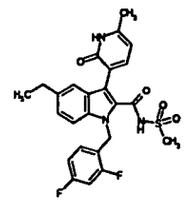
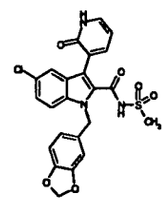
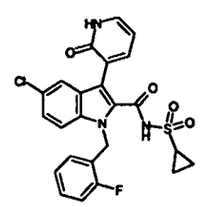
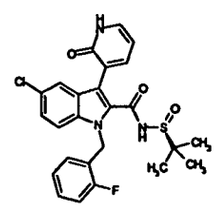
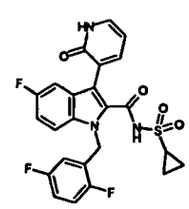
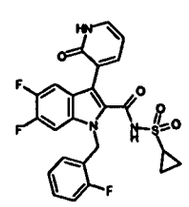
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116		493.5
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119		494.6

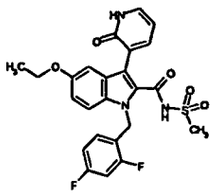
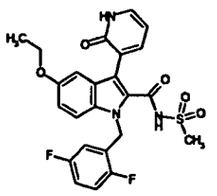
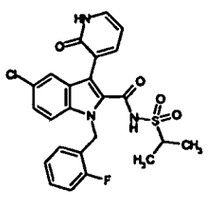
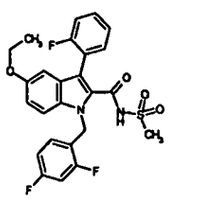
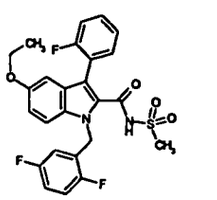
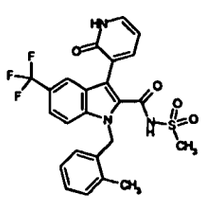
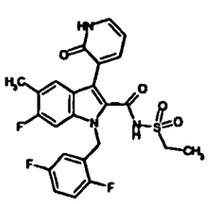
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123		494.6
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126		496.6

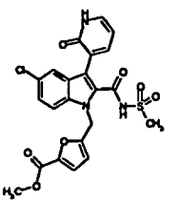
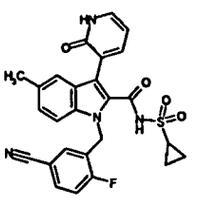
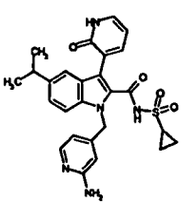
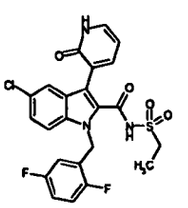
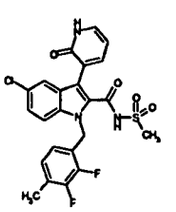
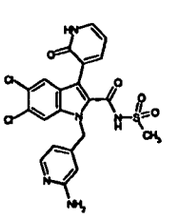
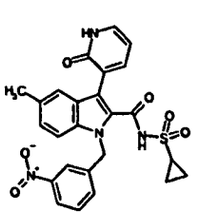
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133		498.5

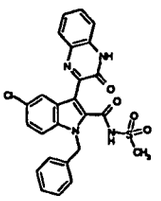
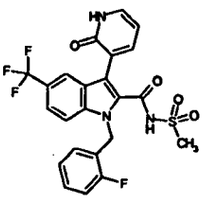
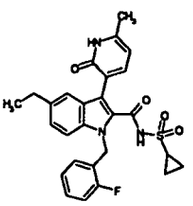
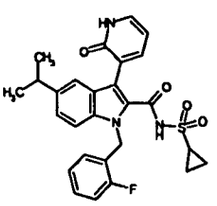
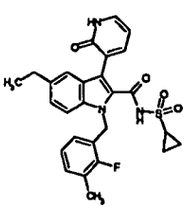
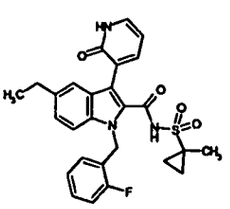
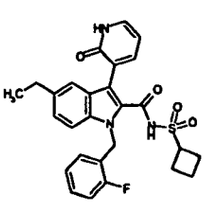
134		498.5
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140		499.9

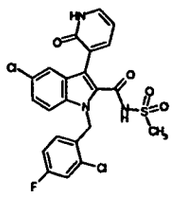
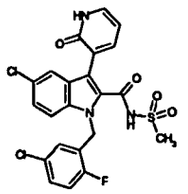
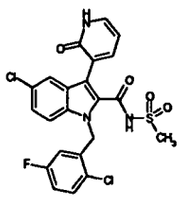
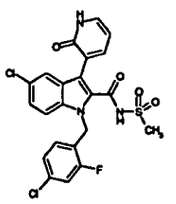
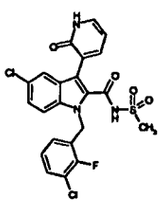
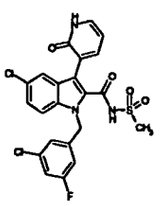
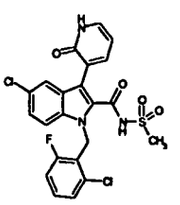
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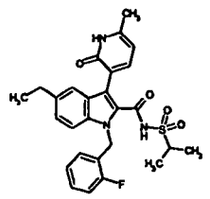
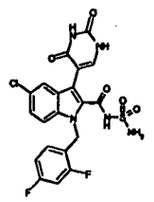
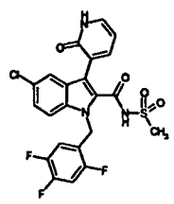
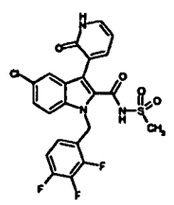
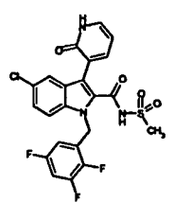
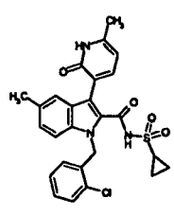
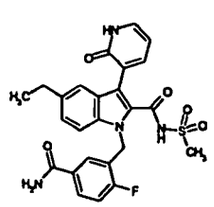
148		500.5
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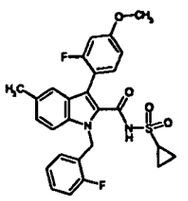
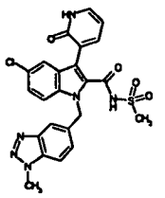
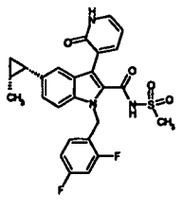
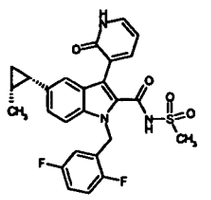
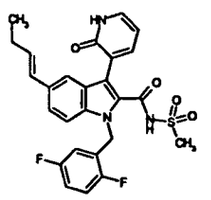
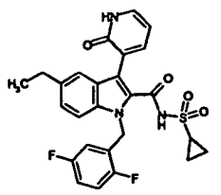
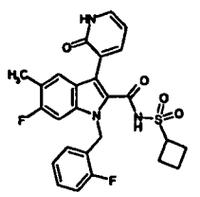
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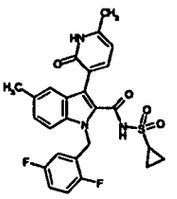
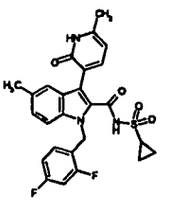
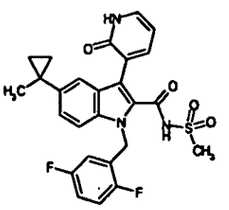
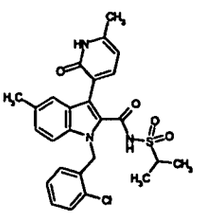
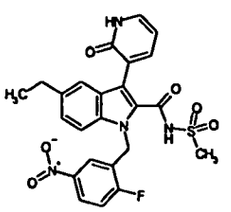
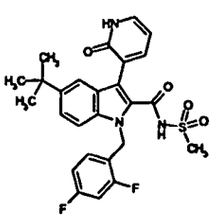
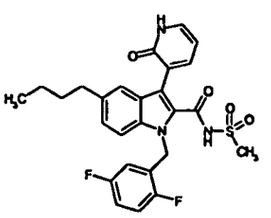
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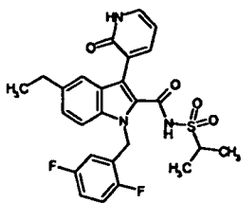
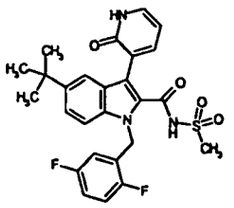
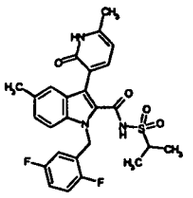
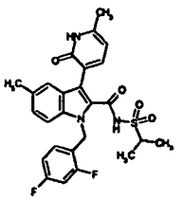
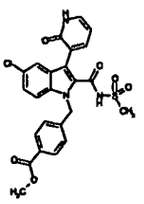
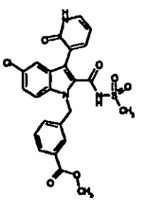
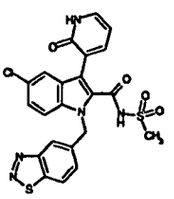
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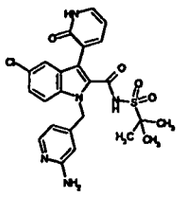
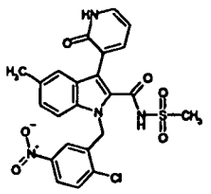
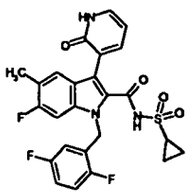
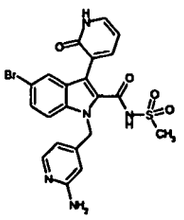
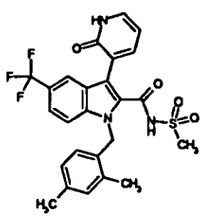
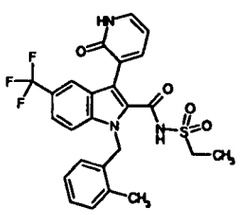
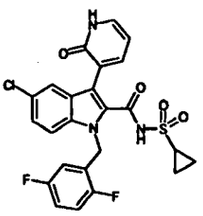
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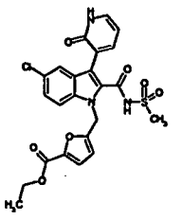
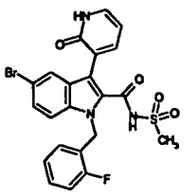
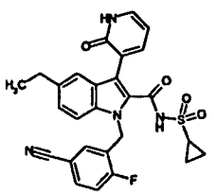
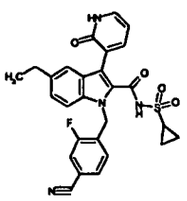
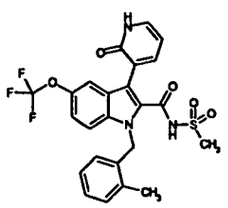
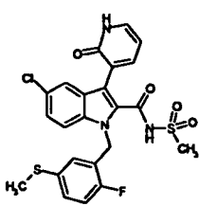
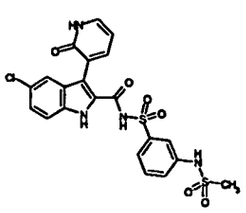
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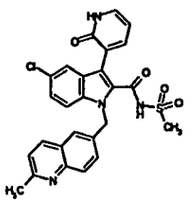
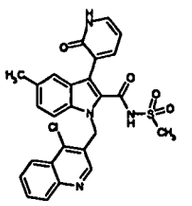
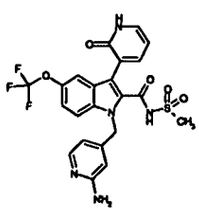
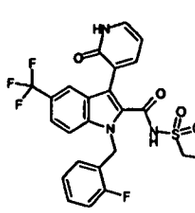
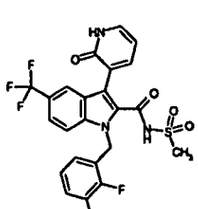
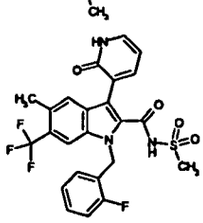
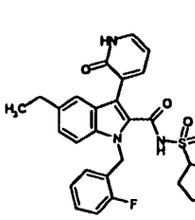
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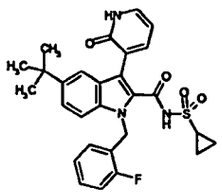
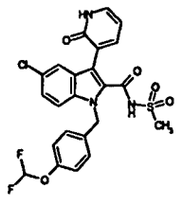
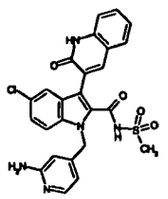
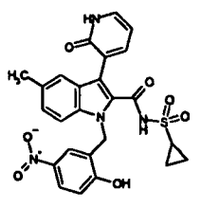
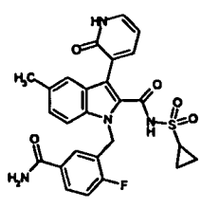
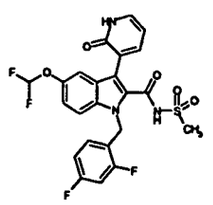
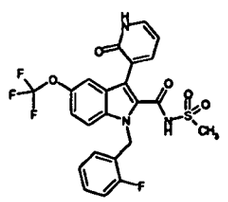
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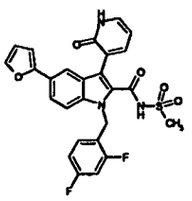
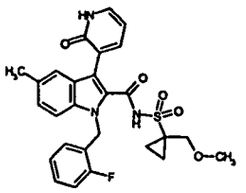
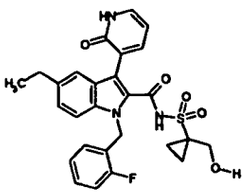
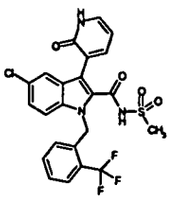
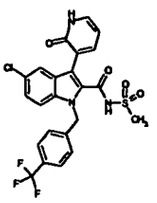
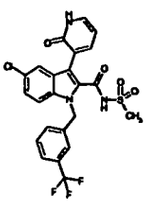
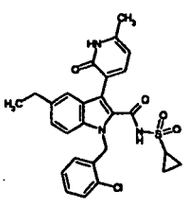
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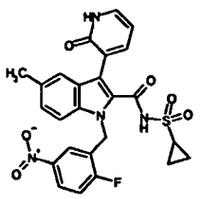
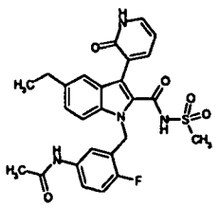
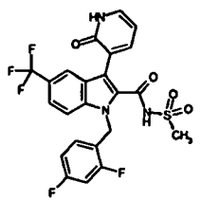
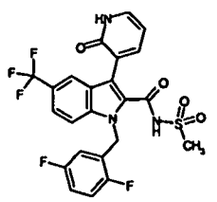
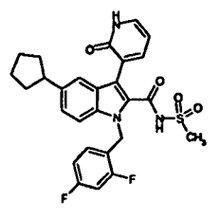
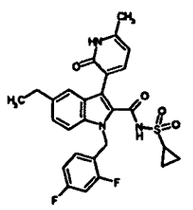
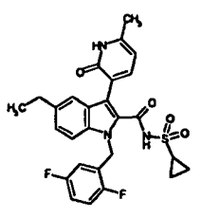
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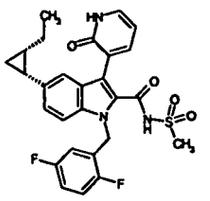
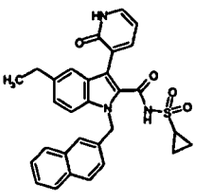
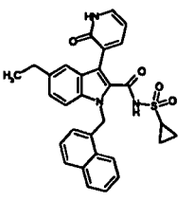
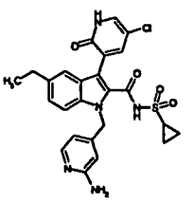
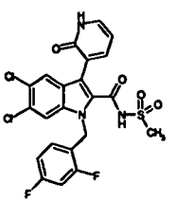
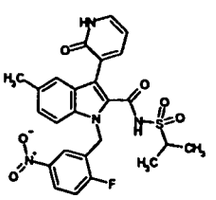
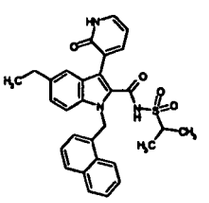
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221		519.6
222		520.5
223		521.0
224		522.0

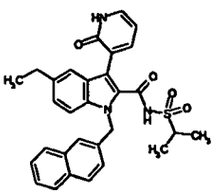
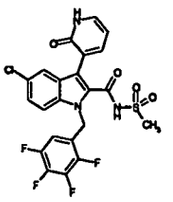
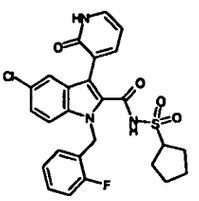
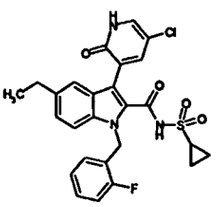
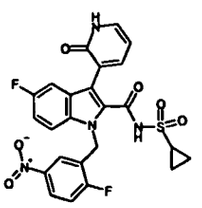
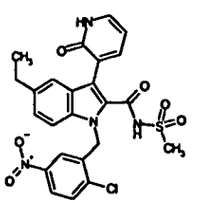
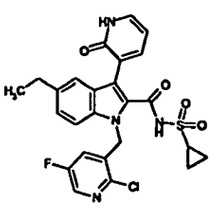
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228		522.5
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230		522.5
231		522.6

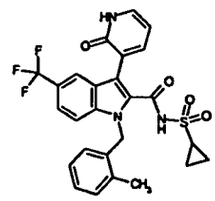
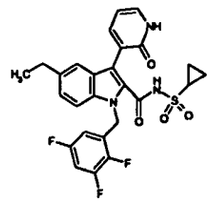
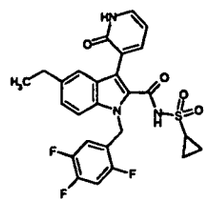
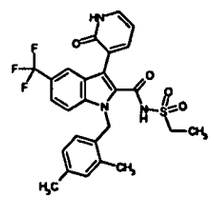
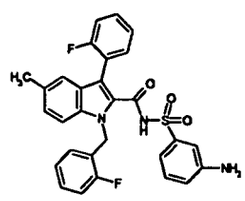
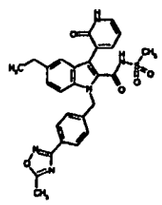
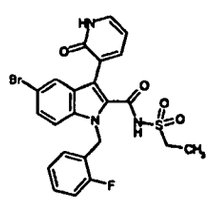
232		522.6
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235		523.5
236		523.6
237		524.5
238		524.5

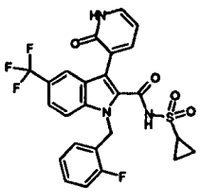
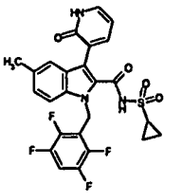
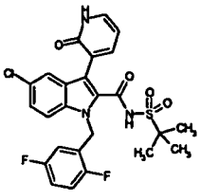
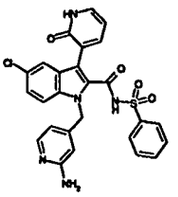
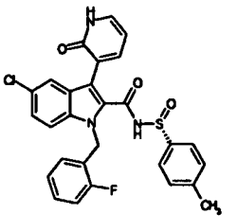
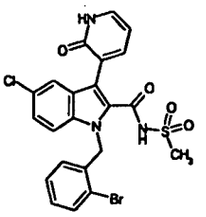
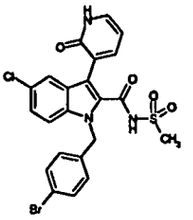
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242		524.9
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245		525.0

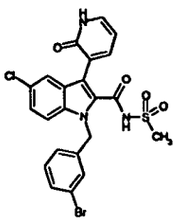
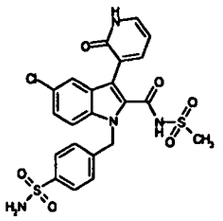
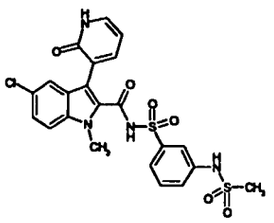
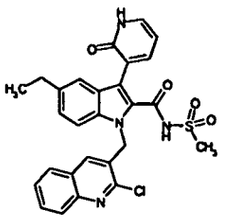
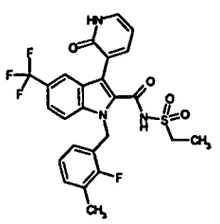
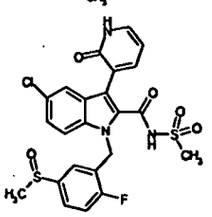
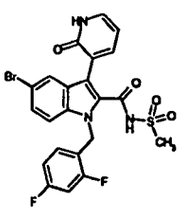
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249		526.5
250		526.6
251		526.6
252		526.6

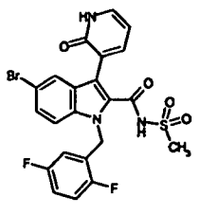
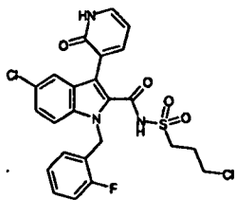
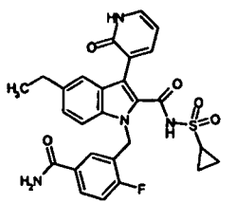
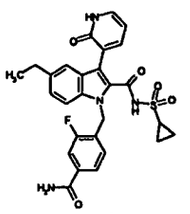
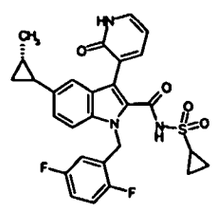
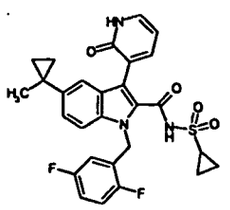
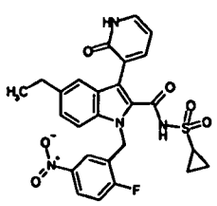
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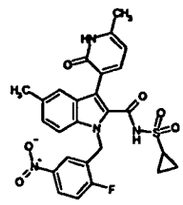
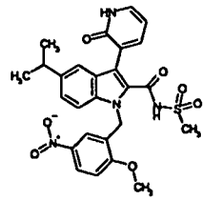
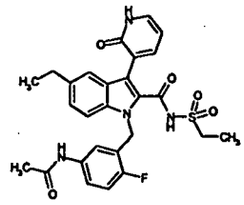
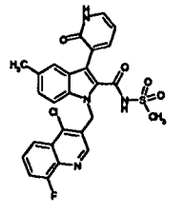
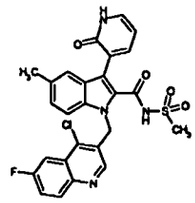
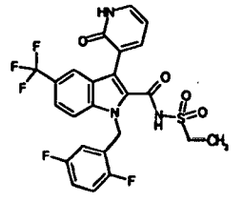
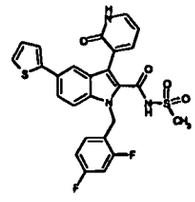
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263		529.0
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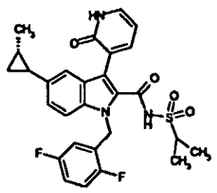
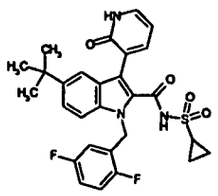
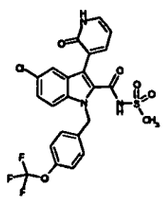
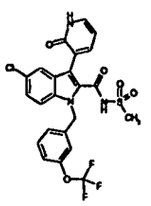
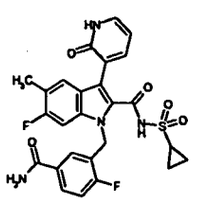
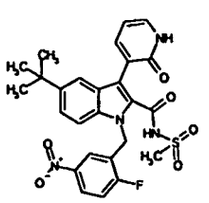
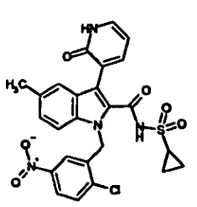
267		530.5
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270		532.6
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273		533.4

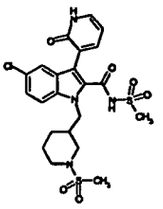
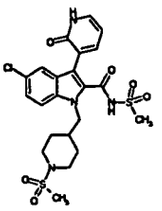
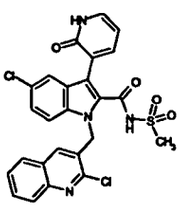
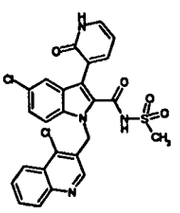
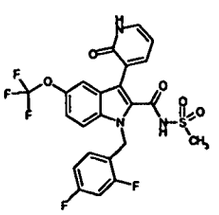
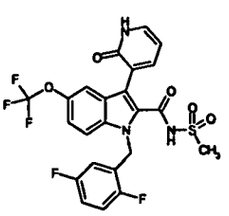
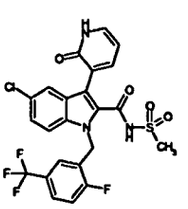
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277		535.0
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280		535.8

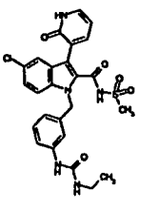
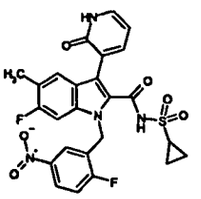
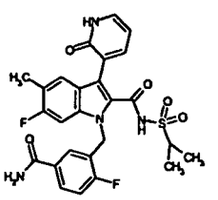
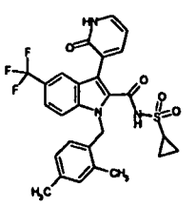
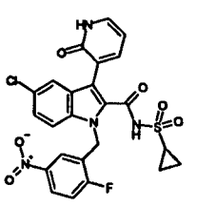
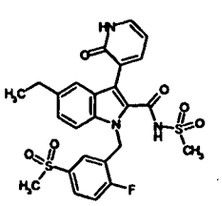
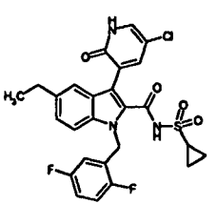
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284		536.0
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287		537.4

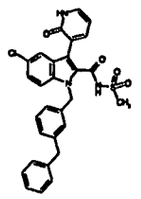
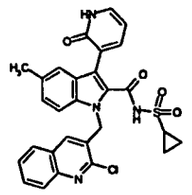
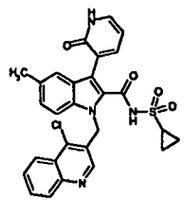
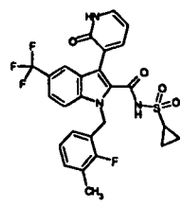
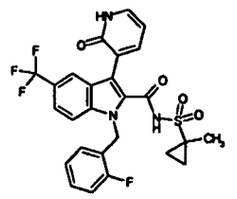
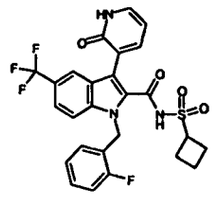
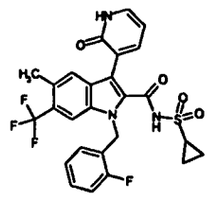
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294		539.6

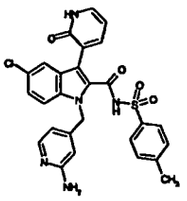
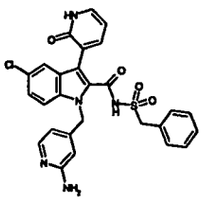
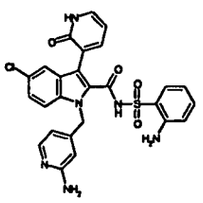
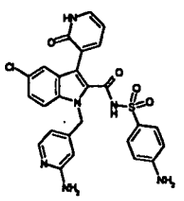
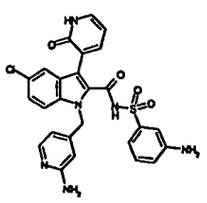
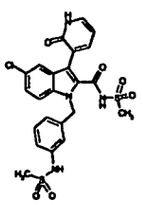
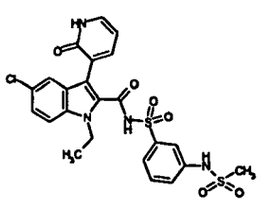
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301		540.6

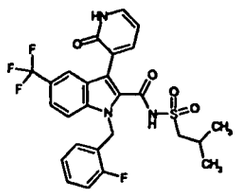
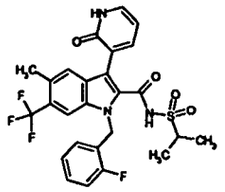
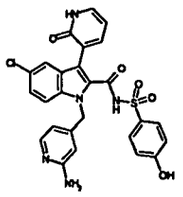
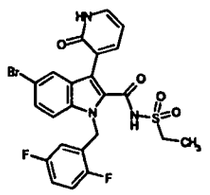
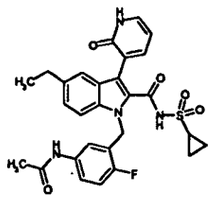
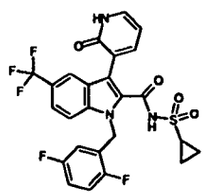
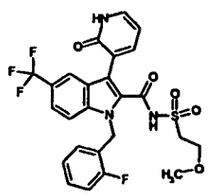
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308		542.0

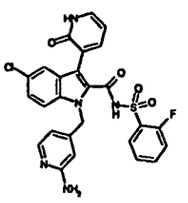
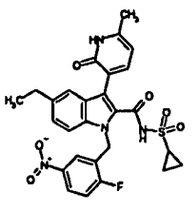
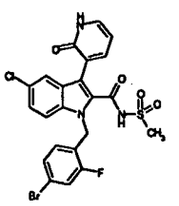
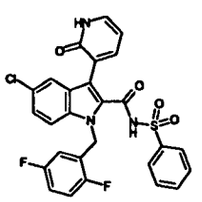
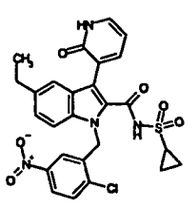
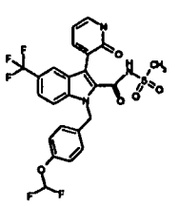
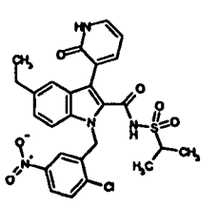
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315		542.9

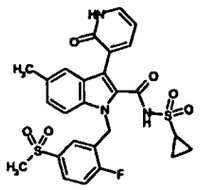
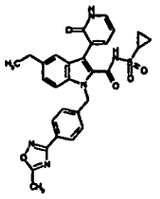
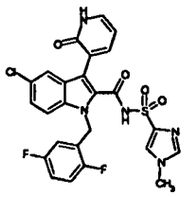
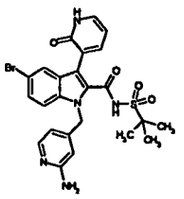
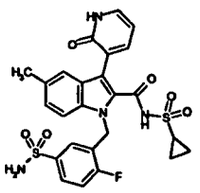
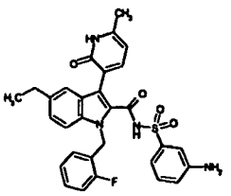
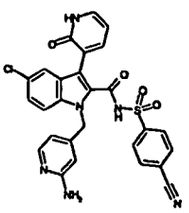
316		543.0
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319		544.6
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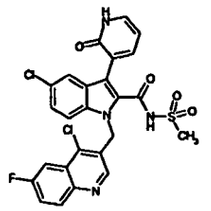
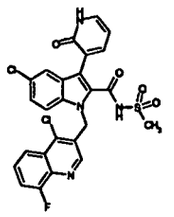
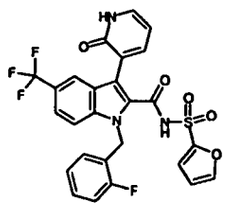
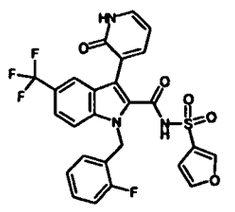
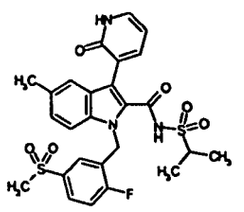
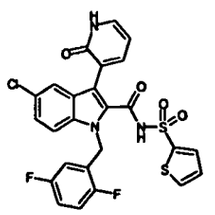
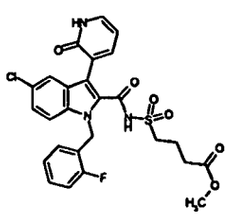
323		547.0
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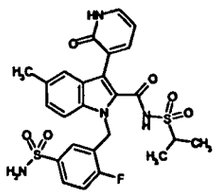
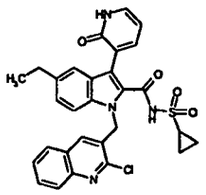
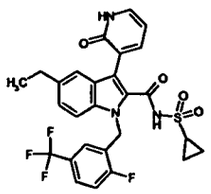
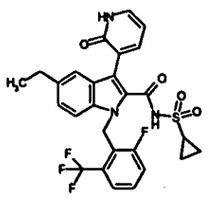
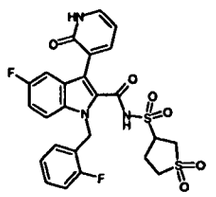
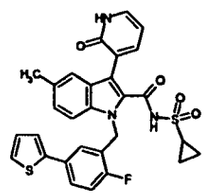
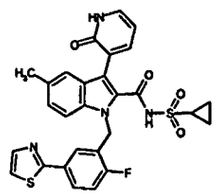
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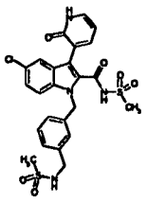
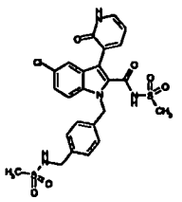
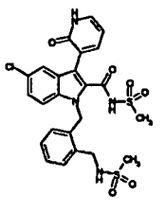
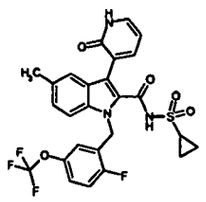
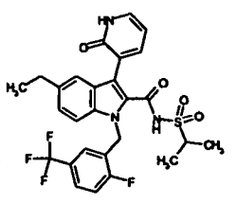
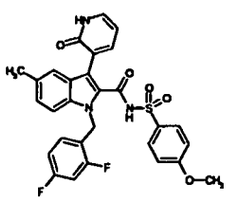
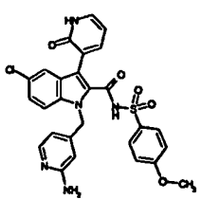
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340		551.4
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343		552.5

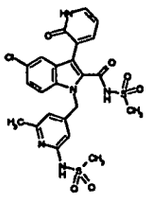
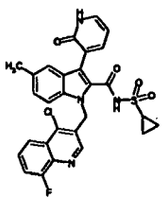
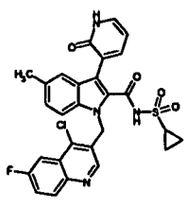
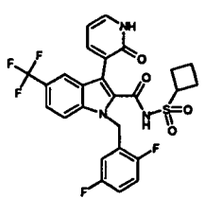
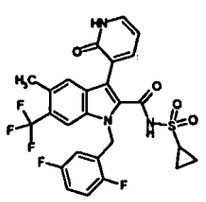
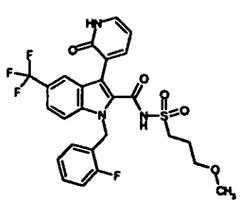
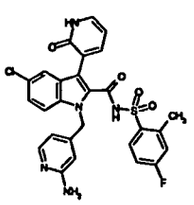
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347		555.0
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349		556.5
350		558.0

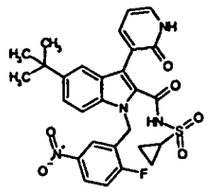
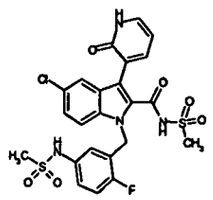
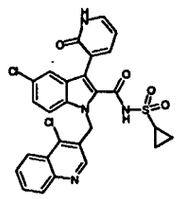
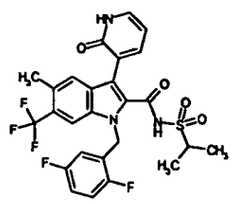
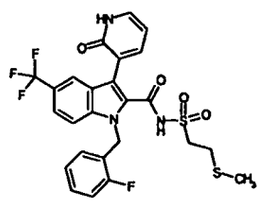
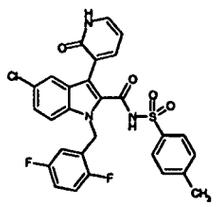
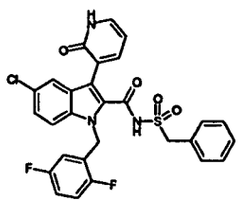
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354		559.5
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357		560.0

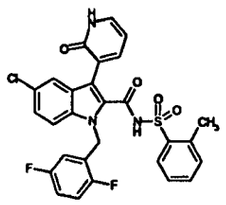
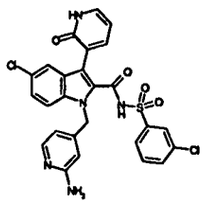
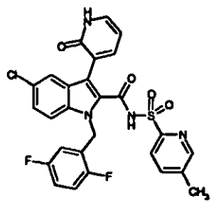
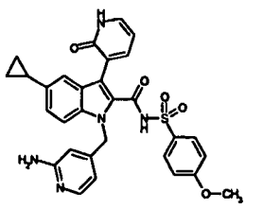
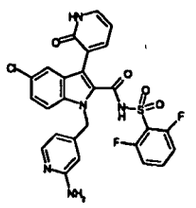
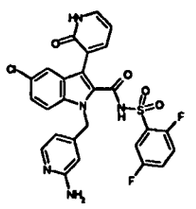
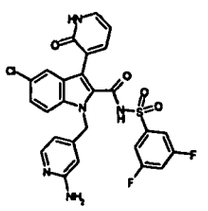
358		560.4
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361		560.5
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363		561.0
364		561.0

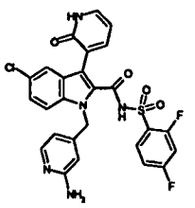
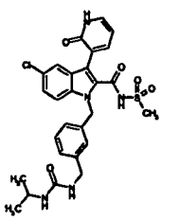
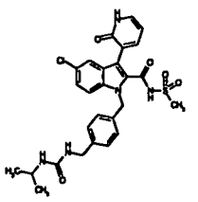
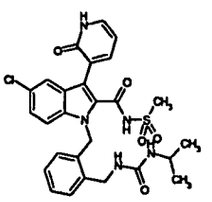
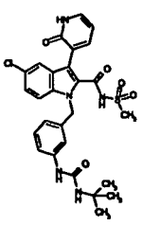
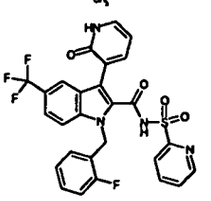
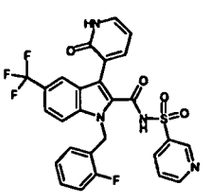
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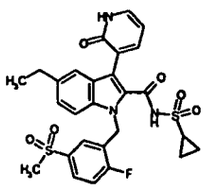
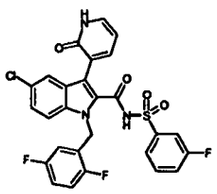
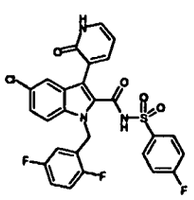
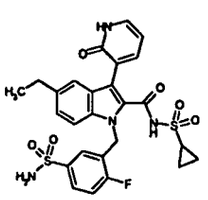
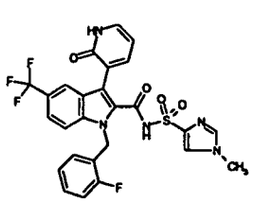
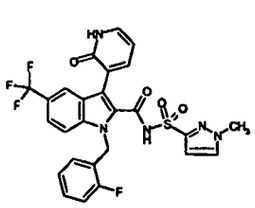
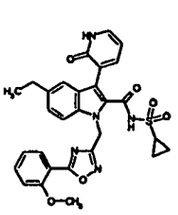
372		564.1
373		564.1
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375		564.5
376		564.6
377		564.6
378		565.0

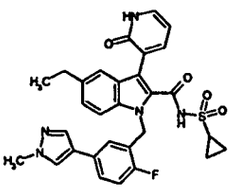
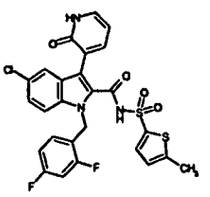
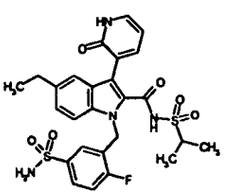
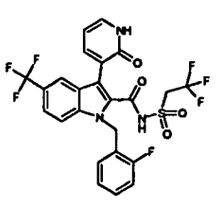
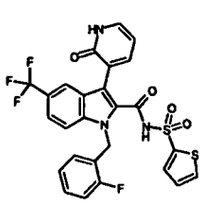
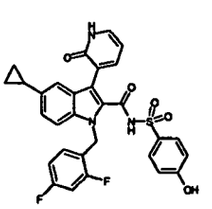
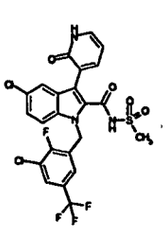
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380		566.0
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384		566.5
385		567.0

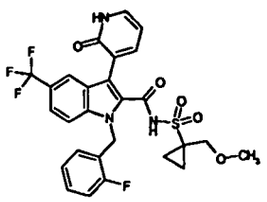
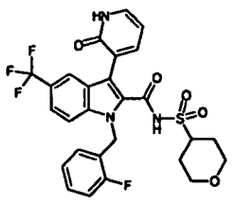
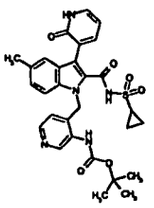
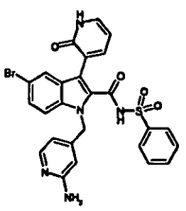
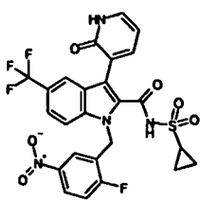
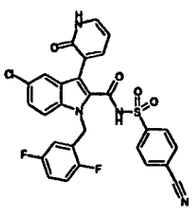
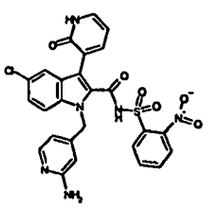
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388		568.5
389		568.5
390		568.6
391		569.0
392		569.0

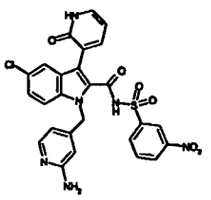
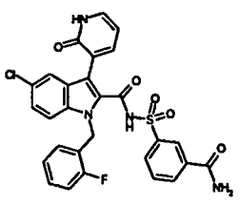
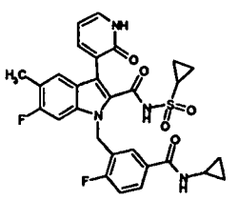
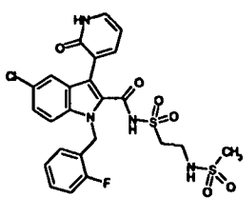
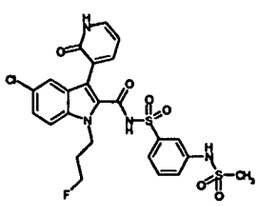
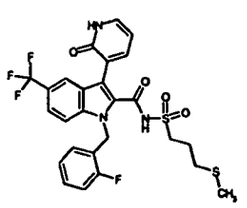
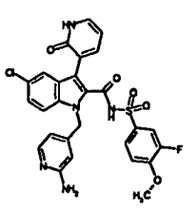
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394		569.4
395		570.0
396		570.6
397		571.0
398		571.0
399		571.0

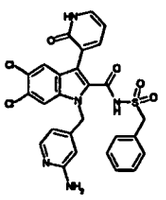
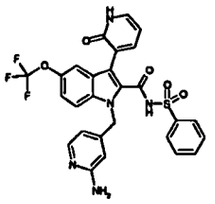
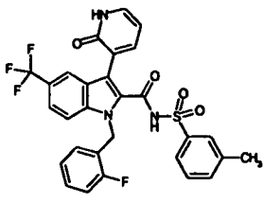
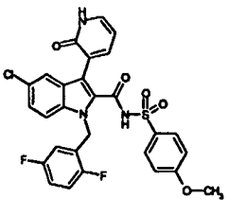
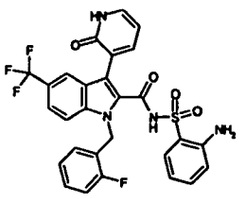
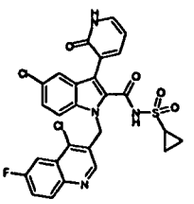
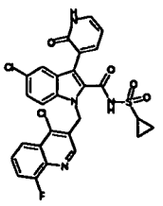
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401		571.1
402		571.1
403		571.1
404		571.1
405		571.5
406		571.5

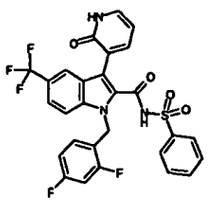
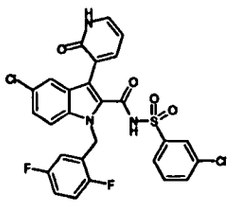
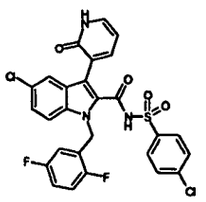
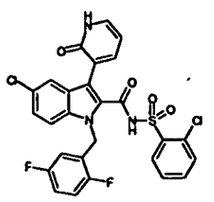
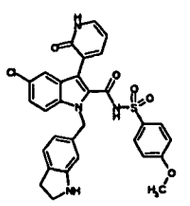
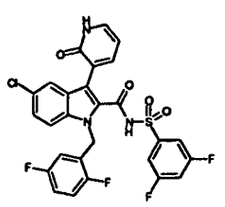
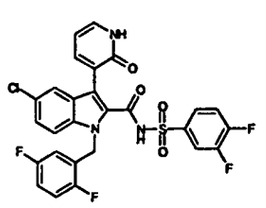
407		572.7
408		573.0
409		573.0
410		573.6
411		574.5
412		574.5
413		574.6

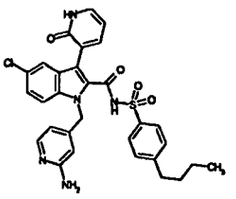
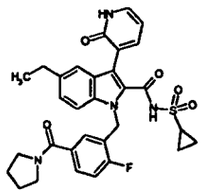
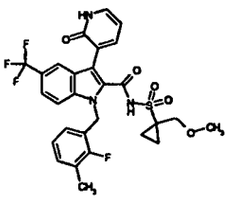
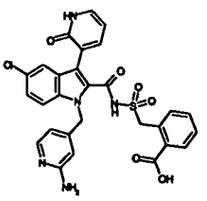
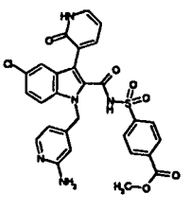
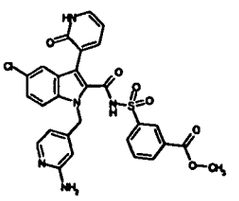
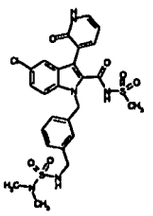
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416		575.7
417		576.5
418		576.6
419		576.6
420		577.4

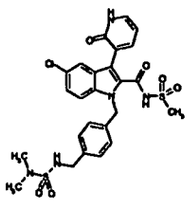
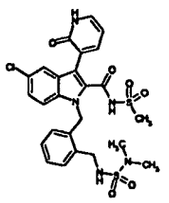
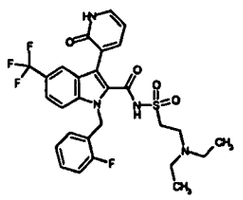
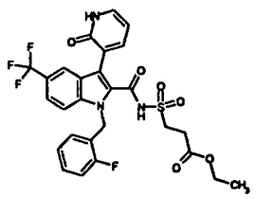
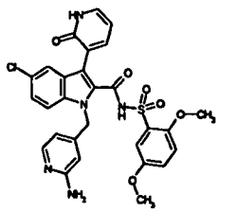
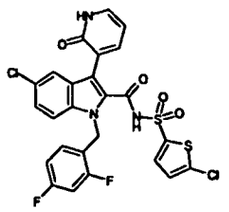
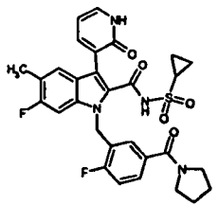
421		578.6
422		578.6
423		578.7
424		579.4
425		579.5
426		580.0
427		580.0

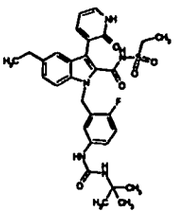
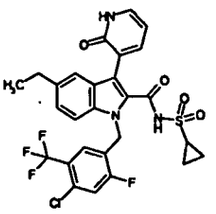
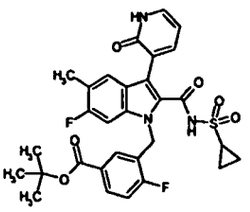
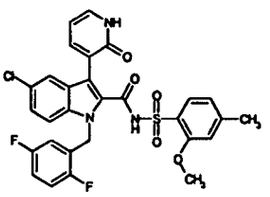
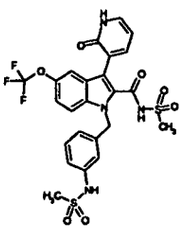
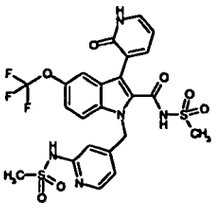
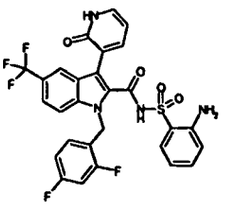
428		580.0
429		580.0
430		581.6
431		582.0
432		582.0
433		582.6
434		583.0

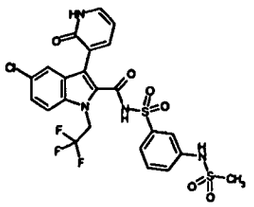
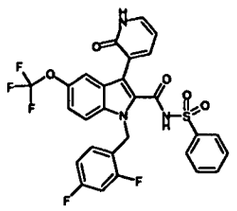
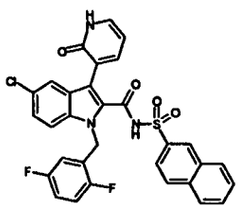
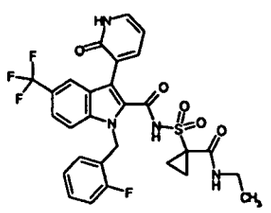
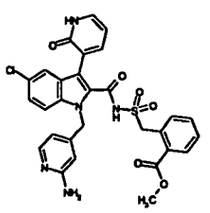
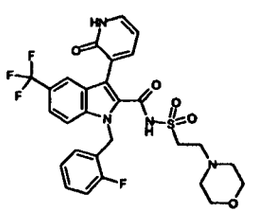
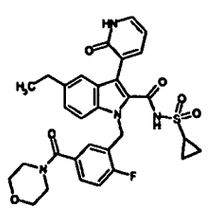
435		583.5
436		584.6
437		584.6
438		585.0
439		585.6
440		586.4
441		586.4

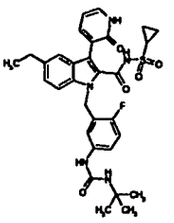
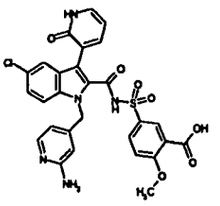
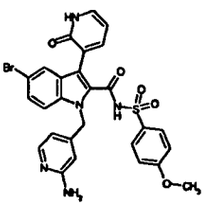
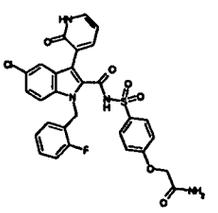
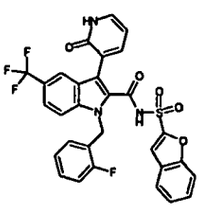
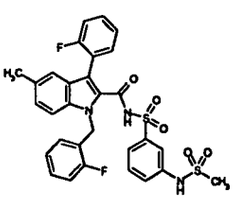
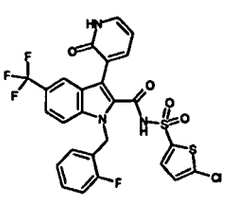
442		588.5
443		589.4
444		589.4
445		589.4
446		590.1
447		591.0
448		591.0

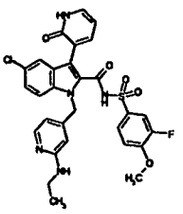
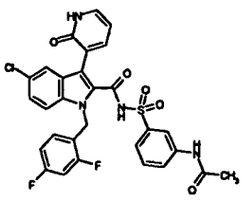
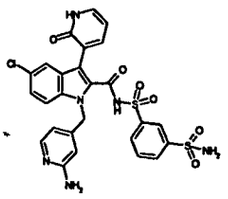
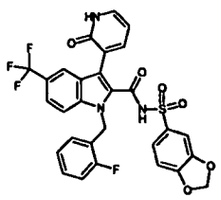
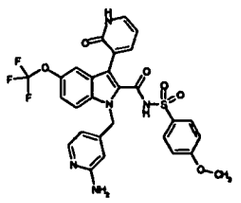
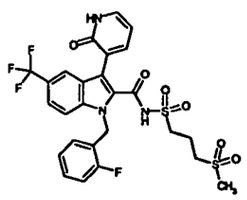
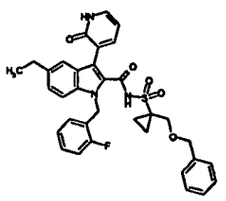
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452		593.0
453		593.0
454		593.0
455		593.1

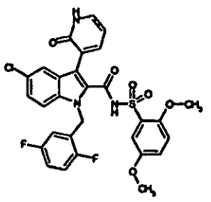
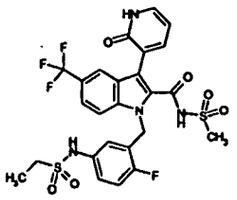
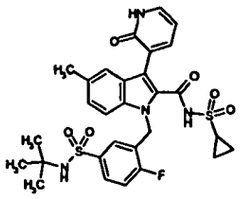
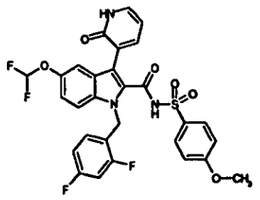
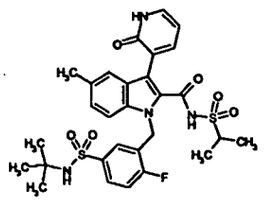
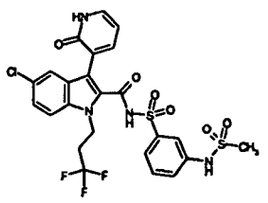
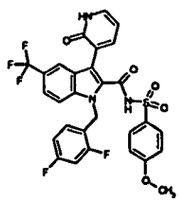
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457		593.1
458		593.6
459		594.6
460		595.1
461		595.4
462		595.6

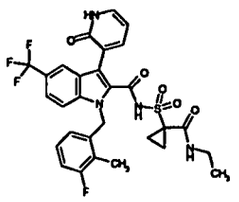
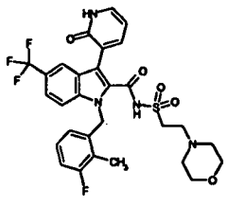
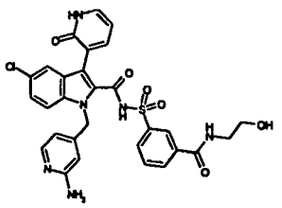
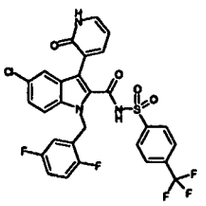
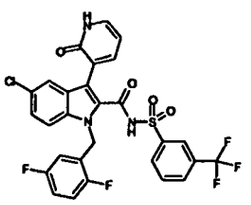
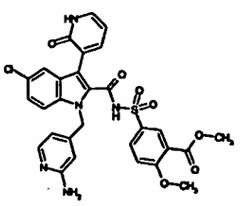
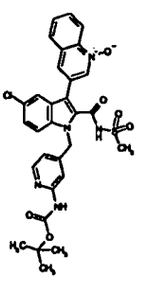
463		596.7
464		597.0
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466		599.0
467		599.6
468		600.6
469		603.5

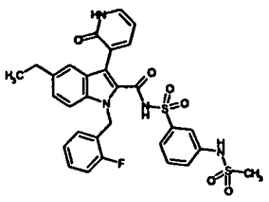
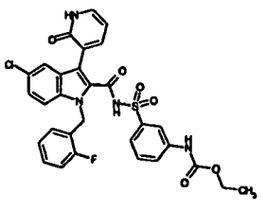
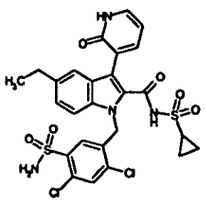
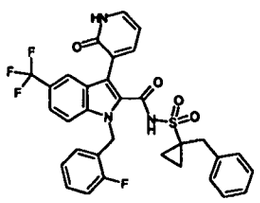
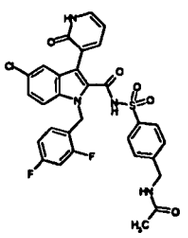
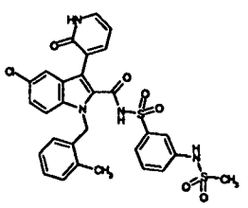
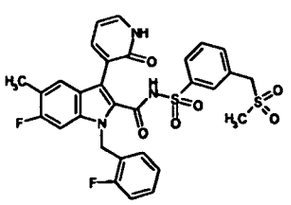
470		604.0
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472		605.0
473		605.6
474		607.1
475		607.6
476		607.7

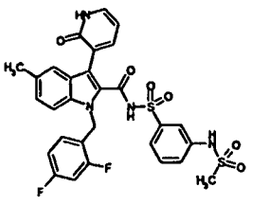
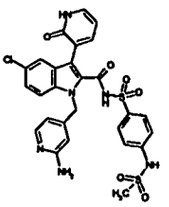
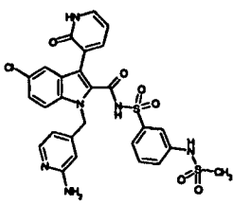
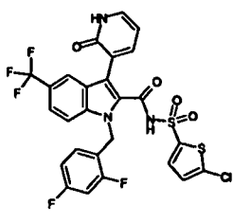
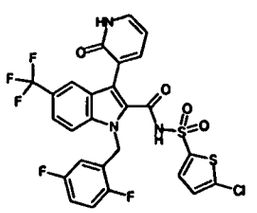
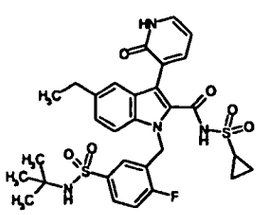
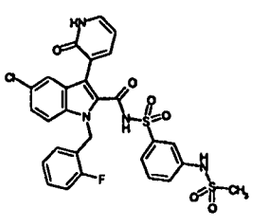
477		608.7
478		609.0
479		609.5
480		610.0
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483		611.0

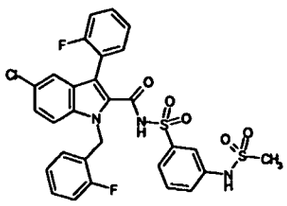
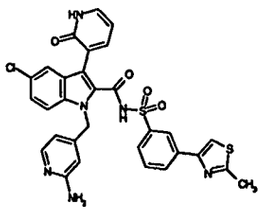
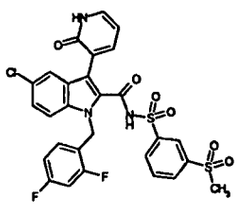
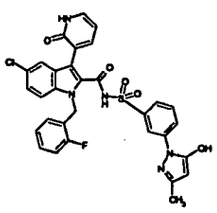
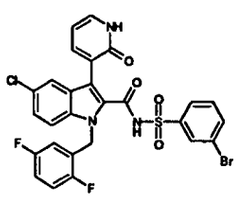
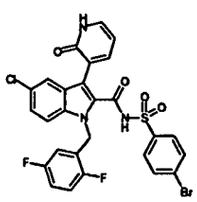
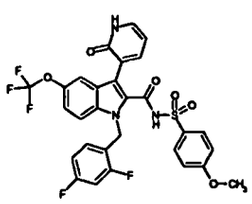
484		611.1
485		612.0
486		614.1
487		614.5
488		614.6
489		614.6
490		614.7

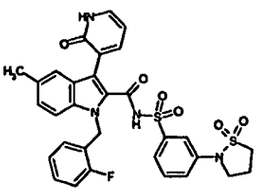
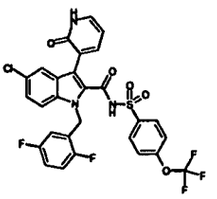
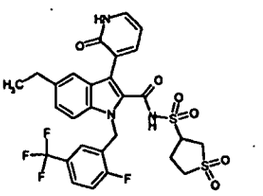
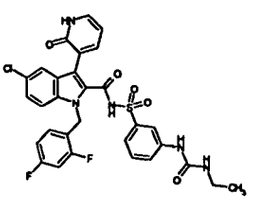
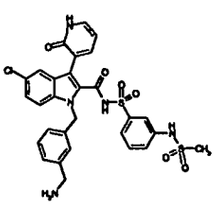
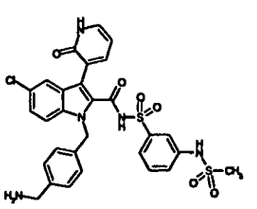
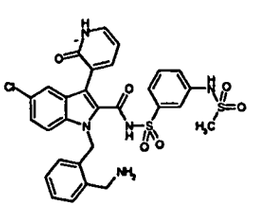
491		615.0
492		615.6
493		615.7
494		616.6
495		617.7
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497		618.6

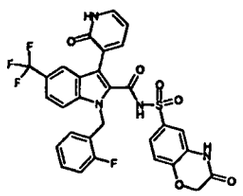
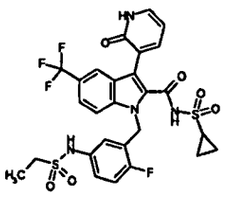
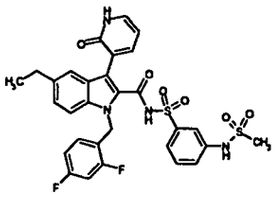
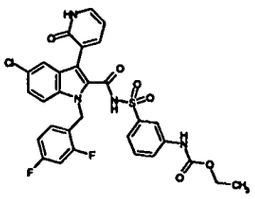
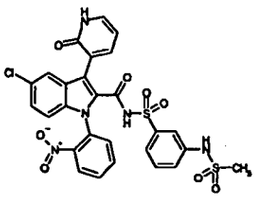
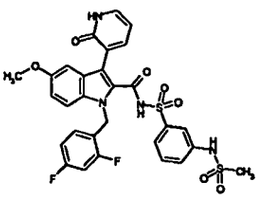
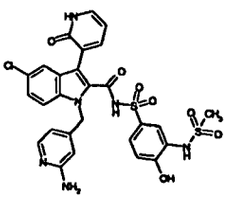
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506		624.1
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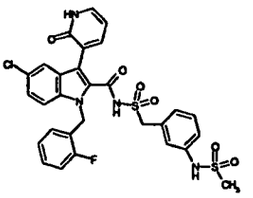
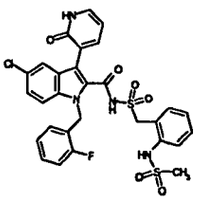
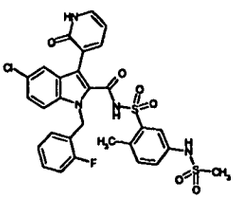
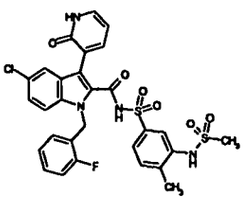
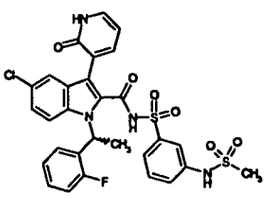
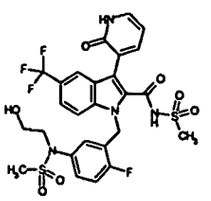
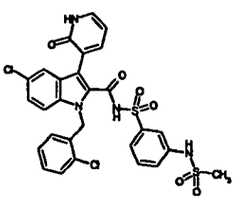
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518		630.1

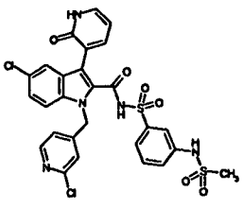
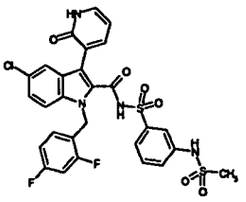
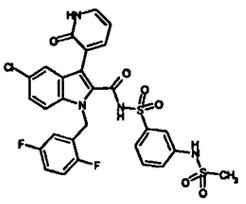
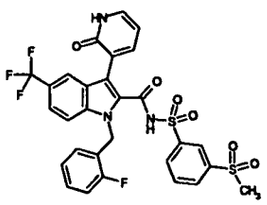
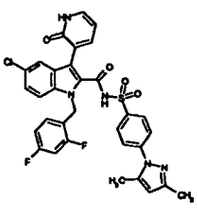
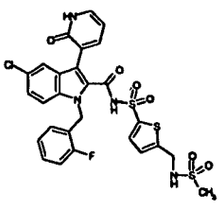
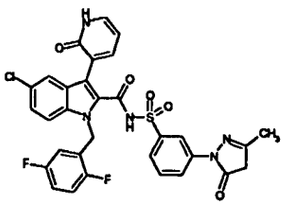
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525		634.6

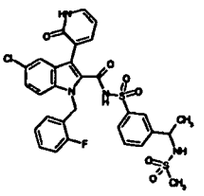
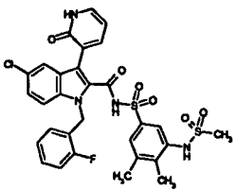
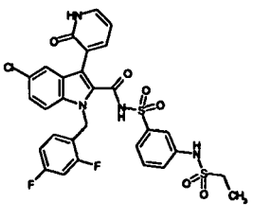
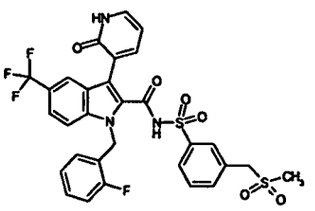
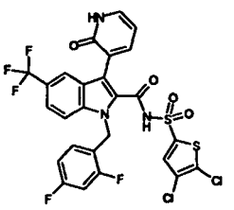
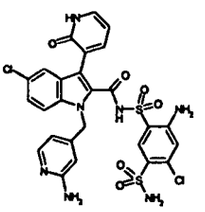
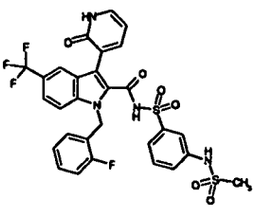
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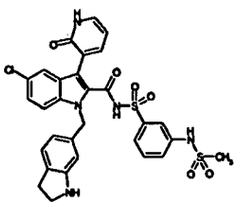
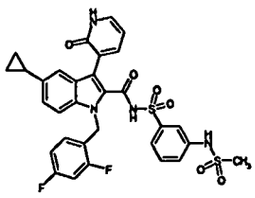
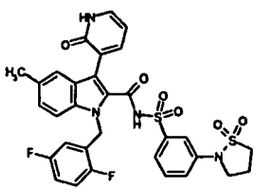
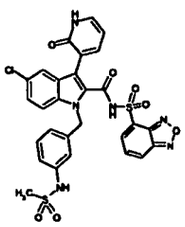
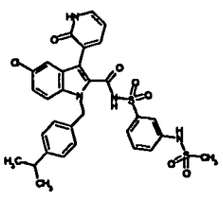
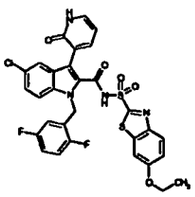
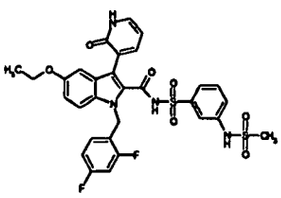
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539		644.1

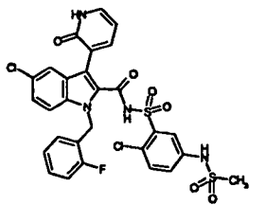
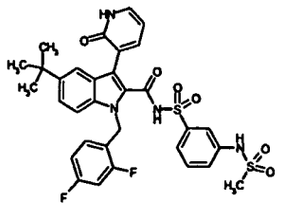
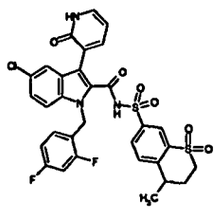
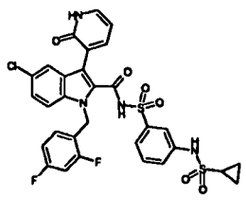
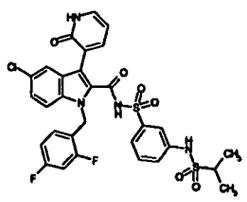
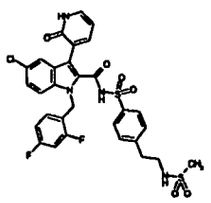
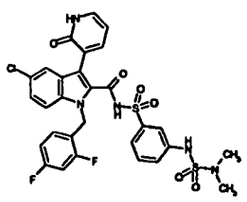
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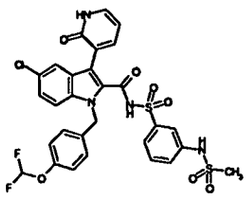
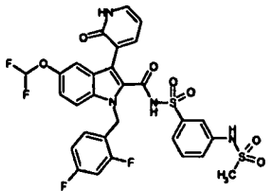
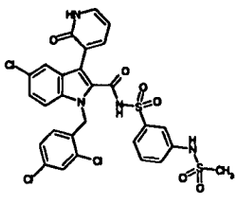
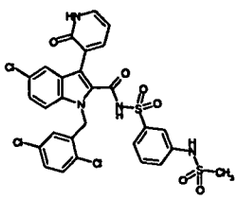
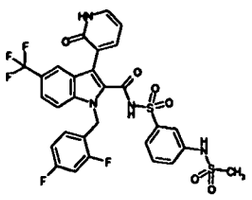
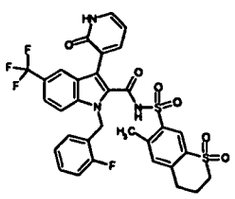
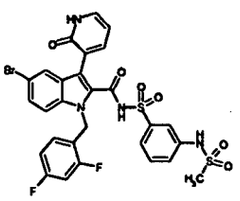
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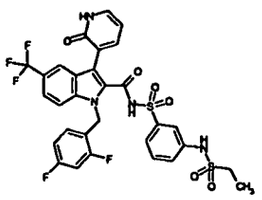
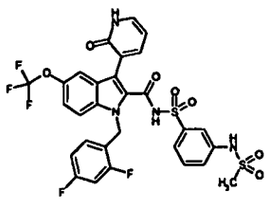
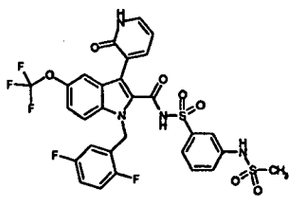
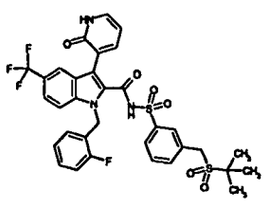
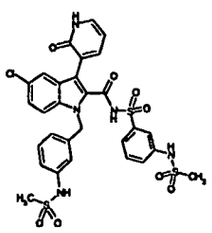
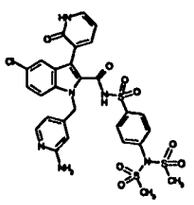
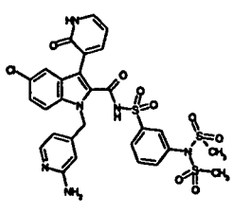
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553		651.1

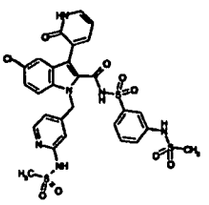
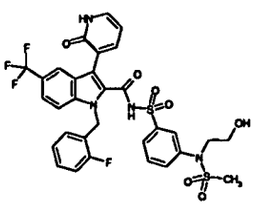
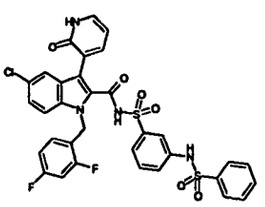
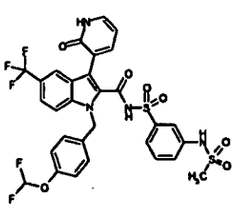
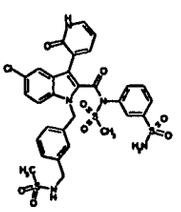
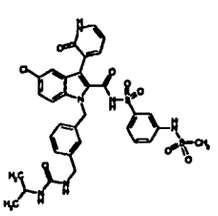
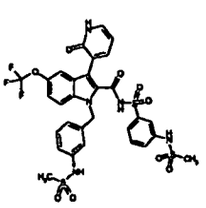
561		658.1
562		658.1
563		662.1
564		662.7
565		663.4
566		663.5
567		663.6

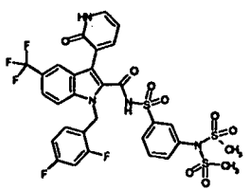
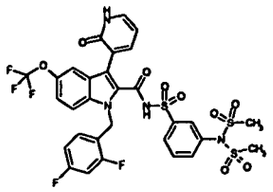
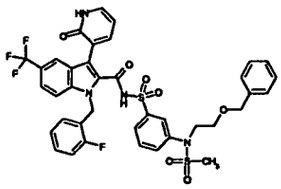
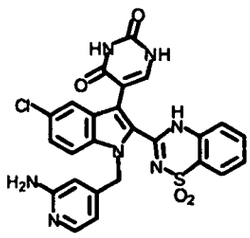
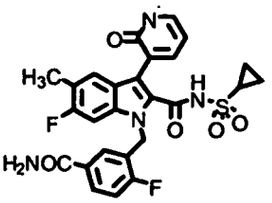
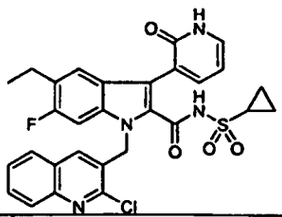
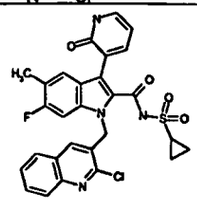
554		653.2
555		653.7
556		653.7
557		654.1
558		654.2
559		656.1
560		657.7

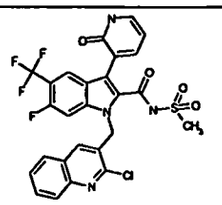
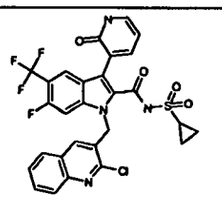
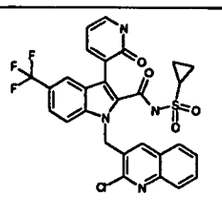
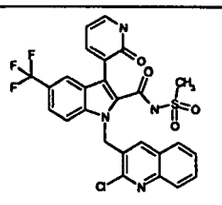
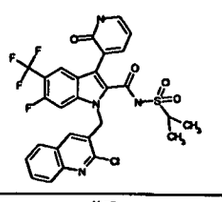
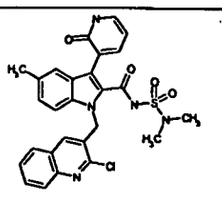
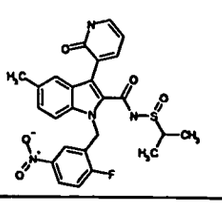
568		664.5
569		669.7
570		673.1
571		674.1
572		676.1
573		676.1
574		677.1

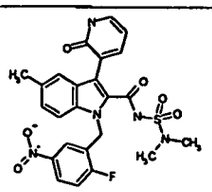
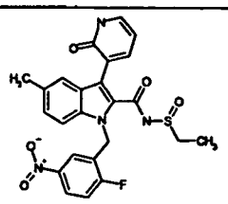
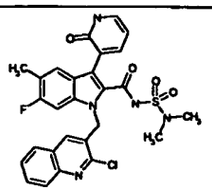
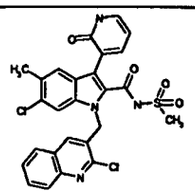
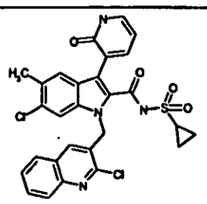
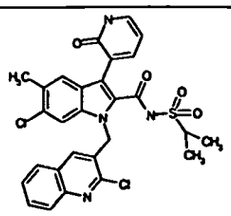
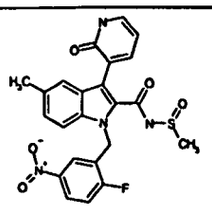
575		678.1
576		679.6
577		681.0
578		681.0
579		681.6
580		688.7
581		692.5

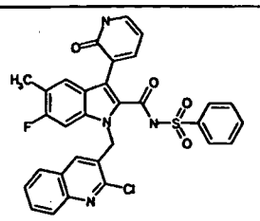
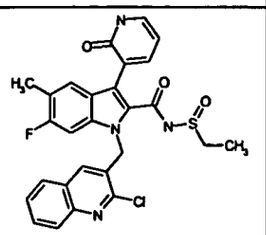
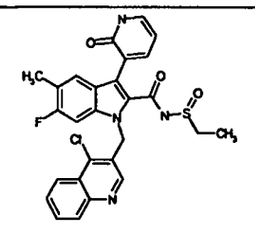
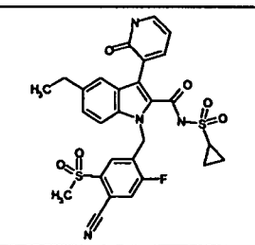
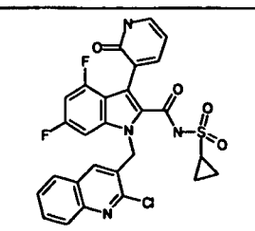
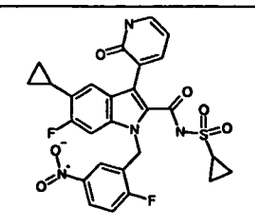
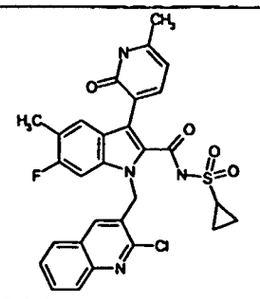
582		695.7
583		697.6
584		697.6
585		704.7
586		705.2
587		706.2
588		706.2

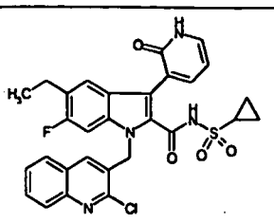
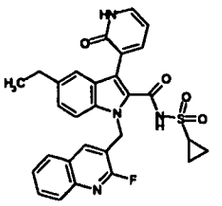
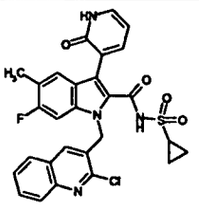
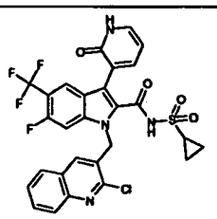
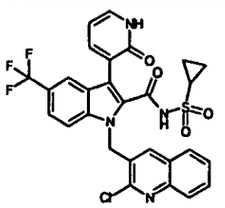
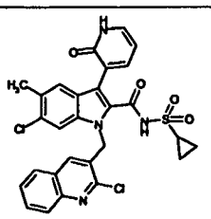
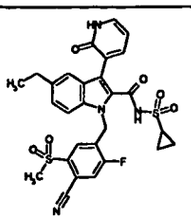
589		706.2
590		707.7
591		710.2
592		711.7
593		719.2
594		726.2
595		754.8

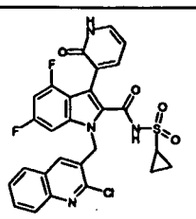
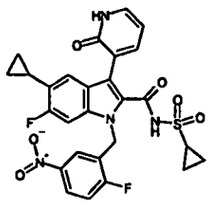
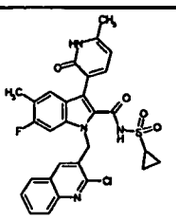
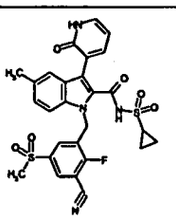
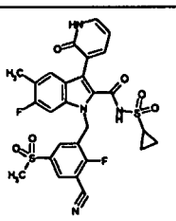
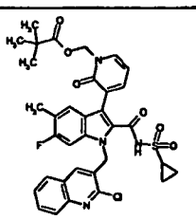
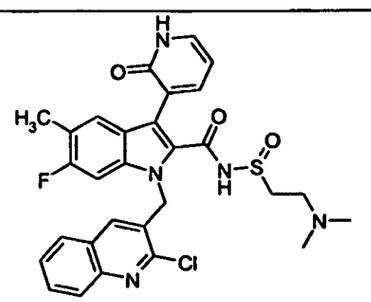
596		759.7
597		775.7
598		797.8
599		548.3
600		541.3
601		NA
602		566.0

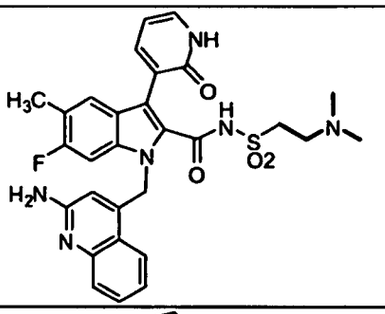
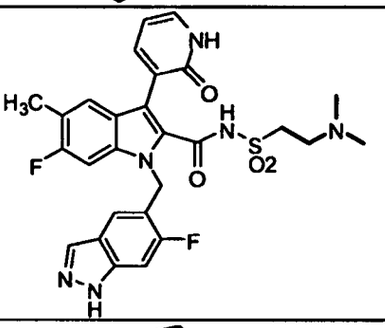
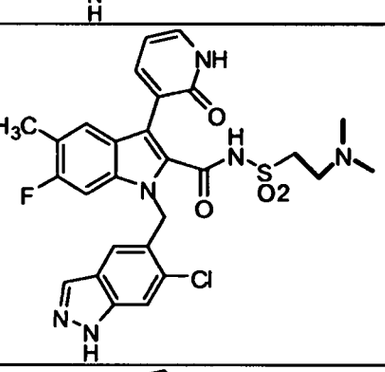
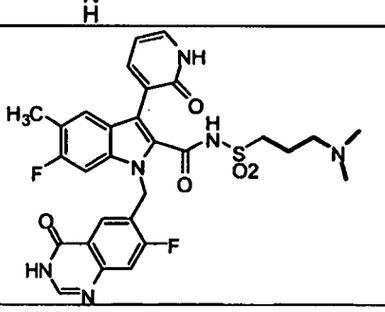
603		594.0
604		620.0
605		602.0
606		576.0
607		622.0
608		551.0
609		511.5

610		528.5
611		497.5
612		569.0
613		556.4
614		582.5
615		584.5
616		483.5

617		602.1
618		538.0
619		538.0
620		597.7
621		570.0
622		569.6
623		580.1

624		580.1
625		545.6
626		566.0
627		620.0
628		602.0
629		582.5
630		597.7

631		570.0
632		569.6
633		580.1
634		583.6
635		601.6
636		680.2
637		NA

638		NA
639		NA
640		NA
641		NA

NA = not available

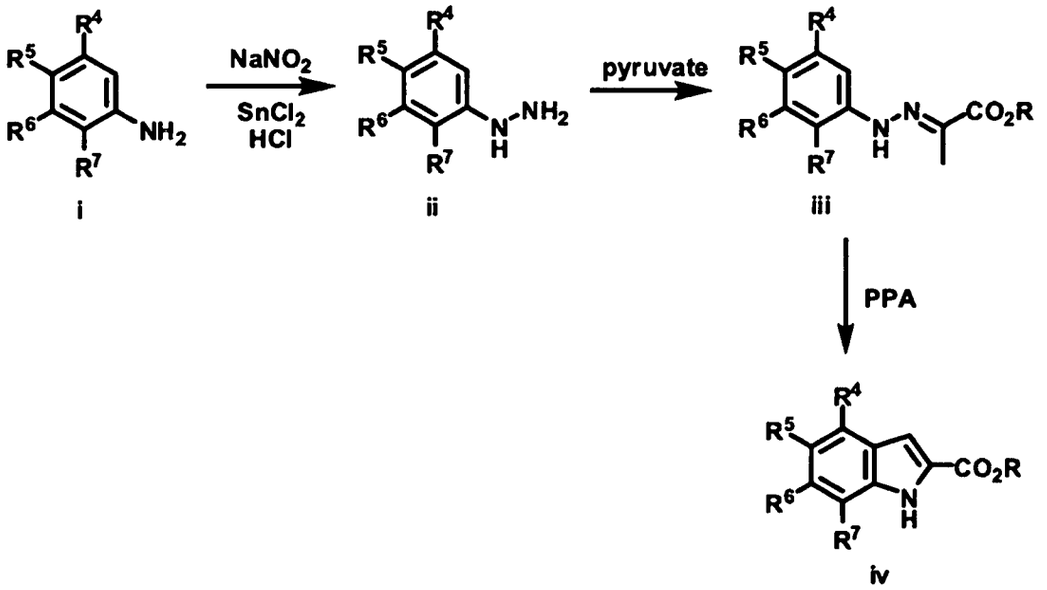
and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof.

Methods For Making the 2,3-Substituted Indole Derivatives

Methods useful for making the 2,3-Substituted Indole Derivatives are set forth in the Examples below and generalized in Schemes 1-6. Examples of commonly known methodologies useful for the synthesis of indoles are set forth, for example, in G. R. Humphrey and J. T. Kuethe, *Chemical Reviews* 106:2875-2911, **2006**.

Scheme 1 shows a method useful for making compounds of formula **iv**, which are useful intermediates for making the 2,3-Substituted Indole Derivatives.

Scheme 1

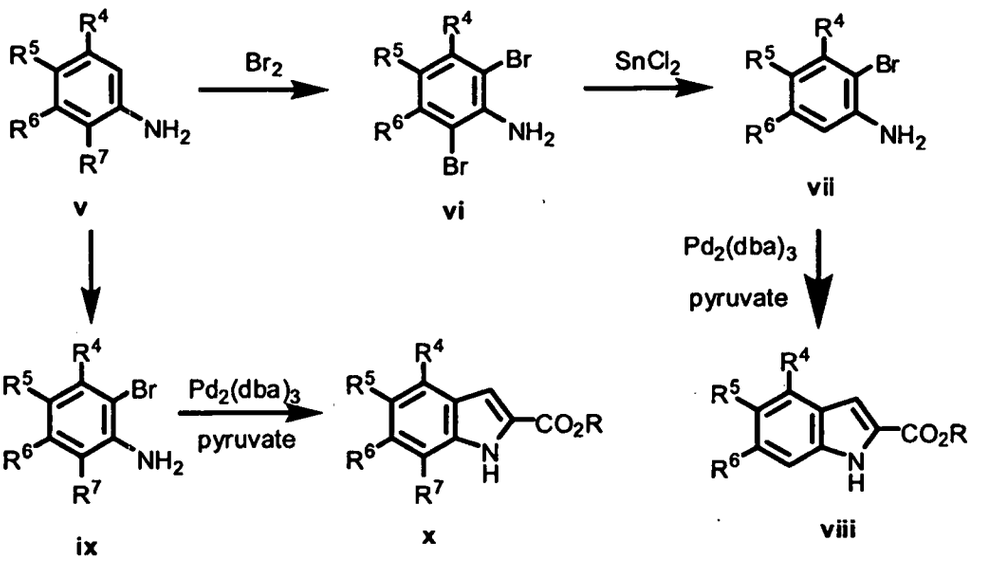


wherein R^4-R^7 are defined above for the compounds of formula (I) and R is H, alkyl or aryl.

An aniline compound of formula **i** can be converted to an indole compound of formula **iv** 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 **ii** and **iii**, the method set forth in Nazare *et al.*, *Angew. Chem.*, 116:4626-4629 (2004). The compounds of formula **iv** can be further elaborated to provide the 2,3-Substituted Indole Derivatives using the method described below in Scheme 4.

Scheme 2 shows methods useful for making compounds of formulas **viii** and **x**, which are useful intermediates for making of the 2,3-Substituted Indole Derivatives.

Scheme 2

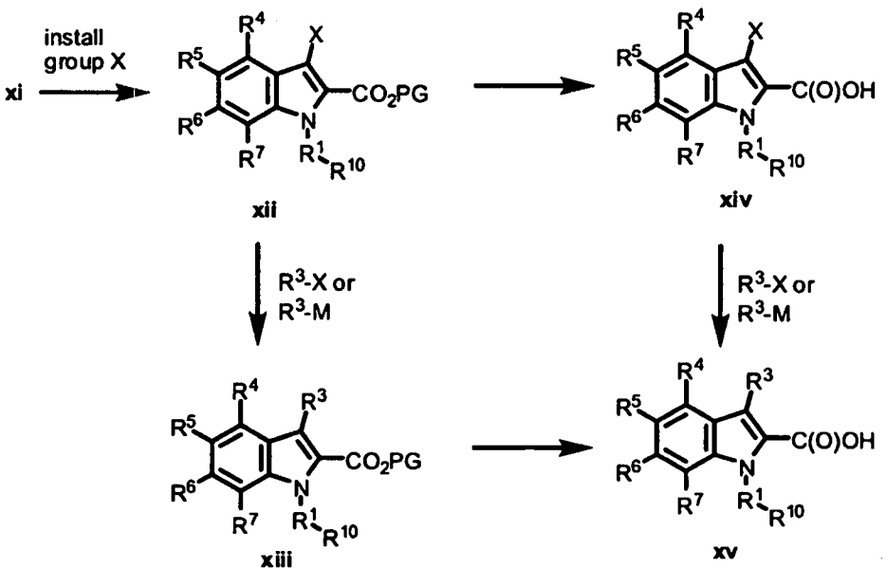


wherein R^4-R^7 are defined above for the compounds of formula (I) and R is H, alkyl or aryl.

A benzene derivative of formula **v**, wherein R^7 is H, can be di-brominated to provide compound **vi**. Selective de-bromination provides the corresponding monobromo analog **vii**, which under palladium catalyzed cyclization conditions provides the desired intermediate **viii**, wherein R^7 is H. Alternatively a compound of formula **v**, wherein R^7 is other than H, can be monobrominated to provide compound **ix**. A compound of formula **ix** can then undergo under palladium catalyzed cyclization conditions provides the desired intermediate **x**, wherein R^7 is other than H.

Scheme 3 illustrates methods by which intermediate compounds of formula **xi** can be further derivatized to provide the 2,3-Substituted Indole Derivatives, which are intermediates to the title 2,3-Substituted Indole Derivatives.

Scheme 3



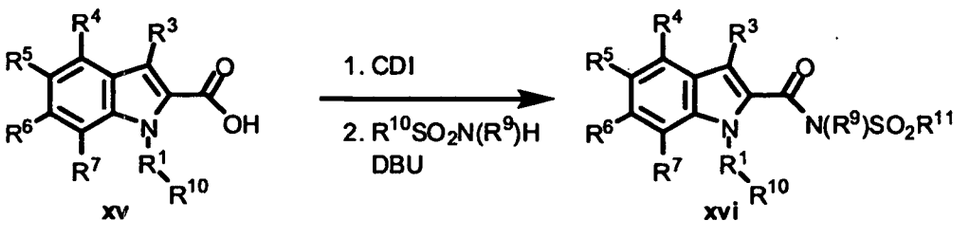
wherein R^1, R^3, R^4-R^7 and R^{10} are defined above for the compounds of formula (I); PG is a carboxy protecting group; and X is halo, -O-triflate, -$B(OH)_2$, -$Si(alkyl)_2OH$, -$Sn(alkyl)_3$, -MgBr, -MgCl, -ZnBr, or –ZnCl; and M is any metal which can participate in an organometallic cross-coupling reaction.

An intermediate compound of formula **xi** can be converted to a 3-substituted indole of formula **xii** using methods well-known to one skilled in the art of organic synthesis. A compound of formula **xii**, wherein X is halo or –O-triflate can then be coupled with an appropriate compound of formula R^3-M (wherein M is -$B(OH)_2$, -$Si(alkyl)_2OH$, -$Sn(alkyl)_3$, -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 **xii**, wherein X is -$B(OH)_2$, -$Si(alkyl)_2OH$, -$Sn(alkyl)_3$, -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)), a silanoate-based coupling (see Denmark *et al.*, *Chem. Eur. J.* 12:4954-4963 (2006)) 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 **F**. The carboxy protecting group, PG, can then be removed from the compound of formula **xiv** and the

resulting carboxylic acid can be derivatized using the methods described below in order to make the appropriate R^2 groups and make the compounds of formula **xv**, which correspond to the compounds of formula (I), wherein R^2 is –C(O)OH. Alternatively, a compound of formula **xii** can first be deprotected and the R^2 group attached using the above methods to provide a compound of formula **xiii**. A compound of formula **xiii** can then be cross-coupled with a compound of R^3-X or R^3-M as described above to provide the compounds of formula **xv**.

Scheme 4 shows a method useful for making the 2,3-Substituted Indole Derivatives, wherein R^2 is -C(O)N(R^9)SO_2R^{11}.

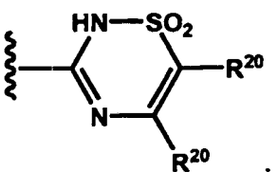
Scheme 4



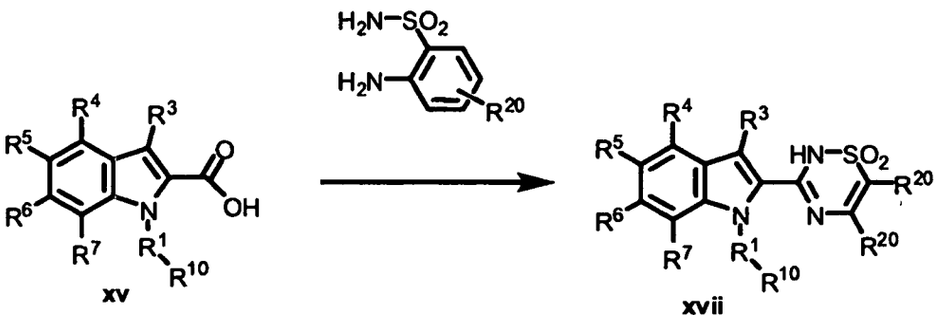
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, etc. and G are as defined for the 2,3-Substituted Indole Derivatives.

A 2-carboxy indole compound of formula **xv** can be coupled with a compound of formula $R^{11}SO_2NH(R^9)$ in the presence of carbonyldiimidazole (CDI) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to provide the compounds of formula **xvi**, which correspond to the 2,3-Substituted Indole Derivatives wherein R^2 is –C(O)NHSO_2R^{11}.

Scheme 5 shows a method useful for making the 2,3-Substituted Indole Derivatives, wherein R^2 is:

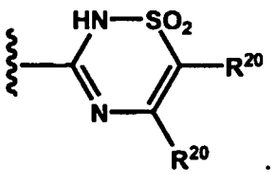


Scheme 5



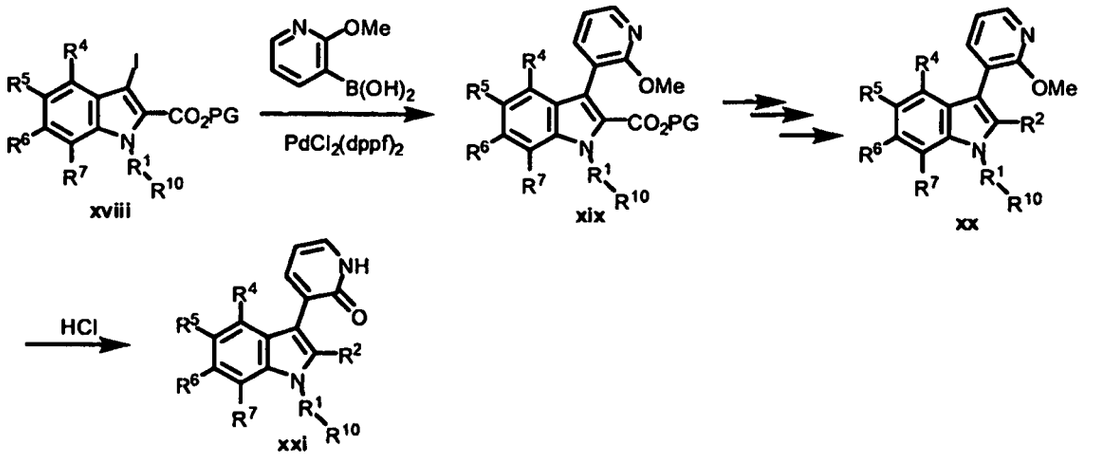
wherein R^1, R^3, R^4-R^7, R^{10} and R^{20} are defined above for the compounds of formulas (I) and (II).

A 2-carboxy indole compound of formula **xv** can be reacted with a 2-amino sulfonamide to provide the compounds of formula **xvii**, which correspond to the 2,3-Substituted Indole Derivatives wherein R^2 is:



Scheme 6 shows a method useful for making the 2,3-Substituted Indole Derivatives, wherein R^3 is 1*H*-pyridin-2-one-3-yl.

Scheme 6



wherein R^1, R^2, R^4-R^7 and R^{10} are defined above for the compounds of formulas (I) and (II).

A 3-iodoindole compound of formula **xviii** can be coupled with 2-hydroxypyridine-3-boronic acid using a Suzuki coupling reaction to provide the R^3-substituted indole compounds of formula **xix**. A compound of formula **xix** can be further elaborated using methods set forth above in Schemes 1-6 to provide the compounds of formula **xx**. The 2-hydroxypyridyl moiety

of a compound of formula **xx** can then be reacted with strong acid, such as hydrochloric acid to provide the compounds of formula **xxi**, which correspond to the 2,3-Substituted Indole Derivatives, wherein R^3 is 1*H*-pyridin-2-one-3-yl.

The starting material and reagents depicted in Schemes 1-6 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives and methods for their installation and removal may be found in Greene *et al.*, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

One skilled in the art will 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 has to be controlled to avoid functional group incompatibilities. One skilled in the art will recognize that a more convergent route (i.e. non-linear or preassembly of certain portions of the molecule) is a more efficient method of assembly of the target compounds. Methods suitable for the preparation of 2,3-Substituted Indole Derivatives are set forth above in Schemes 1-6.

The starting materials and the intermediates prepared using the methods set forth in Schemes 1-6 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

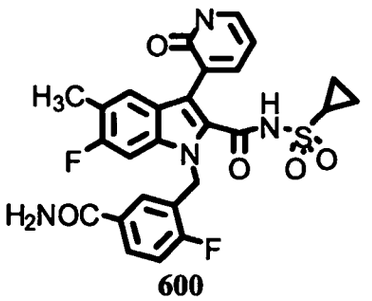
General Methods

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.

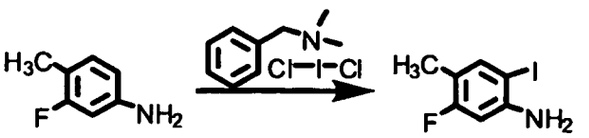
Example 1

Preparation of Compound **600**



600

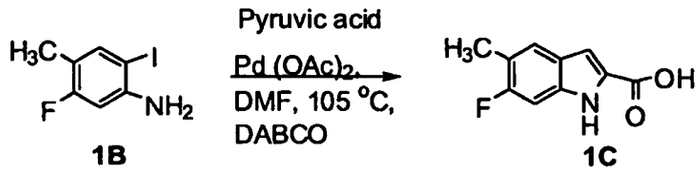
Step 1:



1A **1B**

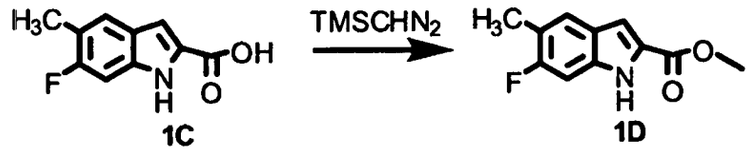
To a solution of 3-Fluoro-4-methyl-phenylamine (**1A**)(8.0 g, 64 mmol) in dicholoromethane (500 mL) and MeOH (100 mL) was added benzyltrimethylammonium dichloroiodate (23.8 g, 67.4 mmol) and calcium carbonate (12.8g, 133 mmol). The suspension was allowed to stir at room temperature for 1h, the solids were removed by filtration and the filtrate was concentrated. The concentrated crude was redissolved in CH_2Cl_2, washed successively with 5% $NaHSO_4$, saturated $NaHCO_3$, water, brine and dried over $MgSO_4$. The organic layer was concentrated and the crude was purified using chromatography over SiO_2 (330 g, flash column) using 0 to 20 % ethyl acetate in hexane to provide compound **1B** (13.4g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 4.2 (broad S, 2H), 6.51 (d, J = 10.8 Hz, 1H), 7.43 (d, J = 8.4 Hz, 1H).

Step 2:



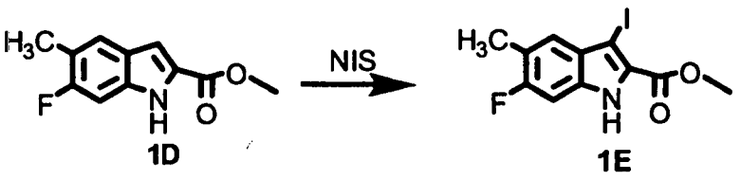
A solution of the 5-fluoro, 4-methyl iodo aniline (**1B**)(13.4g, 53.5 mmol), $Pd(OAc)_2$ (607 mg, 2.7 mmol), pyruvic acid (14.28 g, 162.0 mmol) and DABCO (18.2g, 162 mmol) in DMF (120 mL) was degassed and heated to 105 ° C for 4h, cooled to room temperature and partitioned between ethyl acetate and water. The aqueous layer was extracted two more times with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, concentrated and the brown solid was washed with ethyl acetate/hexanes and filtered to provide compound **1C** as a white solid (8.3g, 83%) which was used directly in the next step. ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.0 (broad s, 1H), 2.25 (s, 3H), 7.0 (s, 1H), 7.15 (d, J = 11 Hz, 1H), 7.49 (d, J = 7.3 Hz, 1H), 11.7(s, 1H).

Step 3:



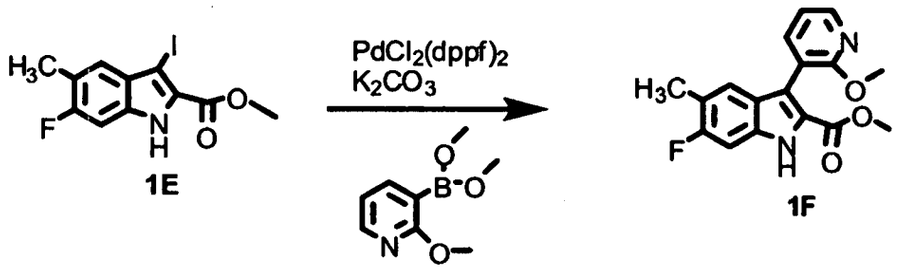
To a cooled solution of 6-Fluoro-5-Methyl-1H-indole-2-carboxylic acid in MeOH/toluene (**1C**)(200 mL, 1 : 1) was added TMS-diazomethane (2.0 M solution in diethylether, 1.05 eq.) dropwise and the reaction was allowed to warm up to room temperature over 1h. The reaction mixture was concentrated and purified using triturating with CH_2Cl_2 and hexane and collecting the solids by filtration to obtain 6-Fluoro-5-Methyl-1*H*-indole-2-carboxylic acid methyl ester **1D** (3.5 g). The concentrated filtrate was purified using chromatography over SiO_2 using 0 to 40 % ethyl acetate in hexanes to provide an additional amount of 6-Fluoro-5-Methyl-1*H*-indole-2-carboxylic acid methyl ester **1D** (1.0 g). Overall yield (60%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.26 (s, 3H), 3.83 (s, 3H), 7.07 (s, 1H), 7.08 (d, J = 10.2 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 11.9 (s, 1H).

Step 4:



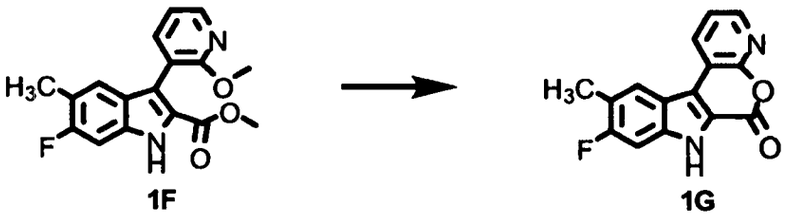
To a solution of 6-Fluoro-5-Methyl-1*H*-indole-2-carboxylic acid methyl ester **1D** (3.53g, 17.03 mmol) in $CHCl_3$/THF (100 mL, 5:1) was added NIS (3.83 g, 17.03 mmol) and the reaction mixture was allowed to stir at room temperature overnight. The reaction mixture was concentrated and redissolved in Ethyl acetate and washed with 1M $Na_2S_2O_3$, saturated $NaHCO_3$, water and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated and the product was triturated using ethyl acetate/hexanes and filtered to provide compound **1E** (5.34g, 94.1%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39(s, 3H), 3.97 (s, 3H), 7.07 (d, J = 9.5 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 9.1 (s, 1H).

Step 5:



2-methoxy-3-pyridine boronic acid (2.94 g, 19.23 mmol) was added to a solution of 6-Fluoro-3-iodo-5-methyl-1*H*-indole-2-carboxylic acid methyl ester **1E** (5.34 g, 16.03 mmol) in 1, 2 dimethoxyethane (105 mL). The mixture was degassed and $PdCl_2(dppf)_2$ (1.3g, 1.60mmol) was added to the reaction mixture. After the resulting orange solution was allowed to stir at room temperature for 30 minutes., a solution of K_2CO_3 (8.86g in 64mL of H_2O) was added. The resulting brown solution was allowed to stir at 90 °C for 4h, cooled to room temperature and diluted using ethyl acetate. The organic layer was washed with water, brine and dried over $MgSO_4$. The concentrated filtrate was purified over SiO_2 using 0 to 30 % ethyl acetate in hexanes to provide compound **1F** as a white solid (4.14g, 82%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 2.06 (s, 3H), 3.68 (s, 3H, 3.76 (s, 3H), 7.08 (m, 1H), 7.19 (m, 2H), 7.65 (d, J = 10.0 Hz, 1H), 8.20 (m, 1H).

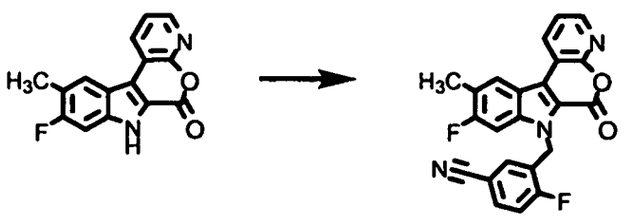
Step 6:



1F 1G

To 6-Fluoro-3-(2-Methoxy-pyridin-3-yl)-5-methyl-1*H*-2-carboxylic acid methyl ester **1F** (4.14g, 13.17 mmol) was added 4N HCl in dioxane (40 mL) and the reaction mixture was heated at 80 °C for 12h, cooled, and concentrated to provide 6-Fluoro-3-(2-hydroxy-pyridin-3-yl)-5-methyl-1*H*-2-carboxylic acid methyl ester. To the crude from last step was added LiOH (1.65g, 39.51 mmol) in THF/MeOH/H_2O (75 mL, 2:2:1) and the slurry was heated at 65 °C for 12 hours, cooled, washed with 1 N HCl and water. The product was filtered, washed with ethyl acetate and dried *in vacuo* to provide 6-Fluoro-3-(2-hydroxy-pyridin-3-yl)-5-methyl-1*H*-2-carboxylic acid (3.59g, 95.2% over 2 steps) and used directly in the next step. To the hydroxy acid (3.59g, 12.54 mmol) from the previous step in DMF (70.0 mL) was added EDCI.HCl (4.8 g, 25.08 mmol) and Et_3N (8.73 mL, 62.7 mmol) and the reaction mixture was allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with ethyl acetate, the slurry was washed with water and filtered. The ethyl acetate layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo* and the crude was added to the filtrate from the prior step and dried *in vacuo* to provide 9-Fluoro-10-methyl-7H-5-oxa-4,7-diaza-benzo[c]fluoren-6-one **1G** as a white solid (3.36g, 75%). ^1H NMR (400 MHz, d_6-DMSO): δ 2.40 (s, 3H), 7.28 (d, J = 10Hz, 1H), 7.54 (m, 1H), 8.40 (m, 2H), 8.87 (d, J = 7.2 Hz, 1H).

Step 7:

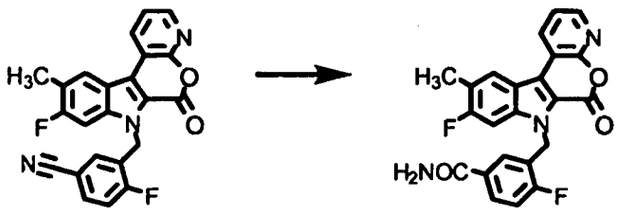


1G 1H

To a solution of 9-Fluoro-10-methyl-7H-5-oxa-4,7-diaza-benzo[c]fluoren-6-one **1G** (167 mg, 0.622 mmol) in DMF (3.0 mL) was added 3-Bromomethyl-4-fluoro-benzonitrile (160.0 mg, 0.747 mmol) and $CsCO_3$ (243 mg, 0.747 mmol) at room temperature and the reaction mixture was allowed to stir overnight. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*.

The concentrated crude was purified using chromatography over SiO_2 using 0 to 30 % ethyl acetate in hexane to provide 4-Fluoro-3-(9-fluoro-10-methyl-6-oxo-6*H*-5-oxa-4,7-diaza-benzo[c]fluoren-7-ylmethyl)-benzonitrile **1H** (200 mg, 80%). M.S. found for C23H13F2N3O2: 402.9 $(M+H)^+$.

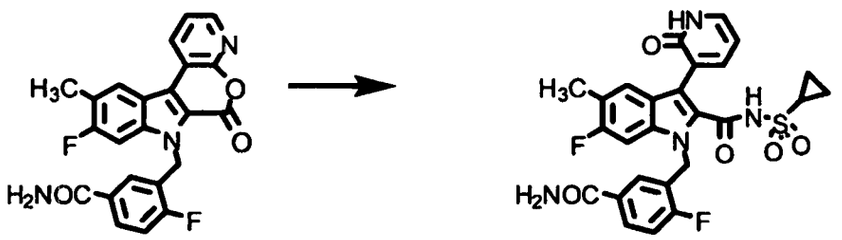
Step 8:



1H **1I**

To a solution of 4-Fluoro-3-(9-fluoro-10-methyl-6-oxo-6*H*-5-oxa-4,7-diaza-benzo[c]fluoren-7-ylmethyl)-benzonitrile **1H** (126 mg, 0.313 mmol) in AcOH (1.0 mL) was added H_2SO_4(4 drops). The reaction mixture was heated at 100 °C for 12h and concentrated *in vacuo*. The solids were washed with water and ethyl acetate and dried under high vacuum to provide compound **1I** as a white solid (124.0 mg, 94%). M.S. found for C23H15F2N3O3: 420.1 $(M+H)^+$.

Step 9 :

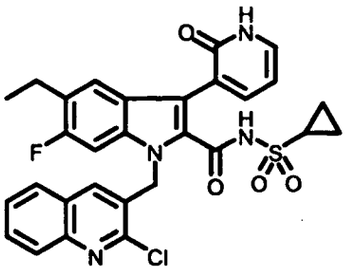


1I **600**

A slurry of 9-Fluoro-10-methyl-7H-5-oxa-4,7-diaza-benzo[c]fluoren-6-one **A9** (34 mg, 0.08 mmol) and cyclopropyl sulfonamide (20.0 mg, 0.165 mmol) in anhydrous DMF (3.0 mL) was treated with NaH (16.0 mg, 0.4 mmol, 60% suspension in mineral oil). The reaction mixture was heated overnight at 40 °C. The pH of the cooled (room temperature) reaction mixture was adjusted to pH=3 with 1N HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine and filtered through Na_2SO_4. The concentrated crude was purified using HPLC using a C-18 column eluting with 20 -90 % CH_3CN/H_2O gradient to provid compound **600**. M.S. found for C26H22F2N4O5S: 541.3 $(M+H)^+$.

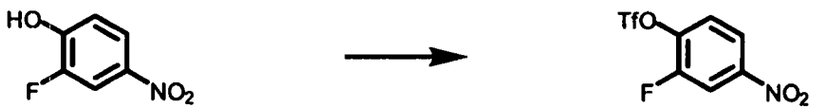
Example 2

Preparation of Compound **601**



601

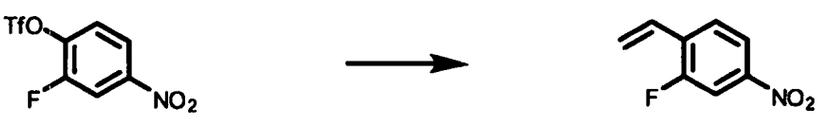
Step 1:



2A **2B**

A solution of 2-fluoro-4-nitro-phenol (**2A**) (2.53 g; 16.1 mmol) in 60 mL of dry dichloromethane and 5 mL of dry THF was ice cooled and treated with pyridine (10 mL) and triflic anhydride (1.1 eq, 5.0 g, d 1.677). The mixture was allowed to stir for 10 min and treated with a catalytic amount of 4-dimethylamino pyridine (tip of spatula). The cooling bath was removed and the reaction was allowed to stir for 1 hour. TLC (10% ethyl acetate in hexanes) showed no more starting material left and the mixture was diluted with ethyl acetate (300 mL) and washed with aq saturated sodium bicarbonate (80 mL) and brine (80 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified on silica gel (Biotage 40-M column; gradient: 0 to 10% ethyl acetate in hexanes) to provide compound **2B** (4.0 g; 87 %) as a colorless oil.

Step 2:

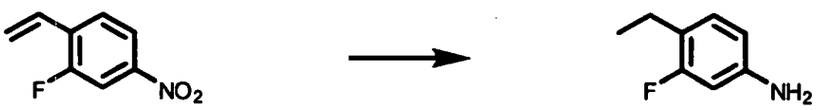


2B **2C**

A solution of trifluoro-methanesulfonic acid 2-fluoro-4-nitro-phenyl ester (**2B**) (13.2 g; 45.64 mmol) in 225 mL of THF was treated with lithium chloride (7.0 eq, 13.5 g) and tributyl(vinyl)tin (2.0 eq, 26.6 mL, d 1.085). The mixture was degassed (vacuum/nitrogen flush) and tetrakis(triphenylphosphine)palladium was added (10 mol%, 5.26 g). The reaction

mixture was heated to 80 °C and stirred overnight. TLC (5% ethyl acetate in hexanes) showed complete consumption of starting material. The mixture was diluted with water (100 mL) and extracted with 1:1 ether/ethyl acetate (900 mL). The organic layer was washed with 10% aqueous ammonium hydroxide (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-S column (gradient: 0 to 4% ethyl acetate in hexanes) to provide compound **2C** (7.6 g; 99 %) as a slightly yellow oil which contains some stannane impurities (ca. 1.4 g)

Step 3:



2C **2D**

A solution of 2-fluoro-4-nitro-1-vinyl-benzene (**2C**) (42.65 mmol) in 140 mL of methanol was treated with a catalytic amount of 10% palladium on carbon (aprox 1.0 g). The mixture was hydrogenated at 35 psi for 2 hours. TLC (10% ethyl acetate in hexanes) showed complete consumption of starting material. The mixture was diluted with dichloromethane (100 mL) and filtered thru a short path of celite. The solids were washed with dichloromethane (100 mL). The filtrate, which contains the product **2D**, was used for next reaction.

Step 4:

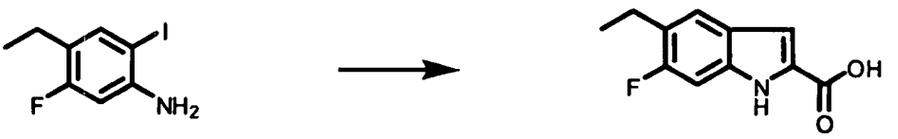


2D **2E**

A solution of 4-ethyl-3-fluoro-phenylamine (**2D**) (the filtrate solution from previous step) was treated with benzyltrimethylammonium dichloroiodate (1.1 eq, 16.3 g) and calcium carbonate (2.0 eq, 8.53 g). The suspension was allowed to stir at room temp for 1 hour. TLC (10% ethyl acetate in hexanes) showed complete consumption of starting material. The solids were removed by filtration (whatman #1) and the filtrate was concentrated *in vacuo* . The residue was partitioned between 800 mL of 1:1 ether/ethyl acetate and aqueous 5% sodium hydrogen sulfate (200 mL). The organic layer was washed with water (200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*.

The residue was adsorbed on silica gel and chromatographed on a Biotage 65-M column (gradient: 0 to 10% ether in hexanes) to provide compound **2E** (8.5 g; 76 %) as a yellow oil which contains some stannane impurities from a previous step.

Step 5:



2E **2F**

A solution of 4-ethyl-5-fluoro-2-iodo-phenylamine (**2E**) (7.29 g; 27.50 mmol) in 60 mL of dry DMF was treated with pyruvic acid (3.0 eq, 7.26 g, d 1.267) and DABCO (3.0 eq, 9.24 g). The mixture was degassed (vacuum/nitrogen flush) and palladium(II) acetate (0.05 eq, 308 mg) was added. The resulting solution was heated to 105 °C for 3 hours. The volatiles were removed *in vacuo* (high vacuum pump) and the residue was partitioned between ethyl acetate (200 mL) and water (200 mL). The aqueous layer was back extracted with ethyl acetate (4 x 100 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **2F** as a dark brown oil. No further purification was carried out.

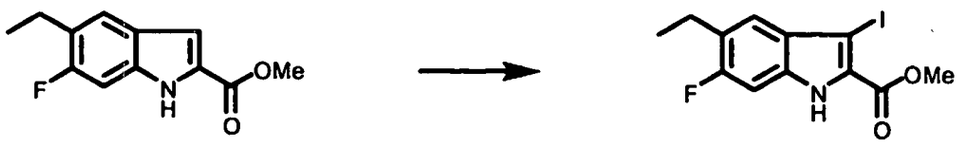
Step 6:



2F **2G**

To an ice-cooled solution of 5-ethyl-6-fluoro-1H-indole-2-carboxylic acid (**2F**) (27.5 mmol) in 300 mL of 2:1 toluene/methanol was slowly added a solution of TMS-diazomethane in ether (2.0 eq, 27.5 mL of 2.0M). After addition was completed the cooling bath was removed and the reaction mixture was allowed to stir for 1 hour. The mixture was concentrated *in vacuo* to provide the crude product as a brown solid. The mixture was adsorbed on silica gel and purified on a Biotage 65-M column (gradient: 10 to 50% dichloromethane in hexanes) to provide compound **2G** (3.0 g; 50 % for two steps) as a white solid.

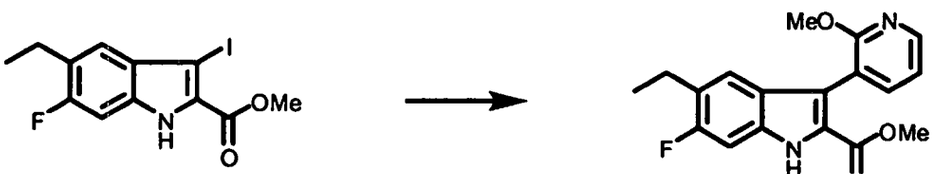
Step 7:



2G 2H

A solution of 5-ethyl-6-fluoro-1H-indole-2-carboxylic acid methyl ester (**2G**) (2.6 g; 11.75 mmol) in 60 mL of 1:1 THF-chloroform was ice-cooled and treated with N-iodosuccinimide (1.15 eq, 3.04 g). The cooling bath was removed and the mixture was allowed to stir for 2 hours. TLC (20% ethyl acetate in hexanes) showed almost complete consumption of starting material. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with aq saturated sodium bicarbonate (2 x 60 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **2H** (4.0 g; 99 %) as a slightly yellow solid which was used without further purification.

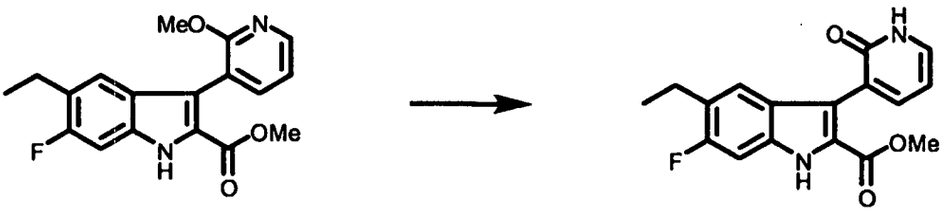
Step 8:



2H 2I

2-Methoxypyridine-3-boronic acid (1.5 eq, 2.69 g) was added to a solution of 5-ethyl-6-fluoro-3-iodo-1H-indole-2-carboxylic acid methyl ester (**2H**) (11.75 mmol) in 120 mL of 1,2-dimethoxyethane. The mixture was degassed (vaccum/argon flush) and palladium catalyst (10 mol%, 960 mg of $PdCl_2(dppf)_2$) was added and the resulting orange solution was allowed to stir for 10 min at room temp. A solution of potassium carbonate (4.0 eq, 23.5 mL of aqueous 2M soln) was added and the resulting brown mixture was allowed to stir at 85 °C for 2 h at which point TLC (20% ethyl acetate in hexanes) showed almost complete consumption of starting material. The reaction mixture was cooled to room temp and diluted with ethyl acetate (300 mL), washed with aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was adsorbed on silica gel and purified on a Biotage 65-M column (gradient: 0 to 15% ethyl acetate in 1:1 hexanes-dichloromethane) to provide compound **2I** (3.3 g; 86 %) as a white solid.

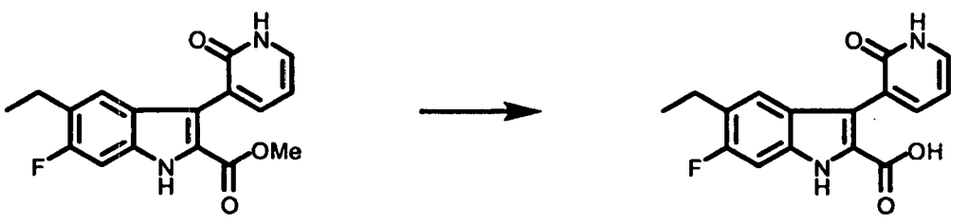
Step 9:



2I **2J**

The 5-ethyl-6-fluoro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid methyl ester (**2I**) (3.3 g; 10.05 mmol) was partially dissolved in 10 mL of methanol followed by addition of 40 mL of 4M HCl solution in dioxane. The resulting solution was heated in a sealed tube at 85 °C for 3 hours. TLC (40% acetone in 1:1 DCM-hexanes) showed aprox 40% conversion. All the volatiles were removed *in vacuo* and the residue was re-dissolved in 4M HCl soln in dioxane (40 mL). The mixture was heated in a sealed tube (90 °C) for 3 hours. TLC showed some starting material left. All the volatiles were again removed *in vacuo* and the residue was adsorbed on silica gel. Purification on a Biotage 40-M column (gradient: 20 to 60% acetone in 1:1 DCM-hexanes) gave the product **2J** (2.0 g; 63 %) as a slightly yellow solid.

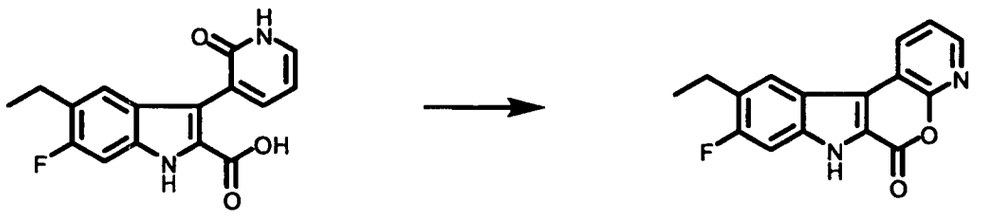
Step 10:



2J **2K**

A solution of 5-ethyl-6-fluoro-3-(2-oxo-1,2-dihydro-pyridin-3-yl)-1H-indole-2-carboxylic acid methyl ester (**2J**) (1.9 g; 6.04 mmol) in 100 mL of 6:1:1 THF/water/methanol was treated with lithium hydroxide monohydrate (2.5 eq, 634 mg). The reaction mixture was allowed to stir at 50 °C and monitored by TLC (50% acetone in 1:1 DCM-hexanes). All the starting material had been consumed after 3 h (the product precipitated in the reaction mixture). The mixture was treated with aqueous 1M HCl (100 mL) and the product **2K** (1.80 g; 99 %) was recovered by filtration (whatman #1) as a white solid.

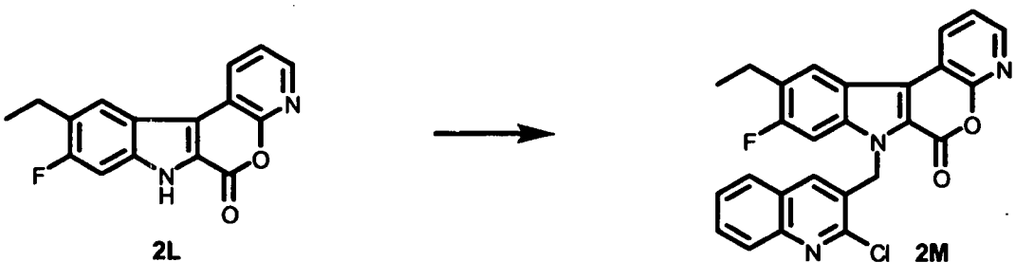
Step 11:



2K **2L**

The 5-ethyl-6-fluoro-3-(2-oxo-1,2-dihydro-pyridin-3-yl)-1H-indole-2-carboxylic acid (**2K**) (500 mg; 1.665 mmol) was suspended in dry DMF (40 mL) and treated with EDCI (2.0 eq, 638 mg) and triethylamine (10.0 eq, 2.33 mL, d 0.72). The mixture was stirred overnight at room temperature. The mixture was concentrated to dryness *in vacuo* (high vacuum pump). The residue was treated with methanol (10 mL) to make a homogeneus suspension. The product was recovered by filtration (whatman #1) and washed with methanol (2 x 5 mL). The product **2L** (282 mg; 60 %) was thus obtained as a white solid.

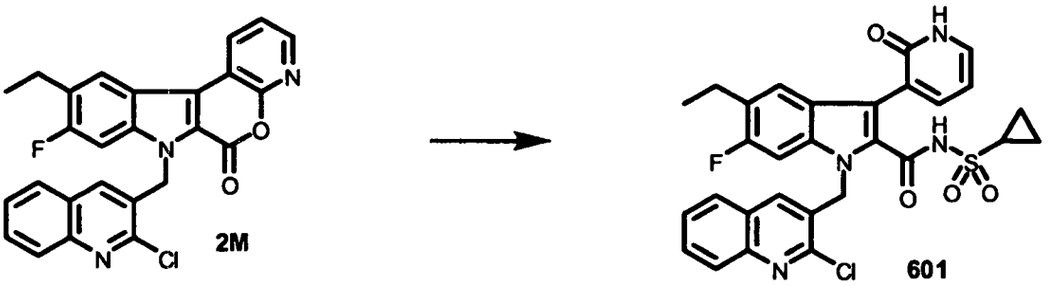
Step 12:



2L **2M**

The lactone **2L** (40 mg, 0.141 mmol) was suspended in 2 mL of dry DMF and treated with 2-chloro-3-chloromethyl-quinoline (1.2 eq, 36 mg) and cesium carbonate (2.0 eq, 92 mg). A catalytic amount of tetrabutylammonium iodide (tip of spatula) was added and the mixture was allowed to stir at room temp. TLC (30% ethyl acetate in hexanes) showed complete consumption of starting material after 1 hour. The mixture was diluted with 50 mL of 4:1 DCM-THF and washed with water (10 mL). The organic layer was concentrated *in vacuo* to provide the crude product **2M** (65 mg, 99 %) which was used without further purification.

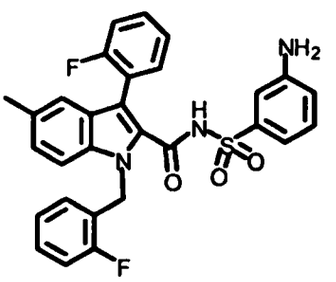
Step 13:



The lactone **2M** (65 mg; 0.141 mmol) was suspended in 3 mL of dry DMF followed by addition of cyclopropane sulfonamide (1.2 eq, 20 mg) and sodium hydride (2.0 eq, 11 mg of 60% suspension in mineral oil). The mixture was allowed to stir at room temp and eventually became a homogeneous solution (after 15 min). TLC (30% ethyl acetate in hexanes) showed complete consumption of starting material after 20 minutes. The reaction was quenched by addition of 5 drops of aq 1M HCl and further diluted with 5 mL of DMF. The solution was injected into an semi-prep HPLC system under the following conditions: Delta Pak Column, C18, 5 micrometer, 300A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; Gradient: 40% acetonitrile (0.01% TFA) in water (0.01% TFA) for 10 min then increase to 90% over 20 min and stay for 10 minutes. The fraction containing the product (27 min) according to MS analysis was concentrated *in vacuo* to provide compound **601** (42 mg; 52 %) as a white solid. Some of the product (23 mg) was dissolved in THF (3 mL) and treated with aqueous 1M NaOH solution (1.2 eq, 0.047 mL of aq. 1M soln). The mixture was allowed to stir for 10 min and then concentrated *in vacuo* to provide the sodium salt of compound **601** (23.8 mg).

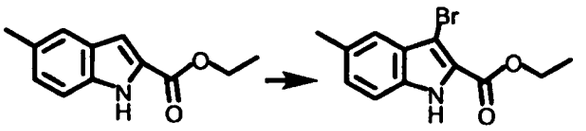
Example 3

Preapartion of Compound **271**



271

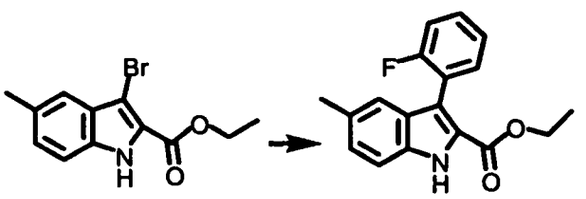
Step 1:



3A 3B

To a solution of 5-methyl-1H-indole-2-carboxylic acid ethyl ester, **3A** (10.17 g, 50.03 mmol) in THF (100 mL) in a room temperature water bath was slowly added NBS (8.91 g, 50.06 mmol). The resulting solution was allowed to stir at room temperature for 3.5 h before water (800 mL) was added. The resulting mixture was allowed to stir at room temperature for 20 min and then filtered. The solid was washed with water (2 x 100 mL), dried *in vacuo* to provide the crude product **3B** as a tan powder (13.8 g, 98% yield). ^{1}H NMR (500 MHz, CDCl3): δ 8.91 (s, 1H), 7.44 (q, J= 0.95 Hz & 0.63 Hz, 1H), 7.28 (d, J= 8.51 Hz, 1H), 7.21 & 7.19 (dd, J= 1.58 Hz & 8.51 Hz, 1H), 4.46 (q, J= 6.94 Hz & 7.25 Hz, 2H), 2.47 (s, 3H), 1.45 (t, J= 7.25 Hz, 3H).

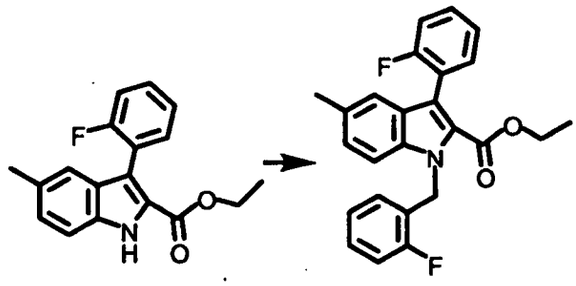
Step 2:



3B 3C

To a solution of 3-bromo-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **3B** (5.00 g, 17.72 mmol) in DME (80 mL) were added 2-fluorophenylboronic acid (3.72 g, 26.58 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]-dichloropalladium(II) dichloromethane (1:1) complex (1.45 g, 1.77 mmol). A solution of sodium carbonate (17 mL of 1.5 M, 25.5 mmol) was added to the above mixture via a syringe. The reaction mixture was de-gassed, and then stirred at reflux for 6 hours. The reaction mixture was then cooled to room temperature, and filtered through a pad of celite. The filtrate was concentrated under reduced pressure, and the residue purified using flash chromatography on silica gel to provide compound **3C** as a white solid (4.79 g, 90% yield). M.S. found for $C_{18}H_{16}FNO_2$: 298.3 $(M+H)^+$.

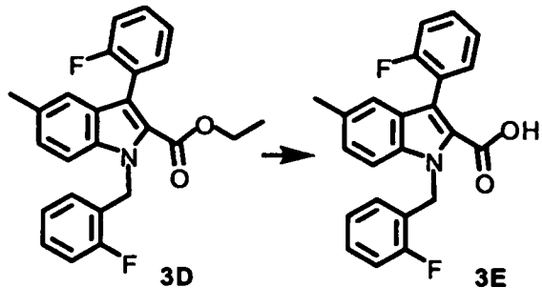
Step 3:



3C 3D

A suspension of 3-(2-fluoro-phenyl)-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **3C** (860 mg, 2.88 mmol), 2-fluorobenzylchloride (570 mg, 3.94 mmol), and cesium carbonate (2.10 g, 6.47 mmol) in DMF (3 mL) was allowed to stir at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (300 mL), and washed with water (3 x 80 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography on silica gel to provide compound **3D** as a colorless oil (0.95 g, 81% yield). M.S. found for $C_{25}H_{21}F2NO_2$: 406.2 $(M+H)^+$.

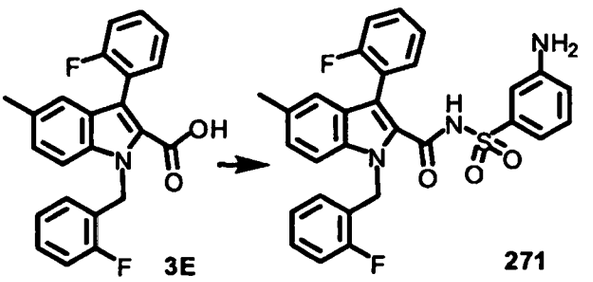
Step 4:



3D 3E

To a solution of 1-(2-fluoro-benzyl)-3-(2-fluoro-phenyl)-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **3D** (950 mg, 2.34 mmol) in THF (20 mL) was added with an aqueous solution of lithium hydroxide (3.5 mL of 1 M, 3.5 mmol). The resulting solution was maintained at reflux for 5 days before cooled to room temperature. After concentration under reduced pressure, the residue was dissolved into methanol (10 mL), neutralized with 1.0 M HCl aqueous solution (8 mL, 8.0 mmol), and then was concentrated again under reduced pressure. The residue was extracted with ethyl acetate (2 x 50 mL). The combined organic layer was concentrated and dried on house vacuum to provide compound **3E** (910 mg, ~100% yield). M.S. found for $C_{23}H_{17}F2NO_2$: 378.2 $(M+H)^+$.

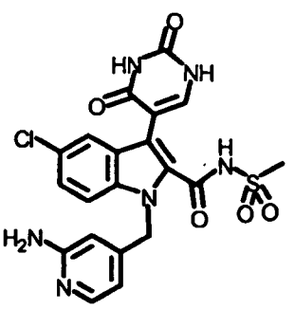
Step 5:



To a solution of 1-(2-fluoro-benzyl)-3-(2-fluoro-phenyl)-5-methyl-1H-indole-2-carboxylic acid, 3E (135 mg, 0.36 mmol) in THF (3 mL) was added 1,1'-carbonyldiimidazole (84 mg, 0.52 mmol). The reaction mixture was heated at reflux under nitrogen for 1 hour. The mixture was then cooled to room temperature, and 3-aminophenylsulfonamide (100 mg, 0.58 mmol) and DBU (90 mg, 0.58 mmol) were added. The reaction mixture was allowed to stir at reflux for 2.5 hours. The mixture was cooled down to room temperature, and concentrated *in vacuo*. The residue was purified using prep TLC on silica gel using 5% methanol in dichloromethane to provide compound **271** (113 mg, 59%). ^{1}H NMR (500 MHz, CD3OD): δ 7.48 (t, J= 6.15 Hz, 1H), 7.43-7.38 (m, 2H), 7.34-7.13 (m, 9H), 7.03 (t, J= 9.30 Hz, 1H), 6.95-6.91 (m, 2H), 6.73 (t, J= 7.09 Hz, 1H), 5.65 (s, 2H), 3.68 (s, 3H), 2.40 (s, 2H). M.S. found for $C_{29}H_{23}F_2N_3O_3S$: 532.3 $(M+H)^+$

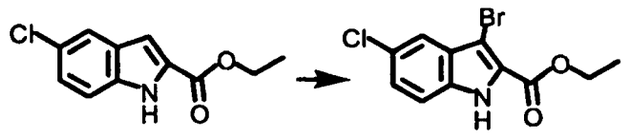
Example 4

Preparation of Compound **103**



103

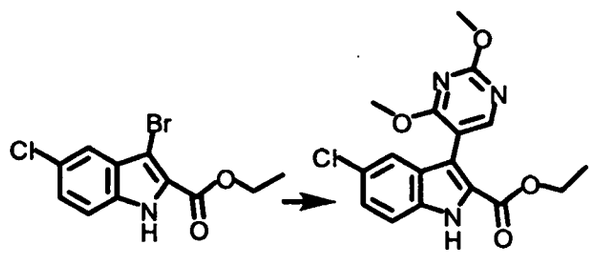
Step 1:



4A 4B

To a solution of ethyl 5-chloroindole-2-carboxylate, **4A** (20 g, 89.6 mmol) in THF (200 mL) in a cooled water bath was added NBS (16.0 g, 89.9 mmol) slowly. The resulting reaction mixture was allowed to stir at room temperature for 18 h before water (700 mL) was added. The mixture was continued to stir at room temperature for 20 min and then filtered. The solids were washed with water (2 x 100 mL), and dried to provide the crude product **4B** (25.8 g, 90% yield). ^{1}H NMR (500 MHz, CDCl3) δ 9.06 (s, 1H), 7.66-7.65 (m, 1H), 7.35-7.31 (m, 2H), 4.47 (q, J= 7.25 Hz, 2H), 1.46 (t, J= 7.09 Hz, 3H).

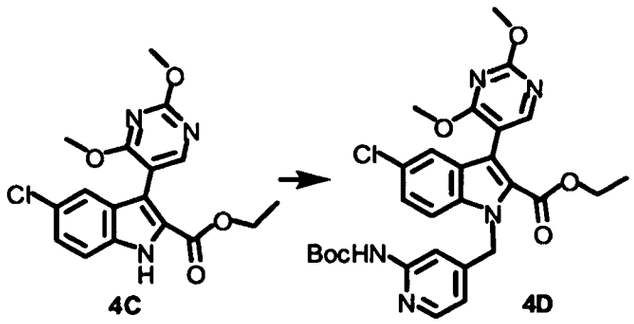
Step 2:



4B 4C

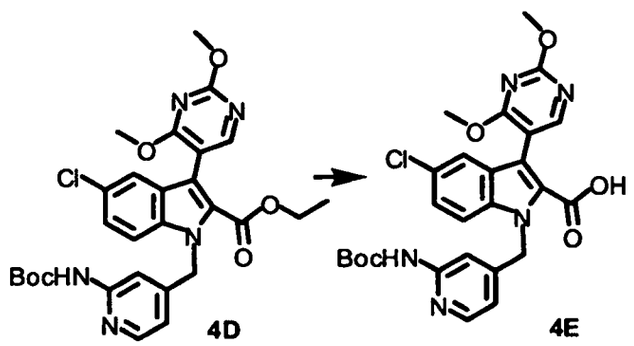
To a mixture of 3-bromo-5-chloro-1H-indole-2-carboxylic acid ethyl ester, **4B** (1.00 g, 3.31 mmol), 2,4-dimethoxypyrimidine-5-boronic acid (0.73 g, 3.97 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) with dichloromethane complex (1:1) (0.26 g, 0.32 mmol) in DME (15 mL) was added a solution of sodium carbonate (4.5 mL of 1.5 M, 6.75 mmol) via a syringe. The reaction mixture was allowed to stir at reflux for 6 h before cooled down to room temperature. The mixture was diluted with dichloromethane (50 mL), and was filtered through a pad of celite. The filtrate was concentrated under reduced pressure. The residue was purified using flash chromatography on silica gel (20 % ethyl acetate in hexanes) to provide compound **4C** as a white solid (0.47 g, 39% yield). M.S. found for $C_{17}H_{16}ClN_3O_4$: 362.2 $(M+H)^+$.

Step 3:



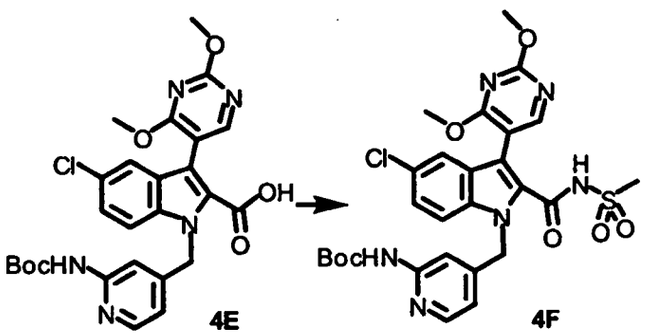
To a solution of 5-chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-1H-indole-2-carboxylic acid ethyl ester, **4C** (620 mg, 1.71 mmol) in DMF were added (4-bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (490 mg, 1.71 mmol) and cesium carbonate (1100 mg, 3.39 mmol). The resulting suspension was allowed to stir at room temperature for 17 hours. The mixture was then diluted with ethyl acetate (80 mL), and washed with water (3 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using chromatography on silica gel using 30% ethyl acetate in hexanes to provide compound **4D** (705 mg, 73% yield). M.S. found for $C_{28}H_{30}ClN_5O_6$: 568.3 $(M+H)^+$.

Step 4:



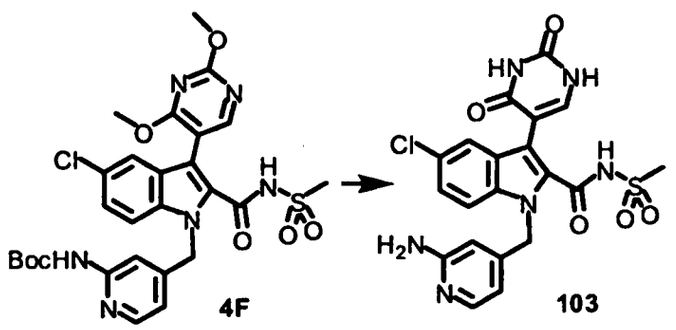
To a solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-5-chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-1H-indole-2-carboxylic acid ethyl ester, **4D** (500 mg, 0.88 mmol) in THF (10 mL) was added an aqueous solution of lithium hydroxide (2.0 ml of 1 M, 2.9 mmol). The resulting reaction mixture was allowed to stir at reflux for 16 hours. TheReaction was then cooled and concentrated *in vacuo*. The residue was dissolved in methanol (80 mL), neutralized with 1.0 M HCl aqueous solution (2.5 mL, 2.5 mmol) and then concentrated again under reduced pressure. The residue was extracted with dichloromethane (3 x 30 mL). The combined organic layer was concentrated under reduced pressure, and dried on house vacuum to provide compound **4E** (440 mg, 92%). M.S. found for $C_{26}H_{26}ClN_5O_6$: 540.3 $(M+H)^+$.

Step 5:



A solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-5-chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-1H-indole-2-carboxylic acid, **4E** (38 mg, 0.070 mmol) and 1,1'-carbonyldiimidazole (13 mg, 0.080 mmol) in THF (4 mL) was allowed to stir at reflux for 1 h before cooled down to room temperature. Methylsulfonamide (10 mg, 0.11 mmol) and DBU (13 mg, 0.086 mmol) were then added. The resulting reaction mixture was allowed to stir at room temperature for 20 h before being concentrated under reduced pressure. The residue was diluted with ethyl acetate (100 mL), washed with aqueous 1.0 M HCl solution (2 mL) and then water (5 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using preparative TLC on silica gel using 5% methanol in dichloromethane as the developing solvent to provide compound **4F** (5 mg, 12%). M.S. found for $C_{27}H_{29}ClN_6O_7S$: 617.3 $(M+H)^+$.

Step 6:



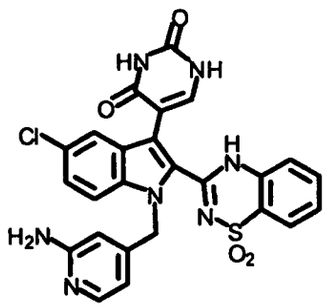
{4-[5-Chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-2-methanesulfonylaminocarbonyl-indol-1-ylmethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester, **4F** (5 mg, 0.0082 mmol) was dissolved in 4.0 M HCl in 1,4-dioxane (0.6 mL, 2.4 mmol). The resulting reaction mixture was allowed to stir at 80 °C in a sealed tube for 15 hours. temperature. The mixture was then

cooled and concentrated *in vacuo*. The residue was washed with toluene (3 x 1 mL), and dried under *in vacuo* to provide compound **103** (3 mg, 75% yield). ^{1}H NMR (500 MHz, CD3OD): δ 7.80 (d, J= 6.31 Hz, 1H), 7.74 (s, 2H), 7.51 (d, J= 8.83 Hz, 1H), 7.41 (d, J= 8.20 Hz, 1H), 7.25-7.12 (m, 1H), 6.72 (d, J= 6.31 Hz, 1H), 6.47 (s, 1H), 5.72 (s, 2H), 3.32 (s, 3H).

M.S. found for $C_{20}H_{17}ClN_6O_5S$: 489.3 $(M+H)^+$.

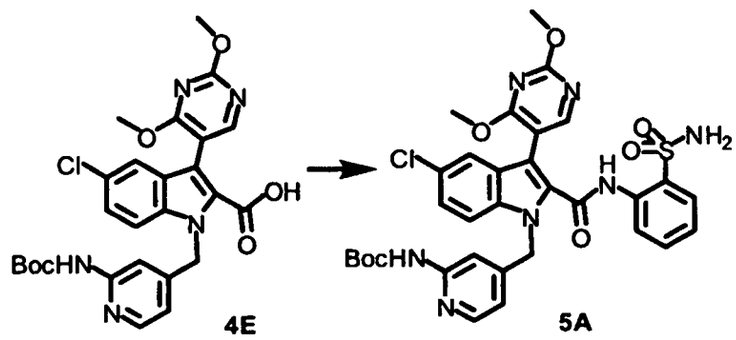
Example 5

Preparation of Compound **599**



599

Step 1:

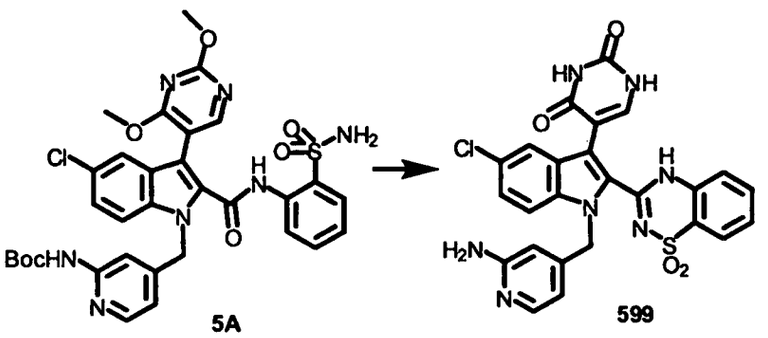


4E **5A**

To a solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-5-chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-1H-indole-2-carboxylic acid, **4E** (120 mg, 0.22 mmol) in dichloromethane (4 mL) in an ice-water bath was added oxalyl chloride (0.2 mL, ~2.3 mmol) via a syringe. The mixture was allowed to stir at room temperature for 30 min and then at room temperature for 5 min before being concentrated under reduced pressure. The residue was dissolved into dichloromethane (4 mL), and 2-aminophenylsulfonamide (180 mg, 1.05 mmol) and triethylamine (0.3 mL) were added. The resulting reaction mixture was allowed to stir at room temperature for 20 h before concentrated under reduced pressure. The residue was purified using preparative TLC on silica gel using 10% methanol in dichloromethane as the

developing solvent to provide compound **5A** (30 mg, 19% yield). M.S. found for $C_{32}H_{32}ClN_7O_7S$: 694.4 $(M+H)^+$.

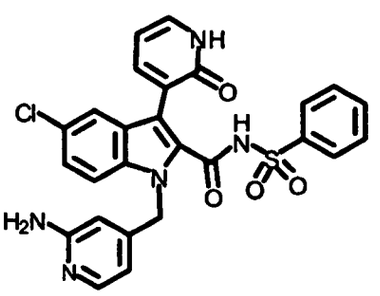
Step 2:



{4-[5-Chloro-3-(2,4-dimethoxy-pyrimidin-5-yl)-2-(2-sulfamoyl-phenylcarbamoyl)-indol-1-ylmethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester, **5A** (30 mg, 0.043 mmol) was dissolved in 4.0 M HCl in 1,4-dioxane (1.0 mL, 4.0 mmol). The resulting solution was allowed to stir at 90 °C in a sealed tube for 17 h before being cooled down to room temperature. The mixture was concentrated under reduced pressure. The residue was purified using prep TLC on silica gel with 10% methanol in dichloromethane as the developing solvent to provide compound **599** (18 mg, 76% yield). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.35 (s, 1H), 11.28 (s, 1H), 11.13 (s, 1H), 7.84 (d, J= 7.88 Hz, 1H), 7.72-7.69 (m, 3H), 7.57 (d, J= 4.73 Hz, 1H), 7.50 (t, J= 8.04 Hz, 1H), 7.39 (d, J= 9.14 Hz, 1H), 7.32 (d, J= 7.88 Hz, 1H), 6.15 (s, 1H), 6.11-6.08 (m, 1H), 5.76 (s, 1H), 5.67 (s, 2H), 4.04 (s, 2H).
M.S. found for $C_{25}H_{18}ClN_7O_4S$: 548.3 $(M+H)^+$.

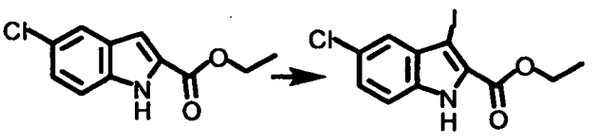
Example 6

Preparation of Compound **277**



277

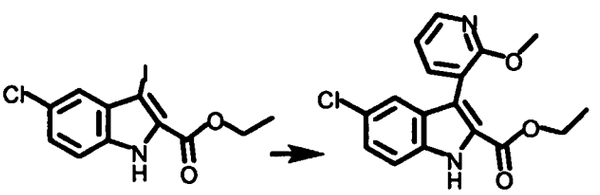
Step 1:



6A 6B

To a solution of 5-chloro-1H-indole-2-carboxylic acid ethyl ester, **6A** (5.0 g, 22 mmol) in chloroform (25 mL) at room temperature was added N-iodosuccinimide (5.0 g, 22 mmol). The resulting suspension was allowed to stir at room temperature for 24 hours. The mixture was then concentrated under reduced pressure, and the residue dissolved into ethyl acetate (300 mL). The mixture was washed with water (100 mL) and brine respectively. The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product **6B** (7.0 g, 91% yield). M.S. found for C11H9ClINO2: 350.2 $(M+H)^+$.

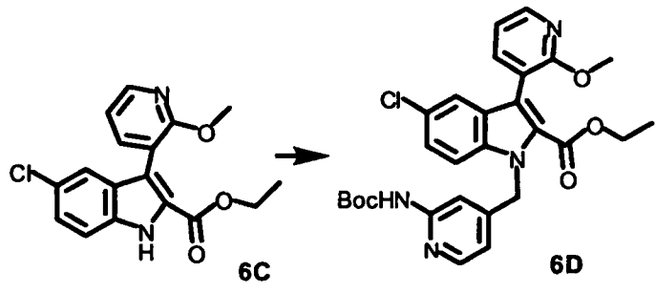
Step 2:



6B 6C

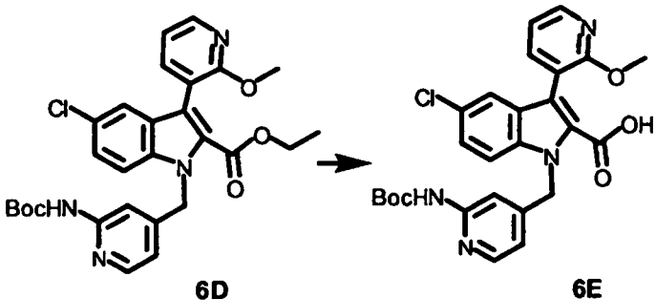
5-Chloro-3-iodo-1H-indole-2-carboxylic acid ethyl ester, **6B** (3.0 g, 8.6 mmol) was dissolved into 1,2-dimethoxyethane (40 mL) and $PdCl_2(dppf)_2$ (0.7 g, 0.86 mmol) was added. The resulting mixture was refluxed at 90 °C for 0.5 hours. To the above mixture was added slowly a solution of 2-methoxy-3-pyridine boronic acid (2.9 g, 18.8 mmol) and potassium carbonate (2.4 g, 17.3 mmol) in water (10 mL). The resulting biphasic mixture was vigorously stirred at 90 °C for 1 h before it was cooled to room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with ethyl acetate (150 mL), and was washed with a solution of sodium sulfite (5 g) in water (50 mL). The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to provide compound **6C** (1.87 g, 66% yield). M.S. found for C17H15ClN2O3: 331.20 $(M+H)^+$.

Step 3:



5-Chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **6C** (1.0 g, 3.0 mmol) was dissolved in DMF (15 mL) at room temperature. (4-bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (1.0 g, 3.6 mmol) and cesium carbonate (0.9 g, 4.5 mmol) were added sequentially and the resulting suspension stirred at room temperature for 20 hours. Ethyl acetate (200 mL) and water (100 mL) were added to the reaction mixture, and the layers were separated. The organic layer was washed with brine, and dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **6D** (1.49 g, 93% yield). M.S. found for C29H30ClN3O5: 537.27 $(M+H)^+$; 437.17 $(M-Boc+H)^+$.

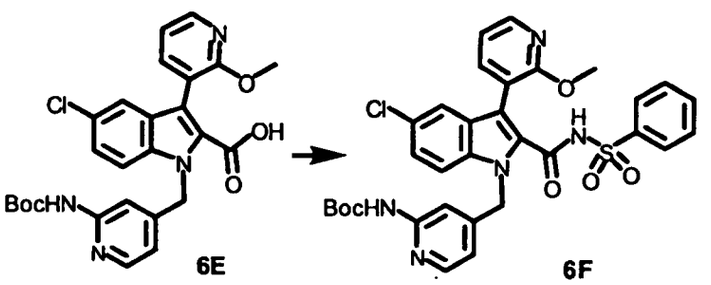
Step 4:



To a solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-5-chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **6D** (1.5 g, 2.79 mmol) in THF (20 mL) was added the solution of lithium hydroxide (0.3 g, 8.37 mmol) in water (5 mL). The resulting suspension was allowed to stir at 60 °C for 20 hours. The mixture was concentrated under reduced pressure. Ethyl acetate (150 mL) and water (100 mL) were added to the residue. The aqueous layer was acidified to pH=1~2 by adding aqueous 1N HCl solution, and was saturated with NaCl salts. The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 X 100 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product **6E** (100% yield). ^1H

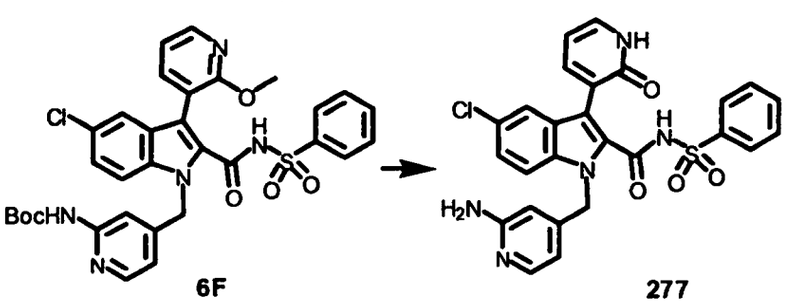
NMR (500 MHz, CDCl3) δ 9.36 (s, 1H), 8.22 & 8.21 (dd, J= 1.89 Hz & 5.04 Hz, 1H), 8.07 (s, 1H), 7.81 (d, J= 5.68 Hz, 1H), 7.70 & 7.68 (dd, J= 1.89 Hz & 7.25 Hz, 1H), 7.45 (d, J= 1.89 Hz, 1H), 7.31 & 7.29 (dd, J= 1.89 Hz & 8.83 Hz, 1H), 7.23 (d, J= 8.83 Hz, 1H), 7.01 (q, J= 5.04 Hz & 2.21 Hz, 1H), 6.36 (d, J= 5.04 Hz, 1H), 5.85 (s, 2H), 3.80 (s, 3H), 1.46 (s, 9H).

Step 5:



1-(2-tert-Butoxycarbonylamino-pyridin-4-ylmethyl)-5-chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **6E** (400 mg, 0.79 mmol) was dissolved into tetrahydrofuran (30 mL) at room temperature. To the mixture was added carbonyl diimidazole (140 mg, 0.87 mmol). The resulting suspension was refluxed at 75 °C for 1 hour, and then cooled to room temperature to proved uncharacterized acylimidazole intermediate in THF (30 mL) solution. To the THF solution of the preceding intermediate (5 mL) were added benzenesulfonamide (30 mg, 0.19 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (30 uL). The resulting reaction mixture was allowed to stir at room temperature for 20 hours. Ethyl acetate (50 mL), tetrahydrofuran (10 mL) and 1% aqueous phosphoric acid (15 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ethyl acetate/THF (3:1) (2 x 40 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to provide compound **6F** (60 mg, 57% yield). M.S. found for C32H30ClN5O6S: 648.27 $(M+H)^+$.

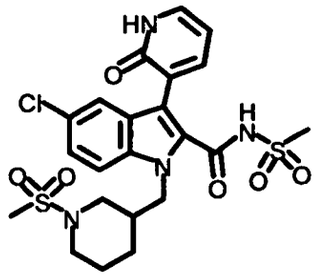
Step 6:



To a solution of {4-[2-benzenesulfonylaminocarbonyl-5-chloro-3-(2-methoxy-pyridin-3-yl)-indol-1-ylmethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester, **6F** (60 mg, 0.09 mmol) in methanol (3 mL) was added 4 N HCl in 1,4-dioxane (3 mL). The resulting reaction mixture was allowed to stir at 90 °C in a sealed tube for 2 hours. The mixture was concentrated under reduced pressure, and the residue was purified using flash chromatography to provide compound **277**. ^{1}H NMR (500 MHz, d_6-DMSO) δ 7.88 (d, J= 7.25 Hz, 2H), 7.84-7.79 (m, 2H), 7.66 (t, J= 6.62 Hz, 2H), 7.54-7.48 (m, 4H), 7.37 (d, J= 8.51 Hz, 1H), 6.76 (s, 1H), 6.56 (s, 1H), 6.19 (s, 1H), 5.64 (s, 2H). M.S. found for $C_{26}H_{20}ClN_5O_4S$: 534.17 $(M+H)^+$.

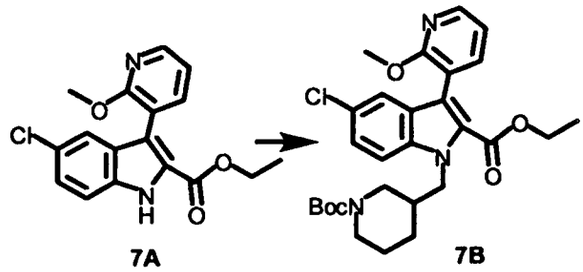
Example 7

Preparation of Compound **310**



310

Step 1:

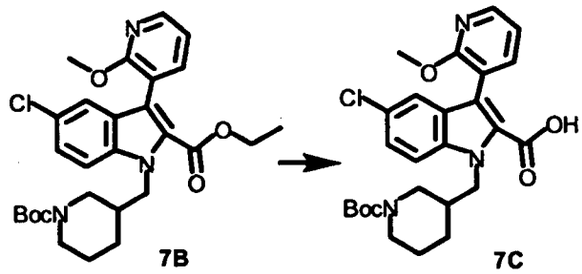


7A **7B**

To a solution of 5-chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **7A** (500 mg, 1.51 mmol) in DMF (3 mL) were added 1-N-boc-3-bromomethylpiperidine (500 mg, 1.78 mmol) and cesium carbonate. The resulting suspension was allowed to stir at 50 °C for 20 hours. The mixture was cooled down to room temperature, diluted with ethyl acetate (100 mL), and washed with water (3 x 20 mL). The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using Combiflash chromatography on silica gel using 0-10% ethyl acetate in hexanes to provide compound **7B** (780 mg, 97% yield). ^{1}H NMR (500 MHz, CDCl3) δ 8.21 & 8.20 (dd,

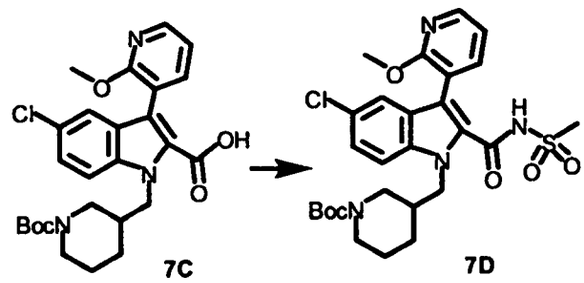
J= 1.89 Hz & 5.04 Hz, 1H), 7.61 & 7.60 (dd, J= 1.58 Hz & 7.25 Hz, 1H), 7.41 (d, J= 1.58 Hz, 1H), 7.33 (d, J= 8.51 Hz, 1H), 7.31 & 7.29 (dd, J= 1.89 Hz & 8.83 Hz, 1H), 7.01 (q, J= 5.04 Hz & 2.21 Hz, 1H), 4.48 (s, 2H), 4.14 (q, J= 6.94 Hz & 7.25 Hz, 2H), 3.94 (d, J= 13.24 Hz, 1H), 3.86 (s, 3H), 2.78-2.72 (m, 1H), 2.63 (t, J= 11.67 Hz, 1H), 1.58 (s, 6H), 1.38 (s, 9H), 1.00 (t, J= 7.09 Hz, 3H).

Step 2:



To a solution of 1-(1-tert-butoxycarbonyl-piperidin-3-ylmethyl)-5-chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **7B** (370 mg, 0.70 mmol) in THF (50 mL) was added an aqueous solution of lithium hydroxide (2.0 mL of 1 M, 2.0 mmol). The resulting mixture was allowed to stir at reflux for 2 days before cooled down to room temperature. The mixture was concentrated under reduced pressure. The residue was dissolved into methanol (5 mL), neutralized with aqueous 1.0 M HCl solution (2.0 mL, 2.0 mmol) and then concentrated again under reduced pressure. The residue was triturated with ethyl acetate (3 x 30 mL), and the combined organic layer was concentrated and dried on house vacuum to provide compound **7C** (290 mg, 83% yield).

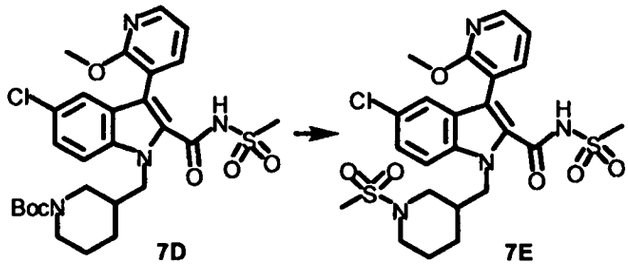
Step 3:



To a solution of 1-(1-tert-butoxycarbonyl-piperidin-3-ylmethyl)-5-chloro-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **7C** (290 mg, 0.58 mmol) in THF (5 mL) was added 1,1'-carbonyldiimidazole (150 mg, 0.92 mmol). The mixture was refluxed for 1.5

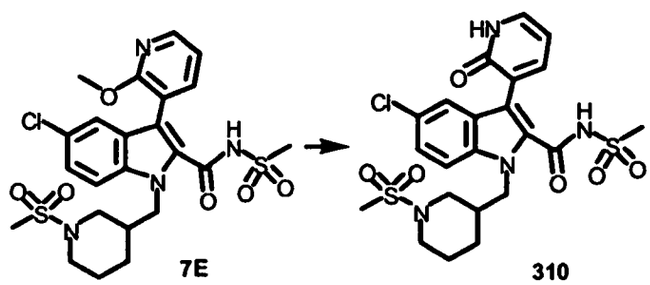
hours, cooled to room temperature and then methylsulfonamide (120 mg, 1.26 mmol) and DBU (190 mg, 1.25 mmol) were added. The resulting reaction mixture was allowed to stir at reflux for 3 h before cooled to room temperature. The mixture was concentrated under reduced pressure. The residue was purified using Combiflash chromatography on silica gel using 0-5% methanol in dichloromethane to provide compound **7D** (280 mg, 84% yield). M.S. found for $C_{27}H_{33}ClN_4O_6S$: 577.3 $(M+H)^+$.

Step 4:



A solution of 3-[5-Chloro-2-methanesulfonylaminocarbonyl-3-(2-methoxy-pyridin-3-yl)-indol-1-ylmethyl]-piperidine-1-carboxylic acid tert-butyl ester, **7D** (85 mg, 0.15 mmol) in trifluoroacetic acid (2 mL) and dichloromethane (2 mL) was allowed to stir at room temperature for 4 hours. The mixture was then concentrated under reduced pressure, dissolved in dichloromethane (3 mL) and treated with triethylamine (0.5 mL) and methylsulfonyl-chloride (50 mg, 0.44 mmol). The resulting mixture was allowed to stir at room temperature for an additional 18 hours. The mixture was then concentrated under reduced pressure, and the residue was purified using Combiflash chromatography on silica gel using 0-5% methanol in dichloromethane to provide compound **7E** (40 mg, 49% yield). M.S. found for $C_{23}H_{27}ClN_4O_6S_2$: 555.3 $(M+H)^+$.

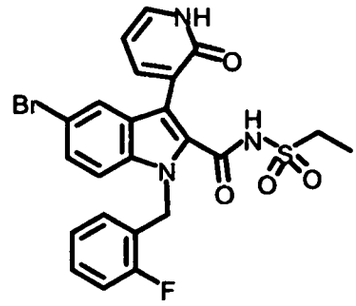
Step 5:



N-[5-Chloro-1-(1-methanesulfonyl-piperidin-3-ylmethyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carbonyl]-methanesulfonamide, **7E** (40 mg, 0.072 mmol) was dissolved in 4.0 N HCl in 1,4-dioxane (2.0 mL, 8.0 mmol). The mixture was allowed to stir at 90 °C in a sealed tube for 1 hour, cooled to room temperature, and then concentrated under reduced pressure. The residue was washed with methanol (2 x 3 mL), and was dried *in vacuo* to provide compound **310** as a white solid (26 mg, 67% yield). ^{1}H NMR (500 MHz, d_6-DMSO); δ 12.78 (s, 1H), 12.42 (s, 1H), 7.79-7.75 (m, 2H), 7.59 (s, 1H), 7.46 (s, 1H), 7.38 & 7.37 (dd, J= 1.89 Hz & 8.51 Hz, 1H), 6.52 (t, J= 6.94 Hz, 1H), 4.47-4.37 (m, 2H), 3.41 & 3.38 (dd, J= 3.15 Hz & 11.67 Hz, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 2.70-2.58 (m, 2H), 2.05-1.99 (m, 1H), 1.74-1.70 (m, 1H), 1.52-1.48 (m,1H), 1.40 (q, J= 11.67 Hz & 13.56 Hz, 1H), 1.09 (q, J= 11.67 Hz & 11.03 Hz, 1H). M.S. found for $C_{22}H_{25}ClN_4O_6S_2$: 541.3 $(M+H)^+$.

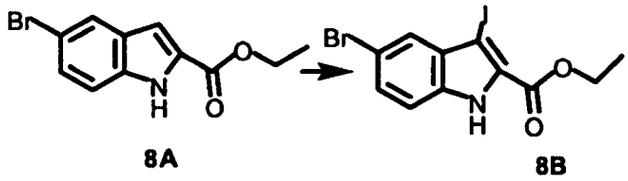
Example 8

Preparation of Compound **273**



273

Step 1:

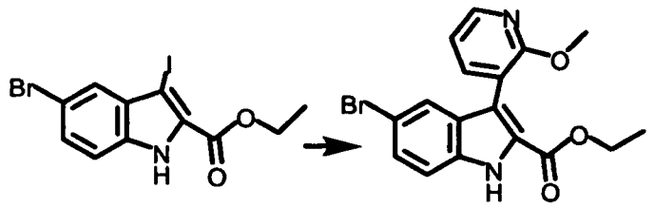


8A **8B**

Ethyl 5-bromo 2-indole carboxylate, **8A** (4.0 g, 14.9 mmol) was dissolved into acetone (200 mL) at room temperature. To the mixture was added N-iodosuccinimide (3.65 g, 15.4 mmol). The resulting suspension was allowed to stir at room temperature for 3 hours. The mixture was concentrated under reduced pressure, and the residue was dissovled into ethyl acetate (150 mL). The mixture was 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 layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide the crude product **8B** (100% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 12.48 (s, 1H), 7.55 (s, 1H), 7.45-7.44 (m, 2H), 4.39 (q, J= 6.59 Hz & 7.32 Hz, 2H), 1.38 (t, J= 7.32 Hz, 3H).

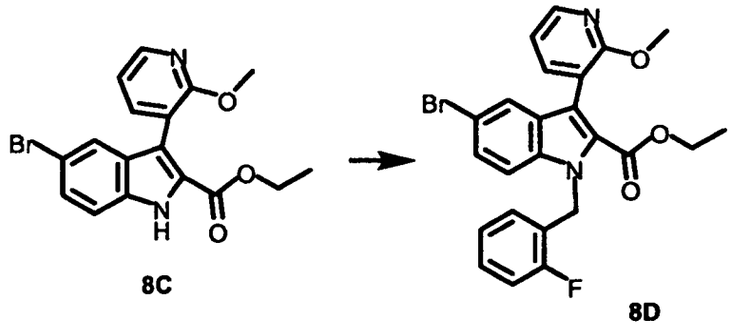
Step 2:



8B **8C**

5-Bromo-3-iodo-1H-indole-2-carboxylic acid ethyl ester, **8B** (8.66 g, 21.9 mmol) was dissolved into 1,2-dimethoxyethane (400 mL). And $PdCl_2(dppf)_2$ (1.80 g, 2.20 mmol) was added. The resulting mixture was de-gassed with nitrogen bubbling for 5 min before it was heated to 90 °C and allowed to stir for 15 minutes. In a second flask, the mixture of 2-methoxy-3-pyridine boronic acid (3.72 g, 24.3 mmol) and potassium carbonate (15.2 g, 110 mmol) in dimethoxyethane (100 mL) and water (100 mL) was de-gassed with nitrogen bubbling for 5 minutes. The mixture was then transferred in three portions to the first flask. The resulting bi-phasic mixture was vigorously stirred at 90 °C for 3.5 h before it was cooled to room temperature. The reaction was quenched by addition of a solution of sodium sulfite (15 g) in water (200 mL) at room temperature. Ethyl acetate (200 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 300 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide the crude product **8C** (100% yield). M.S. calc'd for C17H15BrN2O3: 375.22. Found: 377.00.

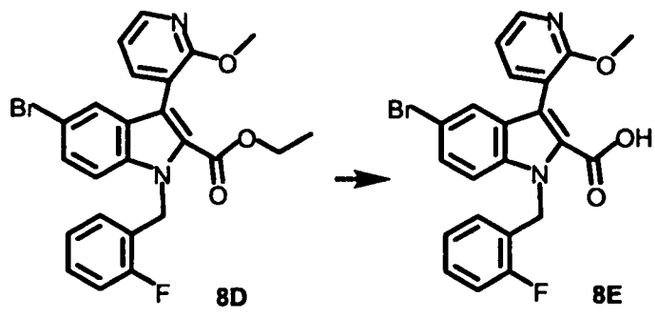
Step 3:



8C 8D

5-Bromo-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **8C** (0.66 g, 1.59 mmol) was dissolved into DMF (50 mL) at room temperature. To the mixture were added 2-fluorobenzyl bromide (0.42 g, 2.23 mmol) and cesium carbonate (0.84 g, 2.40 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 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 the crude product. The crude product was purified using flash chromatography to provide product **8D** (0.32 g, 42 % yield). M.S. calc'd for C24H20N2O3BrF: 483.33. Found: 485.3.

Step 4:

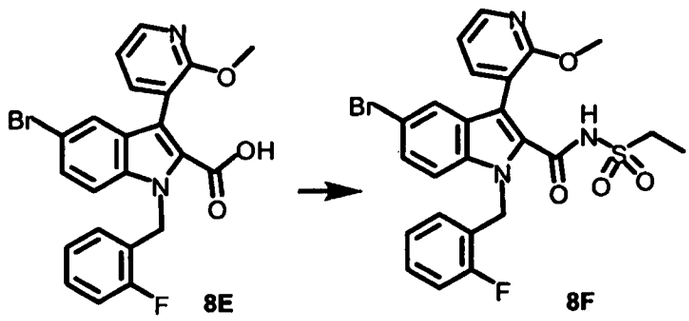


8D 8E

To a solution of 5-bromo-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **8D** (0.32 g, 0.66 mmol) in methanol (5 mL) was added lithium hydroxide monohydrate (110 mg, 2.64 mmol). And water (0.2 mL) was added to improve the solubility. The resulting suspension was allowed to stir at room temperature for 5 min before being placed in microwave reactor for 20 min (120 °C, high power). The mixture was concentrated under reduced pressure. Ethyl acetate (50 mL) and water (50 mL) were added to the residue. The aqueous layer was acidified to pH=2 by adding aqueous 1N HCl solution, and

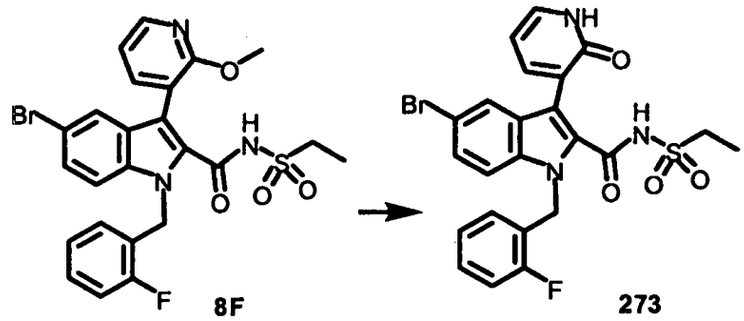
was saturated with NaCl salts. The layers were seperated, and the aqueous layer was further extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried (magnesium sulfate) and filtered and concentrated *in vacuo* to provide the crude product **8E** (93 % yield). M.S. calc'd for C22H16N2O3BrF: 455.28. Found: 456.01 $(M+H)^+$.

Step 5:



5-Bromo-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **8E** (0.11 g, 0.24 mmol) was dissolved into tetrahydrofuran (5 mL) at room temperature. To the mixture was added carbonyl diimidazole (60 mg, 0.36 mmol). The resulting suspension was refluxed at 75 °C for 1.5 hours, and then cooled down to room temperature before adding ethane sulfonamide (77 mg, 0.75 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.12 mL, 0.75 mmol). The resulting reaction mixture was allowed to stir at room temperature for 48 hours. Ethyl acetate (80 mL), tetrahydrofuran (16 mL) and 1% aqueous phosphoric acid (25 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate/THF (3:1) (60 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide **8F** (80 mg, 60% yield). M.S. calc'd for C24H21N3O4FSBr: 546.41. Found: 547.93 $(M+H)^+$.

Step 6:



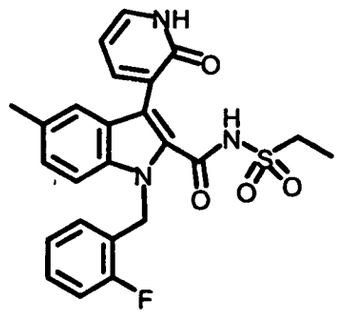
8F 273

Ethanesulfonic acid [5-bromo-1-(2-fluoro-benzyl)-3-(2-oxo-1,2-dihydro-pyridin-3-yl)-1H-indole-2-carbonyl]-amide, **8F** (80 mg, 0.15 mmol) was dissolved into 4N HCl in 1,4-dioxane (4 mL) in a tube. The reaction mixture was allowed to stir at 90 °C in the sealed tube for 1.5 hours. The reaction mixture was cooled down to room temperature before being concentrated under reduced pressure. The crude product was purified using reverse phase HPLC to provide compound **273** (55 mg, 71% yield). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.72 (bs, 2H), 7.82 & 7.80 (dd, J= 1.89 Hz & 6.94 Hz, 1H), 7.66 (d, J= 8.83 Hz, 2H), 7.57 (d, J= 1.89 Hz, 1H), 7.49 & 7.48 (dd, J= 1.58 Hz & 8.83 Hz, 1H), 7.33 (q, J= 7.25 Hz & 7.88 Hz, 1H), 7.21 (t, J= 9.14 Hz, 1H), 7.08 (t, J= 7.57 Hz, 1H), 6.82 (t, J= 7.72 Hz, 1H), 6.59 (t, J= 6.62 Hz, 1H), 5.76 (s, 2H), 3.36 – 3.32 (m, 2H), 1.02 (t, J= 7.25 Hz, 3H); ^{13}C NMR (125 MHz, d_6-DMSO) δ163.04, 162.22, 160.79, 160.63, 158.66, 129.57, 129.51, 128.54, 128.51, 127.70, 127.56, 124.57, 124.44, 124.32, 122.69, 115.41, 115.24, 113.62, 113.27, 107.20, 54.84, 46.72, 7.36.

M.S. calc'd for C23H19BrFN3O4S: 532.38. Found: 534.3.

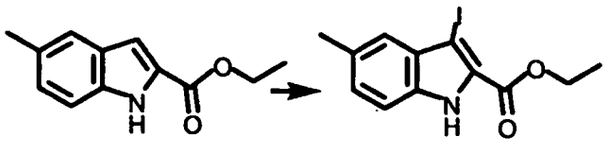
Example 9

Preparation of Compound **34**



34

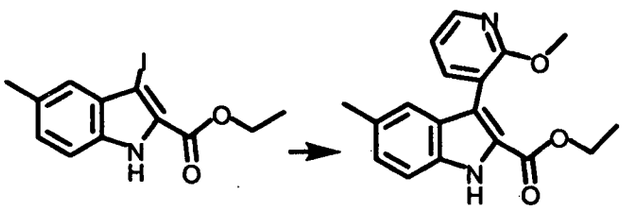
Step 1:



9A **9B**

To a solution of ethyl 5-methyl indole carboxylate, **9A** (5.0 g, 24.6 mmol) in acetone (200 mL) was added N-iodosuccinimide (3.65 g, 15.4 mmol). The resulting suspension was allowed to stir at room temperature for 4 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved into ethyl acetate (200 mL). The mixture was washed with saturated aqueous sodium thiosulfate solution (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 100 mL). The combined organic layer was washed with water (200 mL), and was then dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide the crude product **9B** (7.62 g, 94% yield).

Step 2:

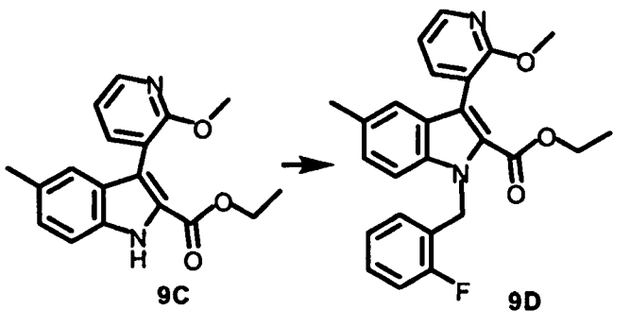


9B **9C**

3-Iodo-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **9B** (7.62 g, 23.2 mmol) was dissolved into 1,2-dimethoxyethane (100 mL) and $PdCl_2(dppf)_2$ (1.89 g, 2.32 mmol) was added. The resulting mixture was de-gassed with nitrogen bubbling for 10 minutes. In a second flask, the mixture of 2-methoxy-3-pyridine boronic acid (4.26 g, 27.8 mmol) and potassium carbonate (16.0 g, 115.8 mmol) in dimethoxyethane (50 mL) and water (50 mL) was de-gassed with nitrogen bubbling for 5 minutes. The mixture was then transferred slowly to the first flask. The resulting biphasic mixture was allowed to stir at room temperature for 15 minutes, and then vigorously stirred at 90 °C for 4 hours. The reaction mixture was cooled to room temperature, and was quenched by addition of a solution of sodium sulfite (5 g) in water (100 mL) at room temperature. Ethyl acetate (200 mL) was added, and the layers were seperated. The aqueous layer was extracted with ethyl acetate (2 x 300 mL). The combined organic layer was filtered through a pad of celite, dried over magnesium sulfate, and concentrated *in vacuo*

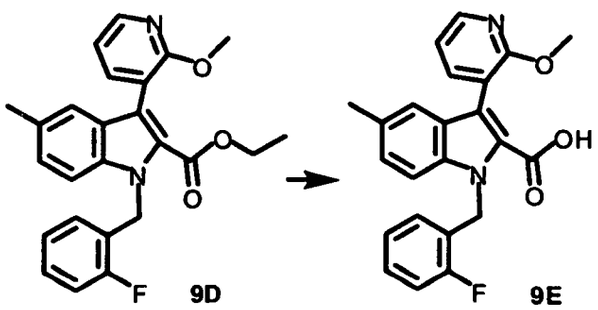
to provide the crude product **9C** (4.12 g, 57% yield). M.S. calc'd for C18H18N2O3: 310.35. Found: 311.15 $(M+H)^+$.

Step 3:



3-(2-Methoxy-pyridin-3-yl)-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **9C** (0.70 g, 2.25 mmol) was dissolved into DMF (25 mL) at room temperature. To the mixture were added 2-fluorobenzyl bromide (0.68 g, 3.60 mmol) and cesium carbonate (1.60 g, 4.50 mmol). The resulting suspension was allowed to stir at room temperature for 18 hours. 300 mL of THF/ethyl acetate (1:3) and 50 mL of water were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with 100 mL of THF/ethyl acetate (1:3). The combined organic layer was washed with water (3 X 100 mL). The separated organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product obtained was purified using flash chromatography to provide compound **9D** (0.75 g, 79 % yield). M.S. calc'd for C25H23FN2O3: 418.46. Found: 419.27 $(M+H)^+$.

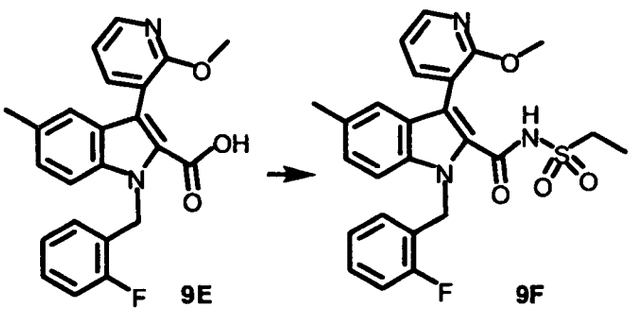
Step 4:



To a solution of 1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-methyl-1H-indole-2-carboxylic acid ethyl ester, **9D** (0.75 g, 1.79 mmol) in methanol (20 mL) was added lithium hydroxide monohydrate (220 mg, 5.24 mmol). Water (0.2 mL) was added to improve the solubility. The resulting suspension was allowed to stir at room temperature for 5 min before

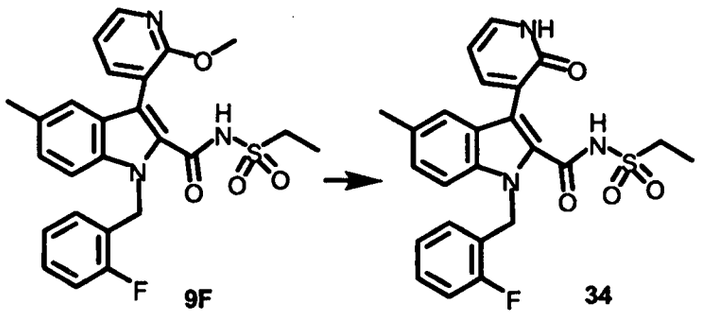
being placed in microwave reactor for 20 min (120 °C, high power). The mixture was concentrated under reduced pressure, and 30 mL of water was added. The aqueous layer was acidified to pH=2 by adding aqueous 1N HCl solution, and the mixture was extracted three times with 100 mL of THF/ethyl acetate (3:1). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **9E** (0.70 g, 99% yield). M.S. calc'd for C23H19FN2O3: 390.41. Found: 391.2 $(M+H)^+$.

Step 5:



1-(2-Fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-methyl-1H-indole-2-carboxylic acid, **9E** (140 mg, 0.36 mmol) was dissolved into tetrahydrofuran (4 mL) at room temperature. To the mixture was added carbonyl diimidazole (87 mg, 0.54 mmol). The resulting suspension was refluxed at 75 °C for 1.5 hours, and then cooled down to room temperature before ethane sulfonamide (114 mg, 1.07 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.16 mL, 1.07 mmol) were added. The resulting reaction mixture was allowed to stir at room temperature for 48 hours. Ethyl acetate (100 mL), tetrahydrofuran (20 mL) and 1% aqueous phosphoric acid (25 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate/THF (3:1) (60 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **9F** (120 mg, 70% yield). ^{1}H NMR (500 MHz, d_6-DMSO) δ 11.57 (s, 1H), 8.20 & 8.19 (dd, J= 1.89 Hz & 5.04 Hz, 1H), 7.85 &7.84 (dd,, J= 1.89 Hz & 7.25 Hz, 1H), 7.55 (d, J= 8.51 Hz, 1H), 7.31-7.25 (m, 2H), 7.25-7.15 (m, 3H), 6.72 (t, J= 6.94 Hz, 2H), 5.72 (s, 2H), 3.76 (s, 3H), 3.25 (q, J= 7.25 Hz & 7.57 Hz, 2H), 2.36 (s, 3H), 0.88 (t, J= 7.41 Hz, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ161.51, 160.45, 160.24, 151.47, 145.48, 140.09, 135.79, 130.14, 129.40, 128.29, 126.61, 125.56, 124.61, 119.47, 116.61, 115.91, 115.22, 115.06, 114.23, 110.74, 54.84, 52.89, 48.63, 20.97, 7.17. M.S. calc'd for C25H24FN3O4S: 481.54. Found: 482.3 $(M+H)^+$.

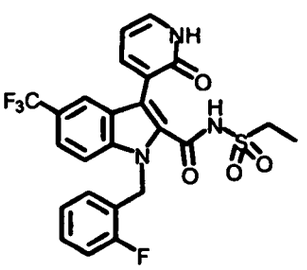
Step 6:



Ethanesulfonic acid [1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-methyl-1H-indole-2-carbonyl]-amide, **9F** (120 mg, 0.25 mmol) was dissolved into 4N HCl in 1,4-dioxane (5 mL) in a tube. Water (0.2 mL) was added afterwards. The reaction mixture was allowed to stir at 90 °C in the sealed tube for 1.5 hours. The reaction mixture was cooled down to room temperature before being concentrated under reduced pressure. The crude product was purified using reverse phase HPLC to provide compound **34** (53 mg, 46% yield). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.75 (d, J= 7.88 Hz, 2H),7.80 d, J= 4.41 Hz, 1H), 7.69 (s, 1H), 7.54-7.52 (m, 1H), 7.33-7.27 (m, 1H), 7.23-7.19 (m, 3H), 7.08-7.04 (m, 1H), 6.78 (s, 1H), 6.64 (s, 1H), 5.74 (s, 2H), 3.34-3.32 (m, 2H), 2.36 (s, 3H), 1.03-0.99 (m, 3H). ^{13}C NMR (125 MHz, d_6-DMSO) δ 162.59, 161.12, 160.55, 158.61, 144.16, 136.15, 135.57, 130.18, 129.28, 128.40, 127.14, 126.20, 124.88, 124.47, 119.62, 115.32, 115.15, 114.66, 110.74, 107.47, 66.92, 41.46, 20.94, 7.38. M.S. calc'd for C24H22FN3O4S: 467.51. Found: 468.3 $(M+H)^+$.

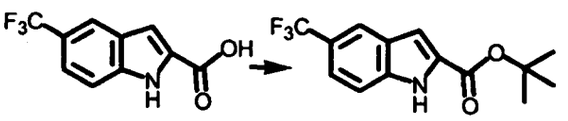
Example 10

Preparation of Compound **228**



228

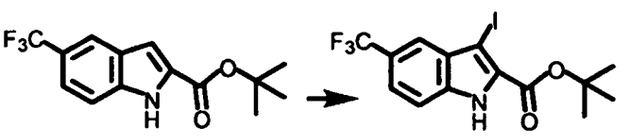
Step 1:



10A **10B**

To a solution of 5-(trifluoromethyl)indole-2-carboxylic acid, **10A** (1.6 g, 6.9 mmol) in toluene (5.0 mL) at room temperature was added N,N-dimethylformamide di-*tert*-butyl acetal (5.0 mL). The mixture was allowed to stir at 90 °C for 12 hours, and then was cooled to room temperature. Another aliquot of *N,N*-dimethylformamide di-tert butyl acetal (5 mL) was added. The reaction mixture was heated to 90 °C for another 12 hours, cooled to room temperature, and was diluted with ethyl acetate (10 mL). The mixture was washed with water (2 X 10 mL), and brine respectively. The separated organic layer was dried over $MgSO_4$, filtered and concentrated to provide compound **10B** (1.2 g, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$); δ9.17 (s, 1H), 7.97 (s, 1H), 7.51 (s, 2H), 7.21 (s, 1H), 1.63 (s, 9H).

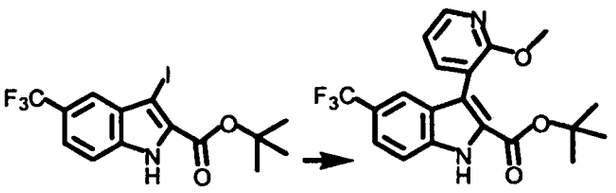
Step 2:



10B **10C**

To a solution of 5-trifluoromethyl-1H-indole-2-carboxylic acid tert-butyl ester, **10B** (1.2 g, 4.2 mmol) in $CHCl_3$ (25 mL) was added *N*-iodosuccinimide (946 mg, 4.2 mmol). The reaction mixture was allowed to stir at room temperature for 12 hours, before it was concentrated under reduced pressure. The residue was diluted into water (100 mL), and was extracted with EtOAc (200 mL). The separated organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The brown residue was taken in minimum amount of CH_2Cl_2 and triturated with hexanes. The product **10C** was separated out as a brown solid after filtration, and dried *in vacuo* (1.23 g, 72% yield). ^{1}H NMR (400 MHz, CDCl3); δ 9.34 (s, 1H), 7.87 (s, 1H), 7.57 (d, J= 8.06 Hz, 1H), 7.49 (d, J= 8.79 Hz, 1H), 1.68 (s, 9H).

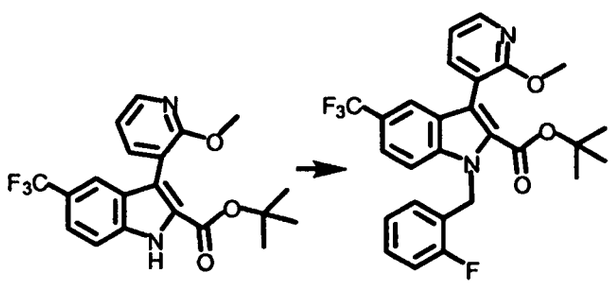
Step 3:



10C 10D

To a solution of 3-iodo-5-trifluoromethyl-1H-indole-2-carboxylic acid tert-butyl ester, **10C** (1.23 g, 3.0 mmol) in DME (30 mL) under nitrogen atmosphere was added 2-methoxy-3-pyridyl boronic acid (0.48 g, 3.15 mmol) and Pd $(dppf)_2Cl_2$ (245 mg, 0.3 mmol). 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 (1.6 g, 12 mmol) in water (12 mL), and the resulting solution was allowed to stir at 90 °C for 1 hour. The reaction mixture was then diluted with EtOAc (200 mL), and the resulting solution was concentrated under reduced pressure. The residue was purified using flash column chromatography to provide compound **10D**(820 mg, 70% yield). M.S. found for C20H19F3N2O3: 393.2 $(M+H)^+$.

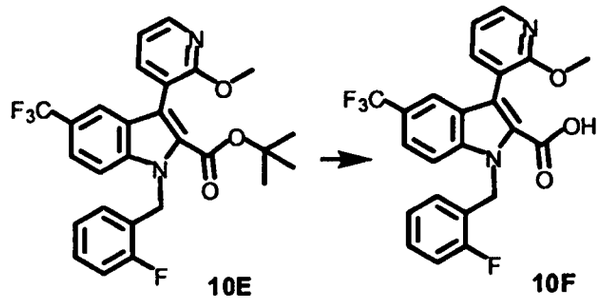
Step 4:



10D 10E

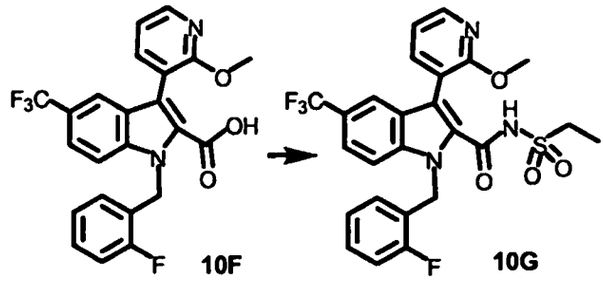
To a solution of 3-(2-methoxy-pyridin-3-yl)-5-trifluoromethyl-1H-indole-2-carboxylic acid tert-butyl ester, **10D** (400 mg, 1.02 mmol) in DMF (8 mL) were added 2-fluorobenzyl bromide (0.14 mL, 1.12 mmol) and cesium carbonate (365 mg, 1.12 mmol). The resulting mixture was allowed to stir at room temperature for 18 hours. Ethyl acetate (200 mL) and water (100 mL) were added to the reaction mixture, and the layers were separated. The organic layer was washed with water (2 x 100 mL) and brine (50 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crystallized product **10E** (100% yield). M.S. found for C27H24F4N2O3: 501.11 $(M+H)^+$.

Step 5:



To a solution of 1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethyl-1H-indole-2-carboxylic acid tert-butyl ester, **10E** (510 mg, 1.02 mmol) in CH_2Cl_2 was added trifluoroacetic acid (3 mL). The reaction mixture was allowed to stir at room temperature for 18 hours. The solvent was removed under reduced pressure. The residue was dissolved into ethyl acetate (200 mL). The ethyl acetate solution was washed with water (4 x 50 mL) and brine. The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide compound **10F** (100% yield). M.S. found for C23H16F4N2O3: 445.06 $(M+H)^+$.

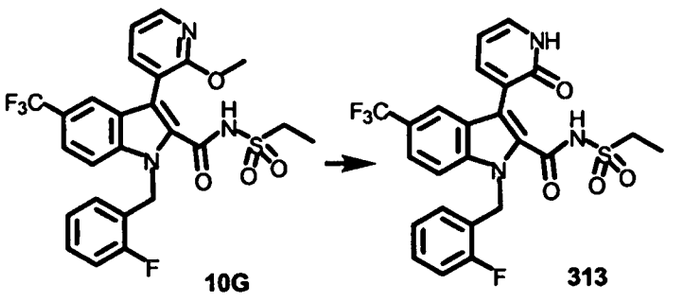
Step 6:



To a solution of 1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethyl-1H-indole-2-carboxylic acid, **10F** (100 mg, 0.23 mmol) in tetrahydrofuran (2 mL) was added carbonyl diimidazole (44 mg, 0.27 mmol). The resulting suspension was refluxed at 70 °C under argon for 1.5 hours, and then cooled down to room temperature. To the mixture were added ethane sulfonamide (37 mg, 0.34 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (67 uL, 0.45 mmol). The resulting reaction mixture was allowed to stir at room temperature for 48 hours. Ethyl acetate (100 mL) and 2% aqueous phosphoric acid (30 mL) were added to the reaction mixture, and the layers were separated. The organic layer was further washed with 2% aqueous phosphoric acid (2 x 30 mL), water (30 mL) and brine respectively. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was

purified using flash chromatography to provide compound **10G** (76 mg, 63% yield). M.S. found for C25H21F4N3O4S: 535.91 $(M+H)^+$; 557.89 $(M+Na)^+$.

Step 7:

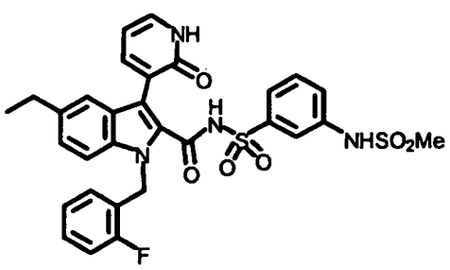


10G **313**

The solution of ethanesulfonic acid [1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethyl-1H-indole-2-carbonyl]-amide, **10G** (76 mg, 0.14 mmol) in 4N HCl in 1,4-dioxane (4 mL) and 5 drops of water was allowed to stir at 90 °C in a sealed tube for 1.5 hours. The mixture was concentrated under reduced pressure, and the residue was purified using flash chromatography to provide compound **228** (37 mg, 51% yield). ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.92-7.76 (m, 4H), 7.64 (s, 2H), 7.33 (q, J= 7.32 Hz, 1H), 7.21 (t, J= 9.52 Hz, 1H), 7.08 (t, J= 7.32 Hz, 1H), 6.87 (t, J= 7.69 Hz, 1H), 6.57 (s, 1H), 5.83 (s, 2H), 3.51-3.22 (m, 2H), 1.02 (t, J= 7.32 Hz, 3H). M.S. found for C24H19F4N3O4S: 522.22 $(M+H)^+$.

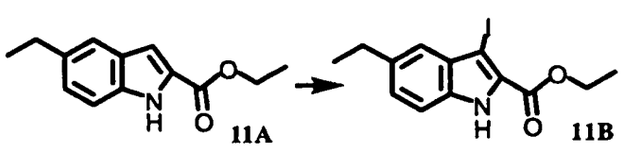
Example 11

Preparation of Compound **505**



505

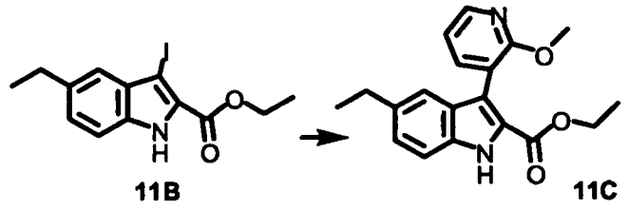
Step 1:



11A **11B**

To a solution of 5-ethylindole-2- carboxylic acid ethyl ester, **11A** (5.0 g, 23 mmol) in chloroform (100 mL) at room temperature was added N-iodosuccinimide (5.20 g, 23 mmol). The resulting suspension was allowed to stir at room temperature for 24 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved into ethyl acetate (200 mL). The mixture was washed with water (100 mL) and brine (60 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product, **11B** (7.35 g, 93% yield). M.S. found for C13H14INO2: 343.94 $(M+H)^+$.

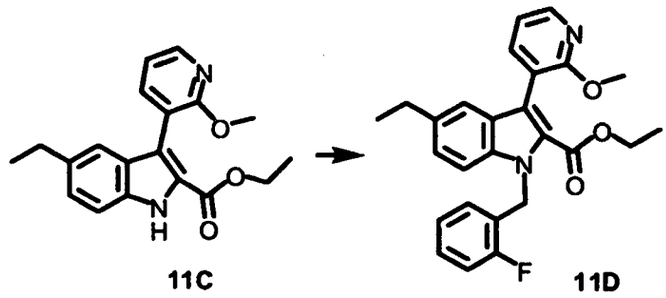
Step 2:



11B **11C**

5-Ethyl-3-iodo-1H-indole-2-carboxylic acid ethyl ester, **11B** (7.35 g, 21.4 mmol) was dissolved into 1,2-dimethoxyethane (150 mL). And $PdCl_2(dppf)_2$ (1.72 g, 0.21 mmol) was added. The resulting mixture was refluxed at 95 °C for 0.5 hours. To the mixture was added slowly the solution of 2-methoxy-3-pyridine boronic acid (9.60 g, 63 mmol) and potassium carbonate (8.7 g, 63 mmol) in water (50 mL). The resulting bi-phasic mixture was vigorously stirred at 95 °C for 1 h before it was cooled to room temperature. The reaction mixture was filtered and concentrated *in vacuo*. The residue was diluted with ethyl acetate (300 mL), and was washed with a solution of sodium sulfite (15 g) in water (200 mL). The aqueous layer was extracted with ethyl acetate (2 x 300 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified using flash chromatography to provide compound **11C** (5.0 g, 74% yield). M.S. found for C19H20N2O3: 325.06 $(M+H)^+$.

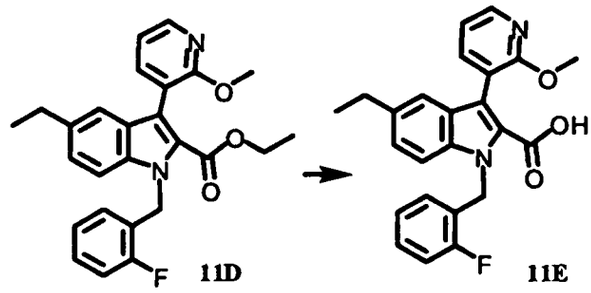
Step 3:



11C 11D

5-Ethyl-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **11C** (500 mg, 1.54 mmol) was dissolved into DMF (20 mL) at room temperature. To the mixture were added 2-fluorobenzyl chloride (224 mg, 1.54 mmol) and cesium carbonate (502 mg, 1.54 mmol). The resulting suspension was allowed to stir at room temperature for 24 hours. Ethyl acetate (100 mL) and water (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 washed with water (2 X 50 mL). The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **11D** (665 mg, 100% yield).

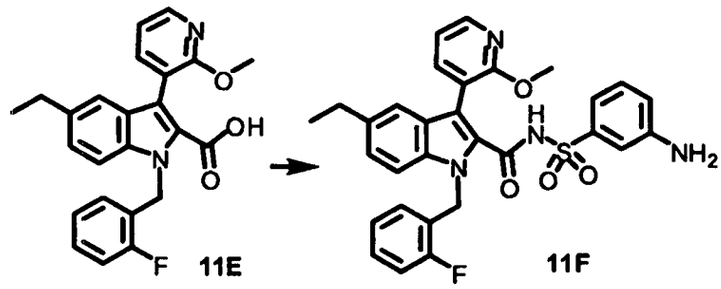
Step 4:



11D 11E

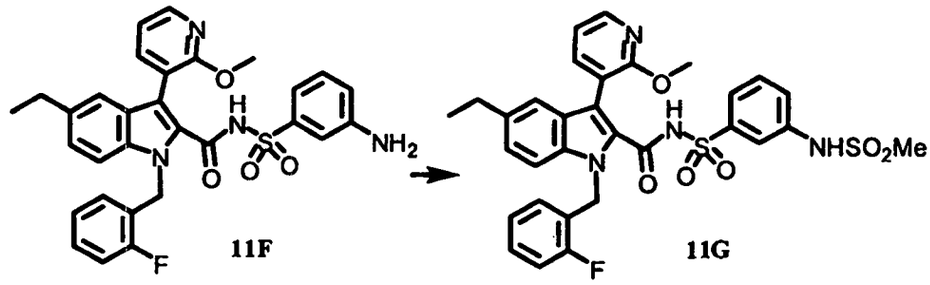
To a solution of 5-ethyl-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **11D** (665 mg, 1.54 mmol) in THF (50 mL) was added the solution of lithium hydroxide (220 mg, 9.24 mmol) in water (15 mL). The resulting suspension was allowed to stir at room temperature until the starting material was all consumed up. The mixture was concentrated under reduced pressure. Ethyl acetate (50 mL) and water (50 mL) were added to the residue. The aqueous layer was acidified to pH=2 by adding aqueous 1N HCl solution, and was saturated with NaCl salts. The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 X 50 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to provide the crude product **11E** (620 mg, 100% yield). M.S. found for C24H21N2O3F: 405.28 $(M+H)^+$.

Step 5:



5-Ethyl-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **11E** (100 mg, 0.25 mmol) was dissolved into tetrahydrofuran (10 mL) at room temperature. To the mixture was added carbonyl diimidazole (49 mg, 0.30 mmol). The resulting suspension was refluxed at 75 °C for 1 hour, and then cooled down to room temperature before the addition of 3-aminobenzenesulfonamide (52 mg, 0.30 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (46 mg, 0.30 mmol). The resulting reaction mixture was allowed to stir at room temperature for 24 hours. The solvent was then evaporated under reduced pressure. Ethyl acetate (80 mL) and 1% aqueous phosphoric acid (25 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 60 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **11F** (30 mg, 21% yield).

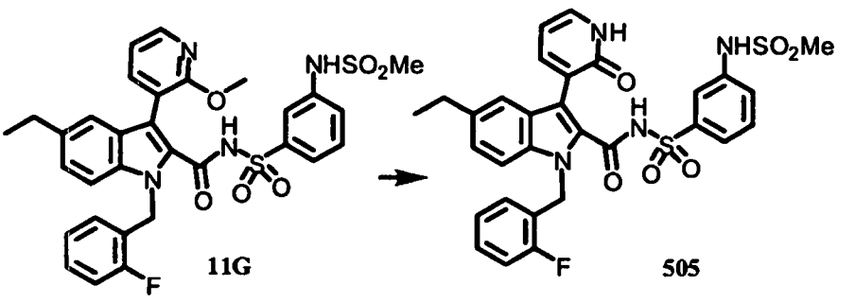
Step 7:



To a solution of 3-amino-N-[5-ethyl-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carbonyl]-benzenesulfonamide, **11F** (30 mg, 0.05 mmol) in THF (5 mL) and pyridine (1 mL) was slowly added $ClSO_2Me$. The resulting reaction mixture was allowed to stir at room temperature for 24 hours, and then was diluted with ethyl acetate (50 mL). The mixture was washed with aqueous 1N HCl solution (20 mL) and brine (20 mL) respectively.

The separated organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **11G** (30 mg, 94% yield).

Step 8:

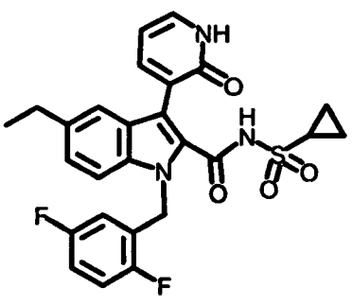


11G 505

To a solution of N-[5-ethyl-1-(2-fluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carbonyl]-3-methanesulfonylamino-benzenesulfonamide, **11G** (30 mg, 0.05 mmol) in dioxane (3 mL) was added HCl (1 mL). The resulting reaction mixture was allowed to stir at 90 °C in a sealed tube for 2 hours. The mixture was concentrated under reduced pressure, and the residue was purified using flash chromatography to provide compound **505** (10 mg, 34% yield). ^{1}H NMR (500 MHz, CD3OD): δ 7.87 (s, 1H), 7.77 (s, 1H), 7.67 (d, J= 7.88 Hz, 1H), 7.59 (d, J= 7.88 Hz, 1H), 7.54 (t, J= 8.35 Hz, 1H), 7.47-7.35 (m, 3H), 7.27 (s, 1H), 7.22 (q, J= 6.94 Hz & 6.62 Hz, 2H), 7.02 (t, J= 9.46 Hz, 1H), 6.90 (t, J= 7.57 Hz, 1H), 6.67 (s, 2H), 5.69 (s, 2H), 2.98 (s, 3H), 2.72 (q, J= 7.25 Hz & 7.57 Hz, 2H), 1.24 (t, J= 7.57 Hz, 3H). M.S. found for $C_{30}H_{27}FN_4O_6S_2$: 623.3 $(M+H)^+$

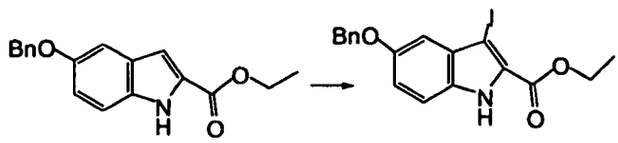
Example 12

Preparation of Compound **195**



195

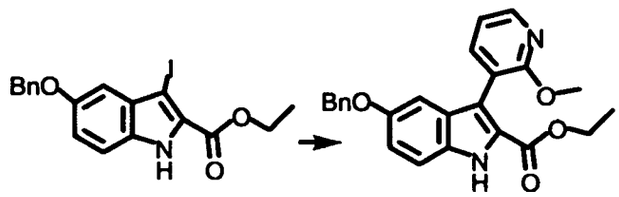
Step 1:



12A 12B

To a solution of ethyl 5-OBn indole carboxylate (**12A**, 10.0 g, 33.9 mmol) in acetone (300 mL) was added N-iodosuccinimide (8.0 g, 33.8 mmol). The resulting suspension was allowed to stir at room temperature for 4 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved into ethyl acetate (300 mL). The mixture was washed with saturated aqueous sodium thiosulfate solution (200 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 200 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **12B** (100% yield). M.S. found for C18H16INO3: 421.89 $(M+H)^+$.

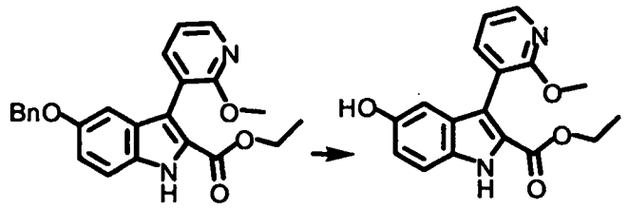
Step 2:



12B 12C

5-Benzyloxy-3-iodo-1H-indole-2-carboxylic acid ethyl ester, **12B** (10.8 g, 24.1 mmol) was dissolved into 1,2-dimethoxyethane (300 mL). And $PdCl_2(dppf)_2$ (2.0 g, 2.45 mmol) was added. The resulting mixture was de-gassed with nitrogen bubbling for 5 min before it was heated to 90 °C and allowed to stir for 15 minutes. In a second flask, the mixture of 2-methoxy-3-pyridine boronic acid (4.3 g, 28.1 mmol) and potassium carbonate (16.7 g, 121 mmol) in dimethoxyethane (100 mL) and water (100 mL) was de-gassed with nitrogen bubbling for 5 minutes. The mixture was then transferred in three portions to the first flask. The resulting biphasic mixture was vigorously stirred at 90 °C for 3.5 h before it was cooled to room temperature. The reaction was quenched by addition of a solution of sodium sulfite (15 g) in water (200 mL) at room temperature. Ethyl acetate (300 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 x 300 mL). The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo* to provide the crude product **12C** (7.37 g, 76% yield). M.S. found for C24H22N2O4: 403.1 $(M+H)^+$.

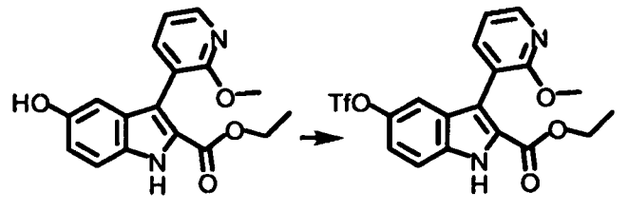
Step 3:



12C **12D**

To a solution of 5-benzyloxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **12C** (4.2 g, 10.4 mmol) in absolute EtOH was added 5% Pd-C (2.0 g). The flask was vacuumed, and then charged with H_2 gas. The reaction mixture was allowed to stir at room temperature for 3 hours. The palladium catalyst was filtered off through a pad of celite, and was washed with 100 mL of MeOH/THF (1:1). The filtrate collected was concentrated under reduced pressure to provide the crude product **12D** (3.25 g, 100% yield). M.S. found for C17H16N2O4: 313.2 $(M+H)^+$.

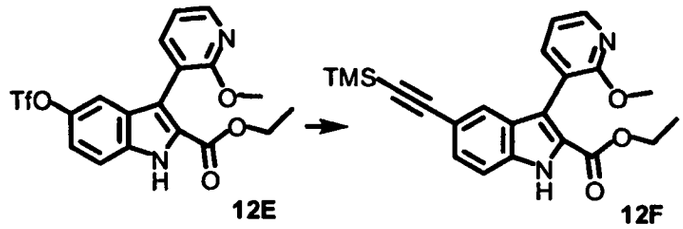
Step 4:



12D **12E**

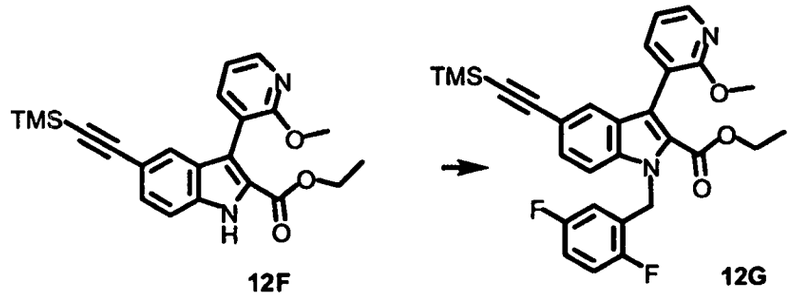
To the mixture of 5-hydroxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **12D** (3.2 g, 10.4 mmol) and triethyl amine (4.0 mL, 28.7 mmol) in dichloromethane (100 mL) was added $PhN(SO_2CF_3)_2$ (5.4 g, 15.1 mmol). The resulting reaction mixture was allowed to stir at room temperature for 4 hours. The mixture was then diluted with dichloromethane (100 mL), and was washed with aqueous 1N sodium carbonate solution (2 x 100 mL). The seperated aqueous solution was again extracted with dichloromethane (100 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **12E** (4.12 g, 88% yield). M.S. found for C18H15F3N2O6S: 445.2 $(M+H)^+$.

Step 5:



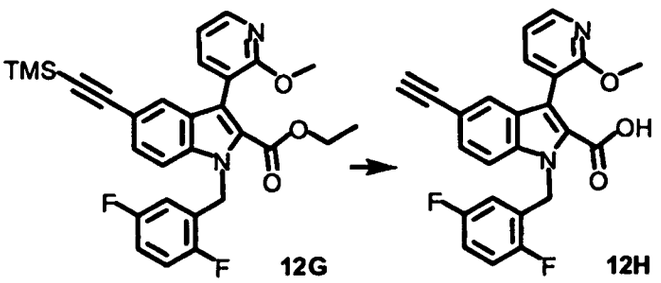
To a solution of 3-(2-methoxy-pyridin-3-yl)-5-trifluoromethanesulfonyloxy-1H-indole-2-carboxylic acid ethyl ester, **12E** (1.0 g, 2.25 mmol), TMS acetylene (2.0 mL, 14.4 mmol) and $nBu_4N^+T^-$ (0.92 g, 2.49 mmol) in DMF (48 mL) were added $PdCl_2(PPh_3)_2$ (160 mg, 0.23 mmol), CuI (130 mg, 0.68 mmol) and triethylamine (2.1 mL, 15.1 mmol). The resulting reaction mixture was stirred in a sealed tube at 65 °C for 18 hours. The mixture was cooled down to room temperature, and was diluted with water (50 mL) and EtOAc (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layer was washed with water (2 x 100 mL) before it was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **12F** (100% yield). M.S. found for C22H24N2O3Si: 393.3 $(M+H)^+$.

Step 6:



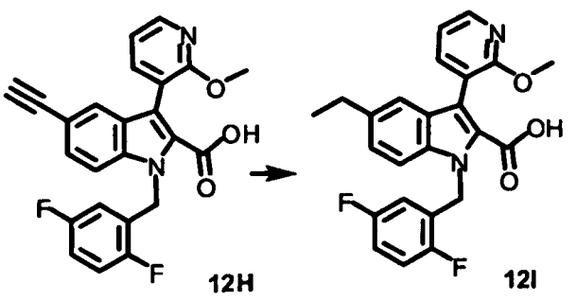
3-(2-Methoxy-pyridin-3-yl)-5-trimethylsilanylethynyl-1H-indole-2-carboxylic acid ethyl ester, **12F** (0.76 g, 1.94 mmol) was dissolved into DMF (40 mL) at room temperature. To the mixture were added 2,5-difluorobenzyl bromide (0.60 g, 2.9 mmol) and cesium carbonate (1.1 g, 3.38 mmol). The resulting suspension was allowed to stir at room temperature for 18 hours. 300 mL of THF/ethyl acetate (1:3) and 50 mL of water 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 washed with water (2 X 100 mL). The separated organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **12G** (0.65 g, 81 % yield). M.S. found for C29H28F2N2O3Si: 519.3 $(M+H)^+$.

Step 7:



To a solution of 1-(2,5-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trimethylsilanylethynyl-1H-indole-2-carboxylic acid ethyl ester, **12G** (0.65 g, 1.25 mmol) in methanol (12 mL) and THF (5 mL) was added lithium hydroxide monohydrate (220 mg, 5.24 mmol). The resulting suspension was allowed to stir at room temperature for 5 min before being placed in microwave reactor for 20 min (120 °C, high power). The mixture was concentrated under reduced pressure, and 30 mL of water was added. The aqueous layer was acidified to pH=2 by adding aqueous 1N HCl solution, and the mixture was extracted three times with 100 mL of THF/ethyl acetate (3:1). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **12H** (100% yield). ^{1}H NMR (400 MHz, CDCl3) δ 8.32 & 8.30 (dd, J= 2.20 Hz & 5.13 Hz, 1H), 7.75 & 7.73 (dd, J= 2.20 Hz & 7.32 Hz, 1H), 7.68 (s, 1H), 7.45 (d, J= 9.52 Hz, 1H), 7.33 (d, J= 8.79 Hz, 1H), 7.09-6.88 (m, 4H), 6.47-6.42 (m, 1H), 5.87 (s, 2H), 3.74 (s, 3H), 3.01 (s, 1H).

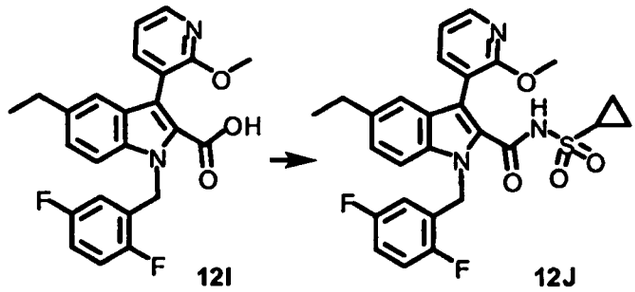
Step 8::



To a solution of 1-(2,5-difluoro-benzyl)-5-ethynyl-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **12H** (0.57 g, 1.25 mmol) in absolute EtOH and THF was added 5% Pd-C (200 mg). The flask was vacuumed, and then charged with H_2 gas. The reaction mixture was allowed to stir at room temperature for 3 hours. The palladium catalyst was filtered off through a pad of celite, and was washed with 100 mL of MeOH/THF (1:1). The filtrate

collected was concentrated under reduced pressure to provide the crude product **12I** (100% yield). M.S. found for C24H20F2N2O3: 423.05 $(M+H)^+$.

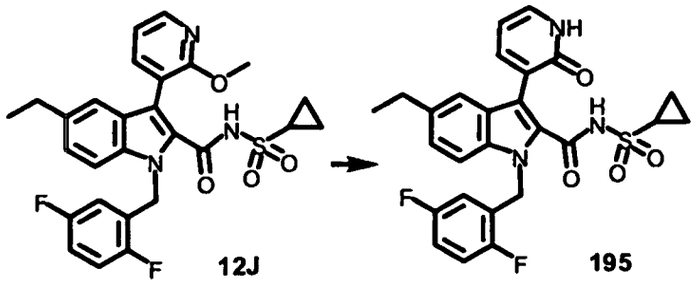
Step 9:



12I **12J**

1-(2,5-Difluoro-benzyl)-5-ethyl-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **12I** (140 mg, 0.36 mmol) was dissolved into tetrahydrofuran (5 mL) at room temperature. To the mixture was added carbonyl diimidazole (78 mg, 0.48 mmol). The resulting suspension was refluxed at 75 °C for 1 hour, and then cooled down to room temperature before it was added cyclopropyl sulfonamide (89 mg, 0.74 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.12 mL, 0.80 mmol). The resulting reaction mixture was allowed to stir at room temperature for 18 hours. Ethyl acetate (150 mL) and 5% aqueous phosphoric acid (100 mL) were added, and the layers were seperated. The aqueous layer was extracted twice with ethyl acetate (2 x 60 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **12J** (155 mg, 80% yield). M.S. found for C27H25F2N3O4S: 526.06 $(M+H)^+$.

Step 10:



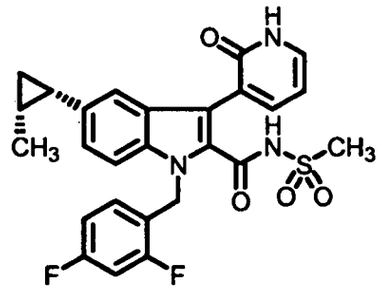
12J **195**

Cyclopropanesulfonic acid [1-(2,5-difluoro-benzyl)-5-ethyl-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carbonyl]-amide, **12J** (155 mg, 0.30 mmol) was dissolved into 4N HCl in 1,4-dioxane (6 mL) in a tube. The reaction mixture was allowed to stir at 90 °C in the sealed tube for 2.5 hours. The reaction mixture was cooled down to room temperature before being

concentrated under reduced pressure. The crude product was purified using reverse phase HPLC to provide compound **195** (57 mg, 38% yield). ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.79 (s, 1H), 12.73 (s, 1H), 7.82 (d, J= 6.62 Hz, 1H), 7.69 (d, J= 5.04 Hz, 1H), 7.57 (d, J= 8.51 Hz, 1H), 7.33-7.15 (m, 4H), 6.64-6.60 (m, 2H), 5.73 (s, 2H), 2.96-2.91 (m, 1H), 2.66 (q, J= 7.25 Hz & 7.57 Hz, 2H), 1.17 (t, J= 7.57 Hz, 3H), 0.98 (d, J= 5.99 Hz, 4H). M.S. found for C26H23F2N3O4S: 512.18 $(M+H)^+$.

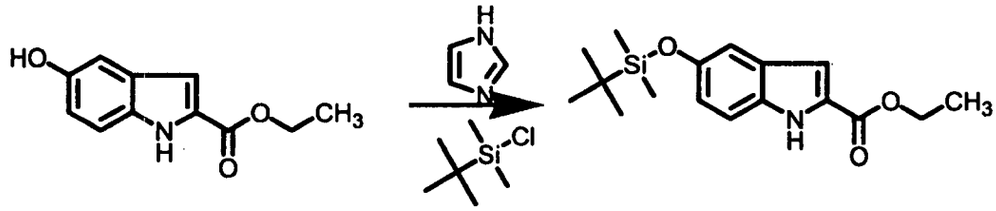
Example 13

Preparation of Compound **192**



192

Step 1:

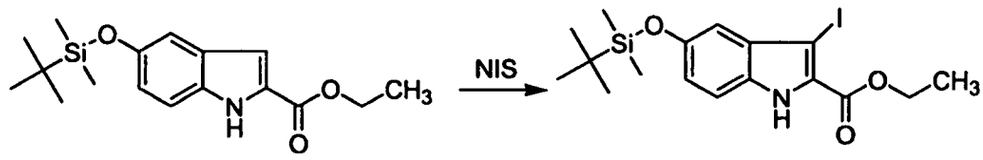


13A **13B**

A solution of ethyl 5-hydroxy-1H-indole-2-carboxylate (**13A**, 6.0 g; 29.24 mmol) in 300 mL of dichloromethane was treated with imidazole (4.0 eq, 7.96 g) and tert-butyldimethylsilyl chloride (2.0 eq, 8.82 g). The reaction was allowed to stir at room temp for 3 hours. A small sample (1 mL) was taken from reaction mixture, diluted with dichloromethane (10 mL) and washed with water. Evaporation of the solvent and NMR analysis showed all starting material had been consumed. The reaction mixture was diluted with dichloromethane (300 mL) and washed with water (2 x 100 mL) and brine (100 mL). The

organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **13B** (9.20 g; 98 %) as a white solid.

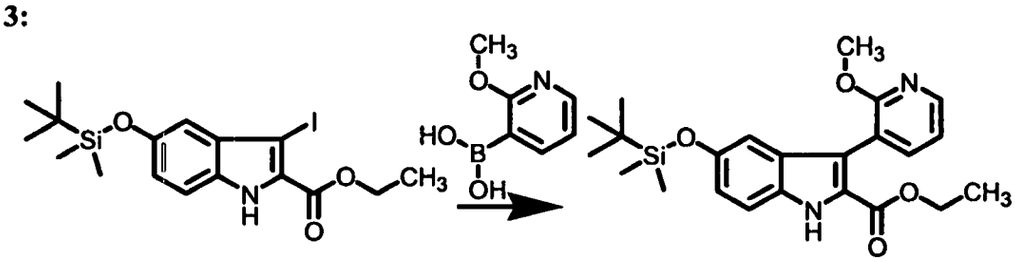
Step 2:



13B **13C**

A solution of ethyl 5-tert-butyldimethylsilyloxy-1H-indole-2-carboxylate **13B** (9.0 g) in 300 mL of chloroform was ice-cooled and treated with N-iodosuccinimide (1.1 eq, 6.97 g). The mixture was allowed to stir at 0 °C for 10 min and then at room temp for 2 hours. NMR analysis of a small aliquot showed complete conversion of starting material. The reaction mixture was diluted with dichloromethane (300 mL) and washed with aq saturated sodium thiosulfate (150 mL), aq saturated sodium bicarbonate (150 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **13C** (11.58 g; 92 %) as a white solid. M.S. found for C17H24INO3Si: 446.36 $(M+H)^+$.

Step 3:

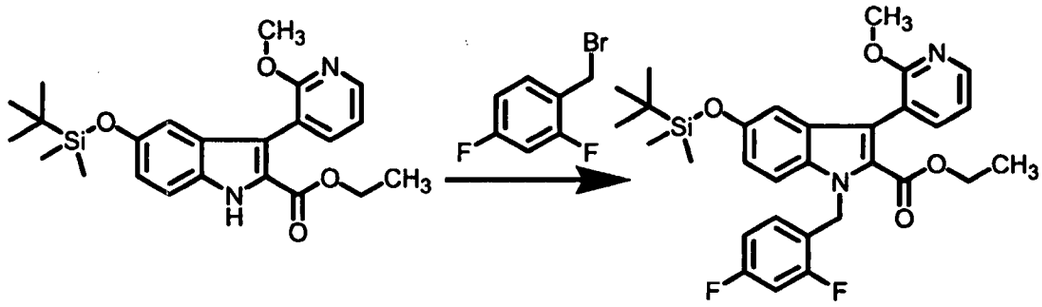


13C **13D**

The 2-methoxy-3-pyridine boronic acid (1.05 eq, 3.27 g) was added to a solution of **13C** (9.06 g; 20.345 mmol) in 100 mL of 1,2-dimethoxyethane. The mixture was degassed (vaccum/argon flush) and $PdCl_2(dppf)_2$ (10 mol%, 1.66 g) was added and the resulting orange solution was allowed to stir for 30 min at room temp. A solution of potassium carbonate (4.0 eq, 81 mL of aq 1M soln) was added and the resulting brown solution was allowed to stir at 90 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was diluted with ethyl acetate (600 mL) and washed with aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium

sulfate, filtered and concentrated. The residue was divided into two equal portions and each was purified using silica gel chromatography (Biotage 75-M column; gradient: 0 to 30 % ethyl acetate in hexanes) to provide compound **13D** as a white solid (6.76 g; 65 %). M.S. found for C23H30N2O4Si: 427.56 $(M+H)^+$.

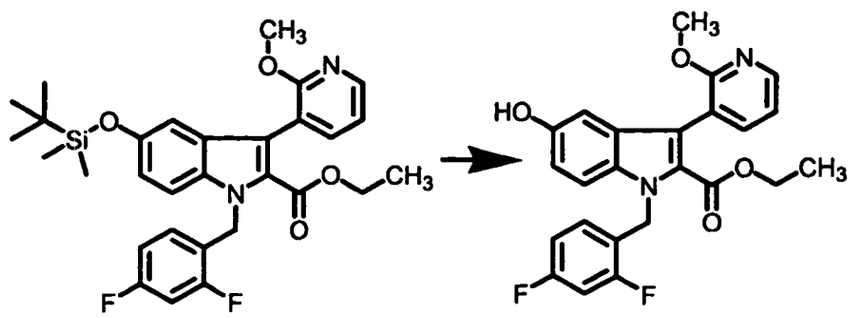
Step 4:



13D **13E**

A solution of indole derivative **13D** (6.5 g, 15.237 mmol) in 50 mL of dry THF was added to an ice-cooled suspension of sodium hydride (1.3 eq, 792 mg of 60% susp in mineral oil) in 50 mL of dry THF. The resulting solution was allowed to stir for 10 min followed by addition of 2,4-difluorobenzyl bromide (1.3 eq, 2.54 mL, d 1.613). A catalytic amount of tetrabutylammonium iodide (0.2 eq, 1.12 g) was added to the reaction mixture and stirring was continued for 18 h (temperature from 0 to 25 °C). The reaction was quenched by addition of water (10 mL) and the mixture was diluted with ethyl acetate (500 mL). The organic layer was washed with water (2 x 100 mL) and brine (80 mL), dried over magnesium sulfate, filtered and concentrated to provide the crude product **13E** as a colorless foam contaminated with undesired bis-N,O-difluorobenzyl product. The crude mixture was used for next reaction without further any further purification. M.S. found for C30H34N2O4Si: 553.65 $(M+H)^+$.

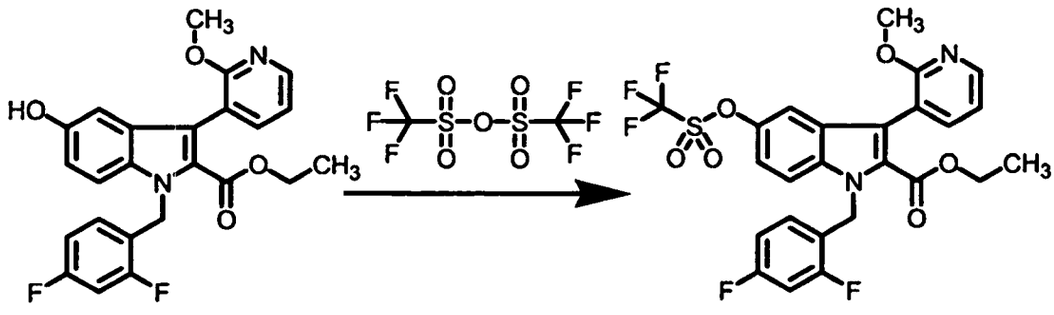
Step 5:



13E **13F**

A solution of crude silylether **13E** (15.237 mmol; 8.4 g) in 100 mL of THF (NOTE: **13E** contains an impurity identified as the bis-N,O-difluorobenzyl compound) was ice-cooled and treated with ca 1.0 eq of TBAF (15 mL of 1.0M soln in THF). The mixture immediately turned yellow-green in color and TLC after 5 min (30% ethyl acetate in hexanes) showed no more starting material left. The mixture was diluted with ethyl acetate (500 mL) and washed with water (100 mL), aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 75-M column; gradient: 10 to 50 % ethyl acetate in hexanes) to provide compound **13F** as a white solid (5.8 g; 88% for two steps). ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.09 (s, 1H), 8.17 & 8.16 (dd, J = 2.20 & 5.13 Hz, 1H), 7.71 & 7.69 (dd, J = 1.46 & 7.32 Hz, 1H), 7.45 (d, J = 8.79 Hz, 1H), 7.26 (t, J = 10.98 Hz, 1H), 7.10-7.06 (m, 1H), 6.97 (dt, J = 8.79 & 2.20 Hz, 1H), 6.88 & 6.86 (dd, J = 8.79 & 2.20 Hz, 1H), 6.76-6.71 (m, 1H), 6.67 (d, J = 2.20 Hz, 1H), 5.77 (s, 2H), 3.99 (q, J = 7.32 Hz, 2H), 3.75 (s, 3H), 0.85 (t, J = 7.32 Hz, 3H).

Step 6:

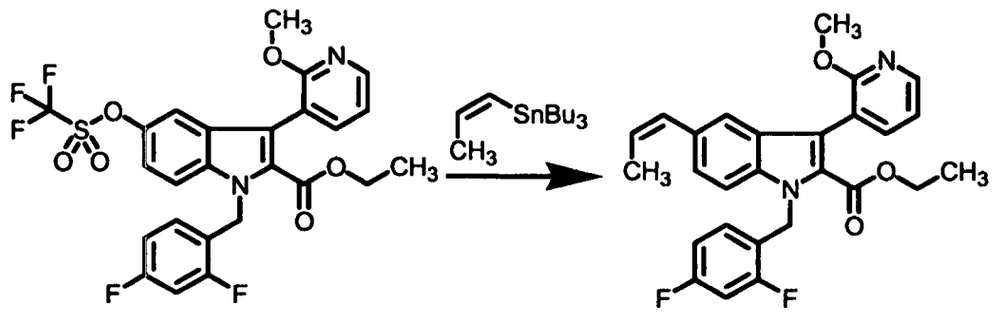


13F **13G**

A solution of 1-(2,4-Difluoro-benzyl)-5-hydroxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester **13F** (2.0 g; 4.56 mmol) in 20 mL of dry dichloromethane was ice cooled and treated with pyridine (4 mL) and triflic anhydride (2.1 eq, 1.61 mL, d 1.677). The mixture was allowed to stir for 10 min and treated with a catalytic amount of 4-dimethylamino pyridine. The cooling bath was removed and the reaction was allowed to stir for 2 hours. TLC (10% ethyl acetate in hexanes) showed no more starting material left and the mixture was diluted with ethyl acetate (200 mL) and washed with water (50 mL) and brine (50

mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 40-M column; gradient: 0 to 20% ethyl acetate in hexanes) to provide compound **13G** (2.50 g; 96 %) as a colorless oil. MS found for C25H19F5N2O6S: 571.12 $(M+H)^+$.

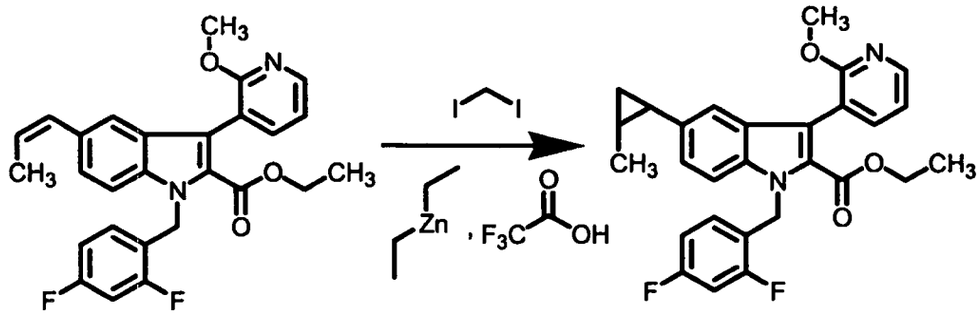
Step 7:



13G **13H**

A solution of 1-(2,4-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethanesulfonyloxy-1H-indole-2-carboxylic acid ethyl ester **13G** (650 mg; 1.13 mmol) in 10 mL of THF was treated with lithium chloride (7.0 eq, 336 mg) and (Z)-1-propenyltributyl stannane (1.5 eq, 0.51 mL, d 1.1). The mixture was degassed (vacuum/nitrogen flush) and tetrakis(triphenylphosphine)palladium was added (10 mol%, 130 mg). The reaction mixture was heated to 70 °C and stirred overnight. TLC (10% ethyl acetate in hexanes) and MS analyses showed complete conversion of starting material. The mixture was diluted with ethyl acetate (80 mL) and washed successively with water (10 mL), 10% aq ammonium hydroxide (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified using silica gel chromatography (Biotage 25-M column; gradient: 80 mL of hexanes then 0 to 25% ethyl acetate in hexanes) to provide compound **13H** (400 mg; 77 %) as a colorless oil. MS found for C27H24F2N2O3: 463.30 $(M+H)^+$.

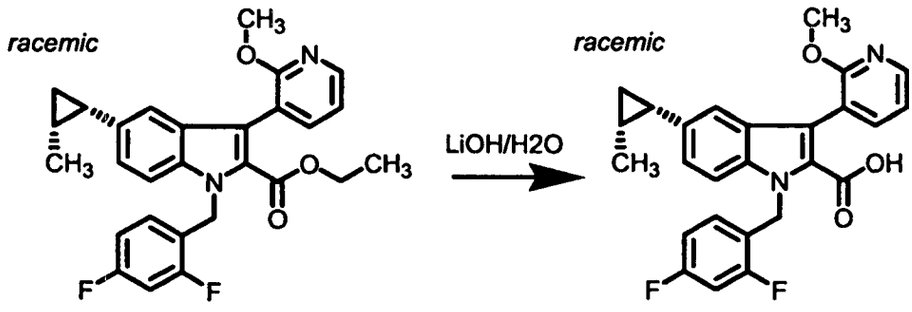
Step 8:



13H 13I

To a vigorously stirred solution of diethylzinc (10.0 eq, 3.9 mL of 1M soln in heptane) in 2 mL of dry dichloromethane at 0 °C (ice-water bath) was added dropwise a solution of trifluoroacetic acid (10.0 eq, 0.299 mL, d 1.480) in 0.5 mL of dichloromethane. The resulting mixture was allowed to stir for 10 min after which a solution of diiodomethane (10.0 eq, 0.31 mL, d 3.325) in 0.5 mL of dichloromethane was added dropwise. The mixture was allowed to stir for 10 min followed by addition of a solution of 1-(2,4-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-prop-Z-enyl-1H-indole-2-carboxylic acid ethyl ester **13H** (180 mg; 0.389 mmol) in 1 mL of dry dichloromethane. The reaction was allowed to stir at 0 °C and monitored by TLC and MS analyses (NOTE: Rf of starting material and product is the same in different solvent systems). After 4 h the reaction was quenched by addition of aq saturated sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with aq 1M HCl (10 mL), aq saturated sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 12-S column, gradient: 0 to 20% ethyl acetate in hexanes) to provide compound **13I** as a colorless oil. M.S. found for $C_{28}H_{26}F_2N_2O_3$: 477.26 $(M+H)^+$.

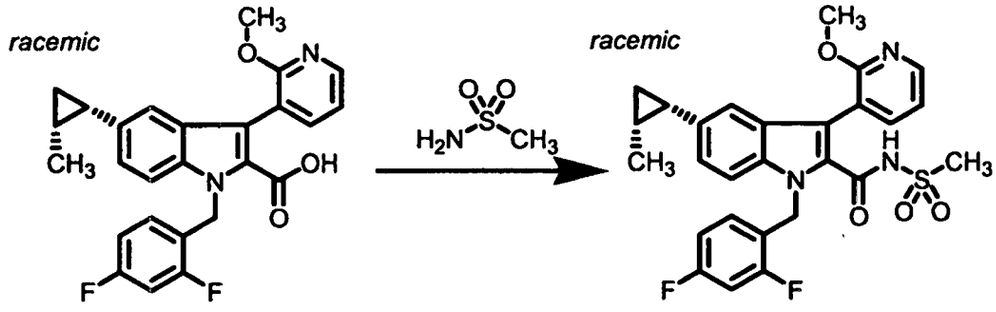
Step 9:



13I 13J

A solution of 1-(2,4-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-cis-methyl-cyclopropyl)-1H-indole-2-carboxylic acid ethyl ester **13I** (230 mg; 0.482 mmol) in 10 mL of a 5:1:1 THF/water/methanol mixture was treated with lithium hydroxide monohydrate (5.0 eq, 101 mg). The mixture was heated to 50 °C for 5 hours. TLC (20% ethyl acetate in hexanes) showed complete consumption of the starting material. The mixture was diluted with aq 1M HCl (40 mL) and the product was taken into dichloromethane (3 x 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to provide compound **13J** (205 mg; 95 % yield) as a white solid.

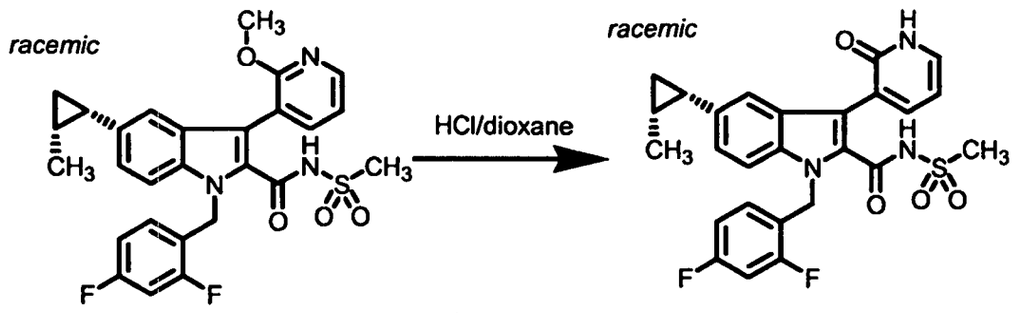
Step 10:



13J **13K**

A solution of 1-(2,4-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-cis-methyl-cyclopropyl)-1H-indole-2-carboxylic acid **13J** (100 mg; 0.222 mmol) in 5 mL of dry THF was treated with carbonyl diimidazole (1.25 eq, 45 mg). The mixture was heated to 70 °C for 2 h and then cooled to room temp. Methanesulfonamide (1.25 eq, 26 mg) and DBU (1.5 eq, 0.049 mL, d 1.018) were added and the mixture was heated to 70 °C overnight. The mixture was diluted with ethyl acetate (60 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified using silica gel chromatography (Biotage 25-S silica gel column, gradient: 0 to 20% acetone in dichloromethane) to provide compound **13K** (85 mg; 73 %) as a white solid. M.S. found for C27H25F2N3O4S: 526.16 $(M+H)^+$.

Step 11:

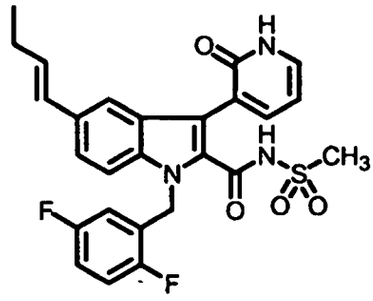


13K **192**

The N-[1-(2,4-Difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-methyl-cyclopropyl)-1H-indole-2-carbonyl]-methanesulfonamide **13K** (0.152 mmol) was dissolved in 3 mL of 4M HCl soln in dioxane. Methanol was added (1 mL) and the solution was heated at 90 °C in a sealed tube for 2.5 hours. The reaction mixture was concentrated to provide the crude product as a white solid. A sample (1 mg) was dissolved in 0.5 mL of DMF and analyzed on analytical HPLC under the following conditions: Column: Delta Pak; C18, 5 micrometer, 300A; 150 x 3.9 mm I.D.; Flow rate: 1 mL/min; Gradient: 40% acetonitrile in water for 5 min then increase to 80% over 25 minutes. The product was purified on semi-prep HPLC under the following conditions: Column: Delta Pak, C18, 5 micrometer, 300A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; Gradient: 50% acetonitrile in water for 20 min then increase to 80% over 30 min and stay there for 10 minutes. The fraction containing the product according to MS analysis was concentrated to remove acetonitrile and water to provide compound **192** (30 mg; 40 %) as a white solid. MS found for C26H23F2N3O4S: 512.06 $(M+H)^+$. ^1H NMR (400 MHz, d_6-DMSO): δ 7.78 & 7.76 (dd, J = 2.20 & 6.59 Hz, 1H), 7.64 (bs,1H), 7.52 (d, J = 8.06 Hz, 1H), 7.29-7.17 (m, 3H), 7.02-6.94 (m, 2H), 6.62-6.58 (m, 1H), 5.67 (s, 2H), 3.25 (s, 3H), 2.14-2.09 (m, 1H), 1.11-1.10 (m, 1H), 0.94-0.89 (m, 1H), 0.68-0.67 (m, 3H), 0.56-0.52 (m, 1H).

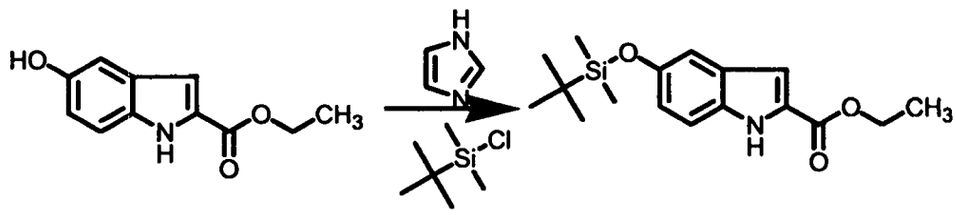
Example 14

Preparation of Compound **194**



194

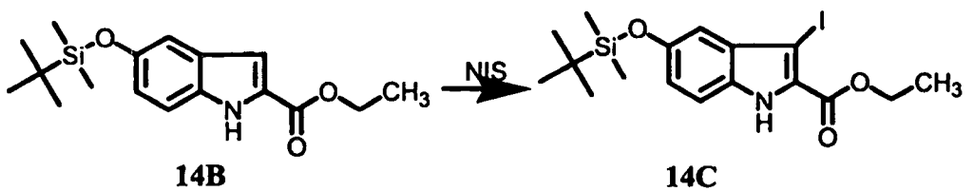
Step 1:



14A **14B**

A solution of ethyl 5-hydroxy-1H-indole-2-carboxylate **14A** (6.0 g; 29.24 mmol) in 300 mL of dichloromethane was treated with imidazole (4.0 eq, 7.96 g) and tert-butyldimethylsilyl chloride (2.0 eq, 8.82 g). The reaction was allowed to stir at room temp for 3 hours. A small sample (1 mL) was taken from reaction mixture, diluted with dichloromethane (10 mL) and washed with water. Evaporation of the solvent and NMR analysis showed all starting material had been consumed. The reaction mixture was diluted with dichloromethane (300 mL) and washed with water (2 x 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **14B** (9.20 g; 98 %) as a white solid.

Step 2:

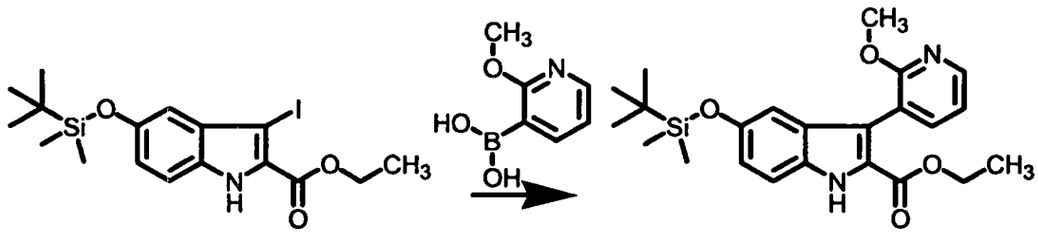


14B **14C**

A solution of ethyl 5-tert-butyldimethylsilyloxy-1H-indole-2-carboxylate **14B** (9.0 g) in 300 mL of chloroform was ice-cooled and treated with N-iodosuccinimide (1.1 eq, 6.97 g). The mixture was allowed to stir at 0 °C for 10 min and then at room temp for 2 hours. NMR

analysis of a small aliquot showed complete conversion of starting material. The reaction mixture was diluted with dichloromethane (300 mL) and washed with aq saturated sodium thiosulfate (150 mL), aq saturated sodium bicarbonate (150 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **14C** (11.58 g; 92 %) as a white solid. M.S. found for C17H24INO3Si: 446.36 $(M+H)^+$.

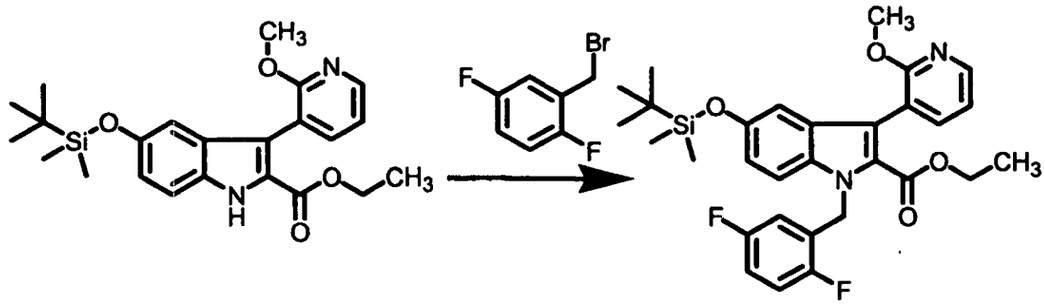
Step 3:



14C **14D**

The 2-methoxy-3-pyridine boronic acid (1.05 eq, 3.27 g) was added to a solution of **14C** (9.06 g; 20.345 mmol) in 100 mL of 1,2-dimethoxyethane. The mixture was degassed (vaccum/argon flush) and $PdCl_2(dppf)_2$ (10 mol%, 1.66 g) was added and the resulting orange solution was allowed to stir for 30 min at room temp. A solution of potassium carbonate (4.0 eq, 81 mL of aq 1M soln) was added and the resulting brown solution was allowed to stir at 90 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was diluted with ethyl acetate (600 mL) and washed with aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was divided into two equal portions and each was purified using silica gel chromatography (Biotage 75-M column; gradient: 0 to 30 % ethyl acetate in hexanes) to provide compound **14D** as a white solid (6.76 g; 65 %). M.S. found for C23H30N2O4Si: 427.56 $(M+H)^+$.

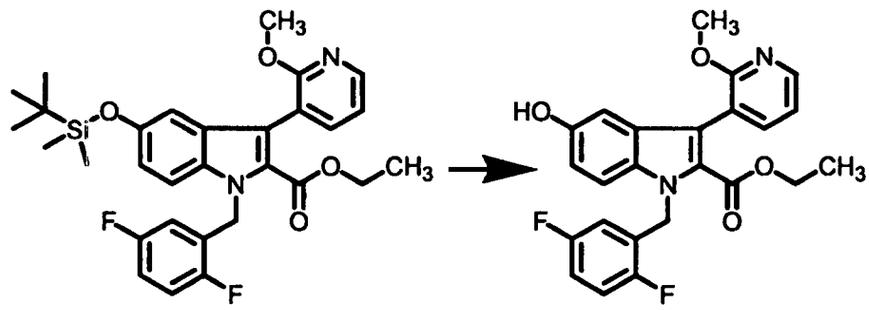
Step 4:



14D **14E**

A solution of indole derivative **14D** (6.5 g, 15.237 mmol) in 50 mL of dry THF was added to an ice-cooled suspension of sodium hydride (1.3 eq, 792 mg of 60% suspension in mineral oil) in 50 mL of dry THF. The resulting solution was allowed to stir for 10 min followed by addition of 2,5-difluorobenzyl bromide (1.3 eq, 2.54 mL, d 1.613). A catalytic amount of tetrabutylammonium iodide (0.2 eq, 1.12 g) was added to the reaction mixture and stirring was continued for 18 h (temperature from 0 to 25 °C). The reaction was quenched by addition of water (10 mL) and the mixture was diluted with ethyl acetate (500 mL). The organic layer was washed with water (2 x 100 mL) and brine (80 mL), dried over magnesium sulfate, filtered and concentrated to provide the crude product **14E** as a colorless foam contaminated with undesired bis-N,O-difluorobenzyl product. The crude mixture was used for next reaction without further any further purification.

Step 5:

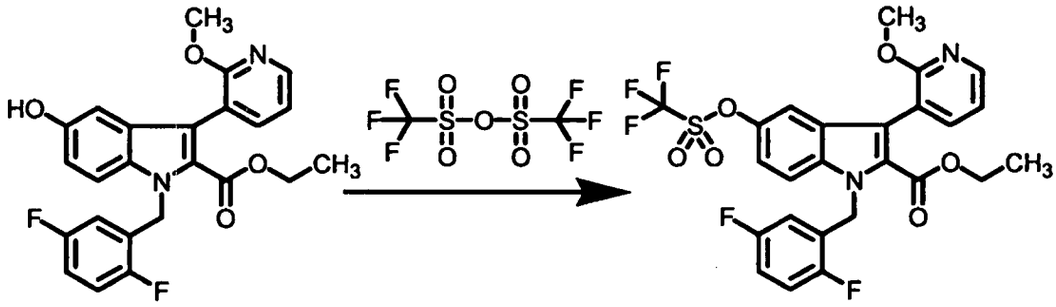


14E **14F**

A solution of crude silylether **14E**(15.237 mmol; 8.4 g) in 100 mL of THF (NOTE: **14E** contains an impurity identified as the bis-N,O-difluorobenzyl compound) was ice-cooled and treated with ca 1.0 eq of TBAF (15 mL of 1.0M soln in THF). The mixture immediately turned yellow-green in color and TLC after 5 min (30% ethyl acetate in hexanes) showed no

more starting material left. The mixture was diluted with ethyl acetate (500 mL) and washed with water (100 mL), aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 75-M column; gradient: 10 to 50 % ethyl acetate in hexanes) to provide compound **14F** as a white solid (5.8 g; 88% for two steps).

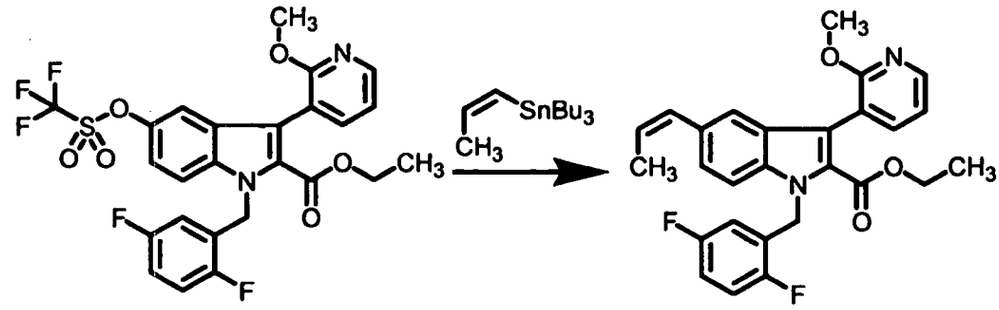
Step 6:



14F **14G**

A solution of 1-(2,5-Difluoro-benzyl)-5-hydroxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester **14F** (2.0 g; 4.56 mmol) in 20 mL of dry dichloromethane was ice cooled and treated with pyridine (4 mL) and triflic anhydride (2.1 eq, 1.61 mL, d 1.677). The mixture was allowed to stir for 10 min and treated with a catalytic amount of 4-dimethylamino pyridine. The cooling bath was removed and the reaction was allowed to stir for 2 hours. TLC (10% ethyl acetate in hexanes) showed no more starting material left and the mixture was diluted with ethyl acetate (200 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 40-M column; gradient: 0 to 20% ethyl acetate in hexanes) to provide compound **14G** (2.50 g; 96 %) as a colorless oil.

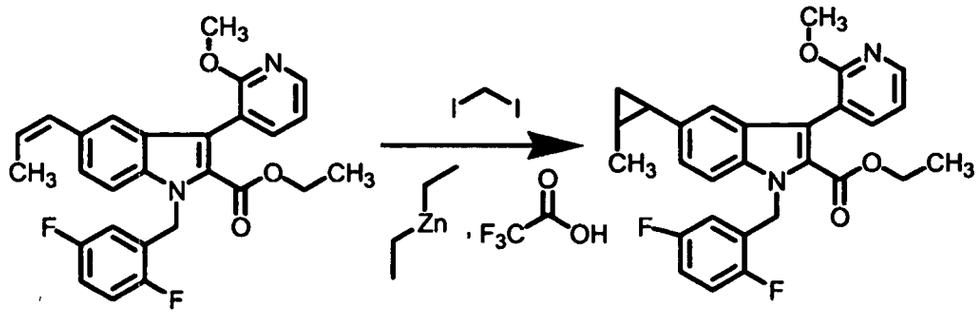
Step 7:



14G **14H**

A solution of 1-(2,5-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethanesulfonyloxy-1H-indole-2-carboxylic acid ethyl ester **14G** (650 mg; 1.13 mmol) in 10 mL of THF was treated with lithium chloride (7.0 eq, 336 mg) and (Z)-1-propenyltributyl stannane (1.5 eq, 0.51 mL, d 1.1). The mixture was degassed (vacuum/nitrogen flush) and tetrakis(triphenylphosphine)palladium was added (10 mol%, 130 mg). The reaction mixture was heated to 70 °C and stirred overnight. TLC (10% ethyl acetate in hexanes) and MS analyses showed complete conversion of starting material. The mixture was diluted with ethyl acetate (80 mL) and washed successively with water (10 mL), 10% aq ammonium hydroxide (10 mL), water (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified using silica gel chromatography (Biotage 25-M column; gradient: 80 mL of hexanes then 0 to 25% ethyl acetate in hexanes) to provide compound **14H** (400 mg; 77 %) as a colorless oil.

Step 8:

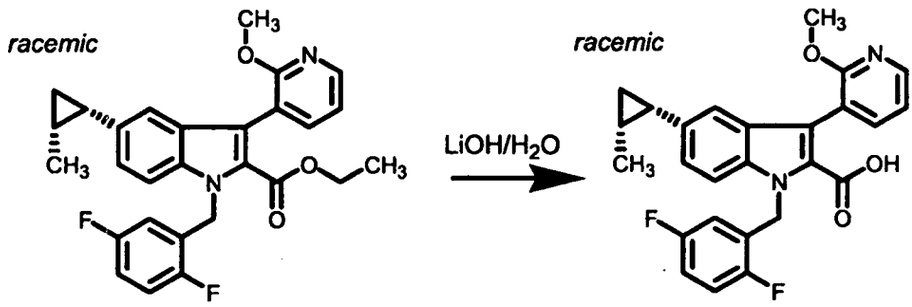


14H **14I**

To a vigorously stirred solution of diethylzinc (10.0 eq, 3.9 mL of 1M soln in heptane) in 2 mL of dry dichloromethane at 0 °C (ice-water bath) was added dropwise a solution of trifluoroacetic acid (10.0 eq, 0.299 mL, d 1.480) in 0.5 mL of dichloromethane. The resulting

mixture was allowed to stir for 10 min after which a solution of diiodomethane (10.0 eq, 0.31 mL, d 3.325) in 0.5 mL of dichloromethane was added dropwise. The mixture was allowed to stir for 10 min followed by addition of a solution of 1-(2,5-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-prop-Z-enyl-1H-indole-2-carboxylic acid ethyl ester **14H** (180 mg; 0.389 mmol) in 1 mL of dry dichloromethane. The reaction was allowed to stir at 0 °C and monitored by TLC and MS analyses (NOTE: Rf of starting material and product is the same in different solvent systems). After 4 h the reaction was quenched by addition of aq saturated sodium bicarbonate (10 mL). The mixture was extracted with ethyl acetate (50 mL). The organic layer was washed with aq 1M HCl (10 mL), aq saturated sodium bicarbonate (10 mL), and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 12-S column, gradient: 0 to 20% ethyl acetate in hexanes) to provide compound **14I** as a colorless oil.

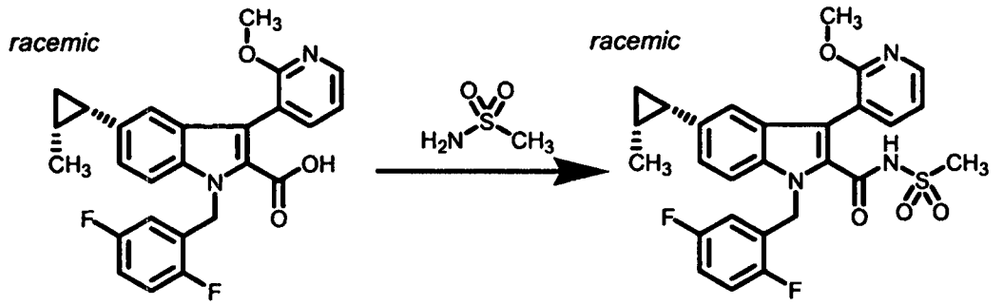
Step 9:



14I **14J**

A solution of 1-(2,5-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-cis-methyl-cyclopropyl)-1H-indole-2-carboxylic acid ethyl ester **14I** (230 mg; 0.482 mmol) in 10 mL of a 5:1:1 THF/water/methanol mixture was treated with lithium hydroxide monohydrate (5.0 eq, 101 mg). The mixture was heated to 50 °C for 5 hours. TLC (20% ethyl acetate in hexanes) showed complete consumption of the starting material. The mixture was diluted with aq 1M HCl (40 mL) and the product was taken into dichloromethane (3 x 25 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to provide compound **14J** (205 mg; 95 %) as a white solid.

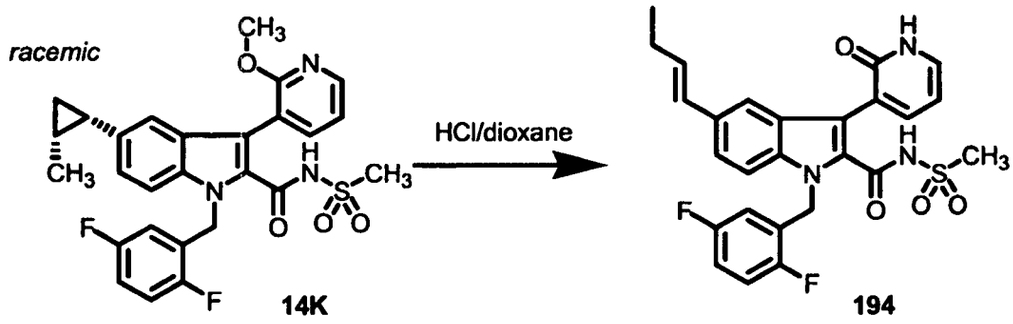
Step 10:



14J **14K**

A solution of 1-(2,5-difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-cis-methyl-cyclopropyl)-1H-indole-2-carboxylic acid **14J** (100 mg; 0.222 mmol) in 5 mL of dry THF was treated with carbonyl diimidazole (1.25 eq, 45 mg). The mixture was heated to 70 °C for 2 h and then cooled to room temp. Methanesulfonamide (1.25 eq, 26 mg) and DBU (1.5 eq, 0.049 mL, d 1.018) were added and the mixture was heated to 70 °C overnight. The mixture was diluted with ethyl acetate (60 mL) and washed with aq 1M HCl (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified using silica gel chromatography (Biotage 25-S silica gel column, gradient: 0 to 20% acetone in dichloromethane) to provide compound **14K** (85 mg; 73 %) as a white solid. M.S. found for C27H25F2N3O4S: 526.22 $(M+H)^+$.

Step 11



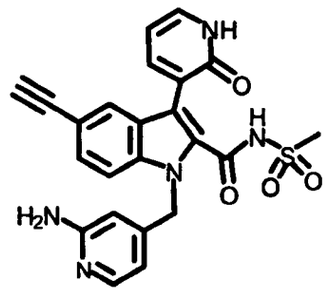
14K **194**

The N-[1-(2,4-Difluoro-benzyl)-3-(2-methoxy-pyridin-3-yl)-5-(2-methyl-cyclopropyl)-1H-indole-2-carbonyl]-methanesulfonamide **14K** (0.152 mmol) was dissolved in 3 mL of 4M HCl soln in dioxane. Methanol was added (1 mL) and the solution was heated at 90 °C in a sealed tube for 2.5 hours. The reaction mixture was concentrated to provide the crude product as a white solid. A sample (1 mg) was dissolved in 0.5 mL of DMF and analyzed on analytical HPLC under the following conditions: Column: Delta Pak; C18, 5 micrometer, 300A; 150 x

3.9 mm I.D.; Flow rate: 1 mL/min; Gradient: 40% acetonitrile in water for 5 min then increase to 80% over 25 minutes. The product was purified on semi-prep HPLC under the following conditions: Column: Delta Pak, C18, 5 micrometer, 300A; 300 x 30 mm I.D.; Flow rate: 30 mL/min; Gradient: 50% acetonitrile in water for 20 min then increase to 80% over 30 min and stay there for 10 minutes. The fraction containing the product according to MS analysis was concentrated to remove acetonitrile and water to provide a major product as a white solid and a minor product, which was identified as Compound **194**. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.84 & 7.82 (dd, J = 2.20 & 7.32 Hz, 1H), 7.65 (bs,1H), 7.55 (d, J = 8.79 Hz, 1H), 7.49 (d, J = 8.79 Hz, 1H), 7.34 (bs, 1H), 7.31-7.25 (m, 1H), 7.19-7.12 (m, 1H), 6.60 (t, J = 6.59 Hz, 2H), 6.46-6.42 (m, 1H), 6.27-6.20 (m, 1H), 5.70 (s, 2H), 3.24 (s, 3H), 2.16 (quintet, J = 6.59 & 7.32 Hz, 2H), 1.02 (t, J = 7.32 Hz, 3H). M.S. found for C26H23F2N3O4S: 512.16 $(M+H)^+$.

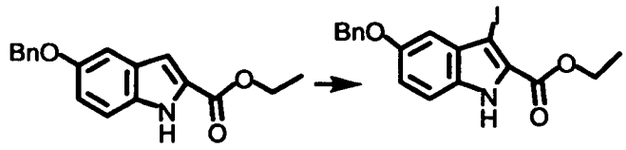
Example 15

Preparation of Compound **26**



26

Step 1:

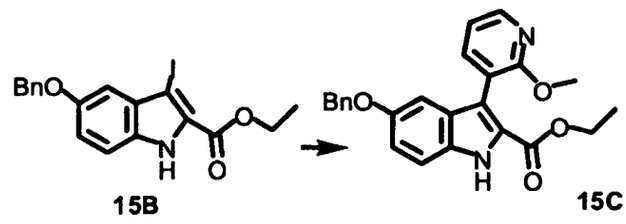


15A **15B**

Ethyl 5-benzyloxyindole-2-carboxylate, **15A** (5.0 g, 16.9 mmol) was dissolved into acetone (400 mL) at room temperature. To the mixture was added N-iodosuccinimide (4.0 g, 16.9 mmol). The resulting suspension was allowed to stir at room temperature for 3 hours. The mixture was concentrated under reduced pressure, and the residue was dissolved into ethyl acetate (300 mL). The mixture was washed with saturated aqueous sodium thiosulfate solution (100 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 150 mL). The combined organic layer was dried over magnesium sulfate, filtered and

concentrated *in vacuo* to provide the crude product **15B** (100% yield). M.S. found for C18H16INO3: 421.89 $(M+H)^+$.

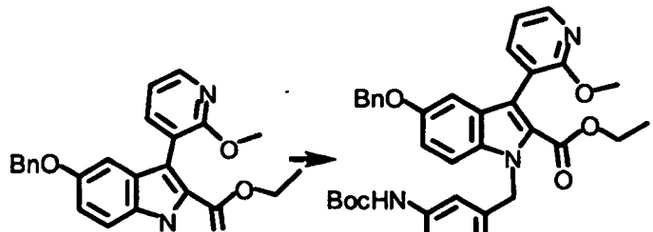
Step 2:



15B **15C**

5-Benzyloxy-3-iodo-1H-indole-2-carboxylic acid ethyl ester, **15B** (4.0 g, 9.48 mmol) was dissolved into 1,2-dimethoxyethane (90 mL). And $PdCl_2(dppf)_2$ (775 mg, 0.95 mmol) was added. The resulting mixture was de-gassed with argon bubbling for 5 min before it was heated to 90 °C and allowed to stir for 30 minutes. In a second flask, the mixture of 2-methoxy-3-pyridine boronic acid (1.95 g, 11.4 mmol) and potassium carbonate (6.6 g, 47.8 mmol) in dimethoxyethane (30 mL) and water (30 mL) was de-gassed with argon bubbling for 5 minutes. The mixture was then transferred in three portions to the first flask. The resulting bi-phasic mixture was vigorously stirred at 90 °C for 4 h before it was cooled to room temperature. The reaction was quenched by addition of a solution of sodium sulfite (10 g) in water (400 mL) at room temperature. Ethyl acetate (500 mL) was added, and the layers were seperated. The aqueous layer was extracted with ethyl acetate (2 x 500 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **15C** (3.2 g, 84% yield). M.S. found for C24H22N2O4: 403.2 $(M+H)^+$.

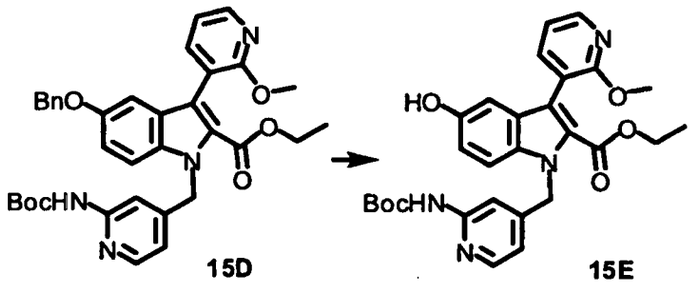
Step 3:



15C **15D**

5-Benzyloxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **15C** (2.0 g, 4.96 mmol) was dissolved into DMF (60 mL) at room temperature. To the mixutre were added (4-bromomethyl-pyridin-2-yl)-carbamic acid tert-butyl ester (1.4 g, 4.88 mmol) and

cesium carbonate (3.6 g, 11.0 mmol). The resulting suspension was allowed to stir at room temperature for 18 hours. Ethyl acetate (200 mL) and water (150 mL) were, and the layers were seperated. The aqueous layer was extracted with ethyl acetate (2 x 150 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **15D** (1.95 g, 65% yield). M.S. found for C35H36N4O6: 609.4 $(M+H)^+$.

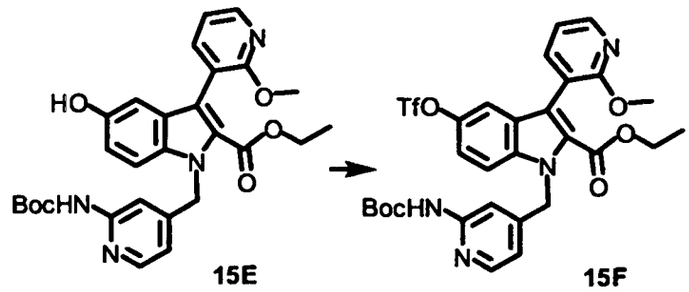


15D **15E**

Step 4:

To a solution of 5-benzyloxy-1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **15D** (1.90 g, 3.12 mmol) in EtOH was added 10% Pd-C (1.0 g). The flask was vacuumed, and then charged with H_2 gas. The reaction mixture was allowed to stir at room temperature under H_2 gas for 3 hours. The palladium catalyst was filtered off through a pad of celite, and was washed with 100 mL of MeOH/THF (1:1). The filtrate collected was concentrated under reduced pressure to provide the crude product **15E** (1.54 g, 95% yield). M.S. found for C28H30N4O6: 519.5 $(M+H)^+$.

Step 5:

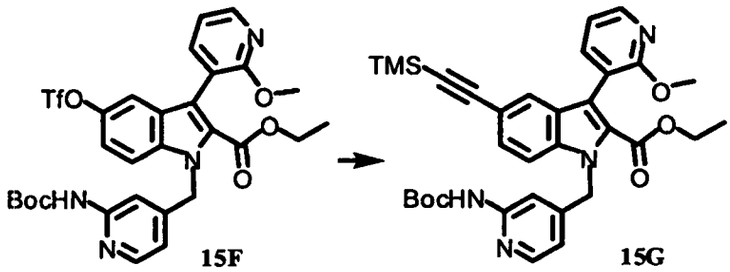


15E **15F**

To the mixture of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-5-hydroxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester, **15E** (1.54 g, 2.97 mmol) and triethyl amine (1.0 mL, 7.17 mmol) in dichloromethane (50 mL) was added $PhN(SO_2CF_3)_2$ (1.35 g, 3.78 mmol). The resulting reaction mixture was allowed to stir at 0 °C to room temperature for 18 hours. The mixture was then diluted with dichloromethane (100 mL), and

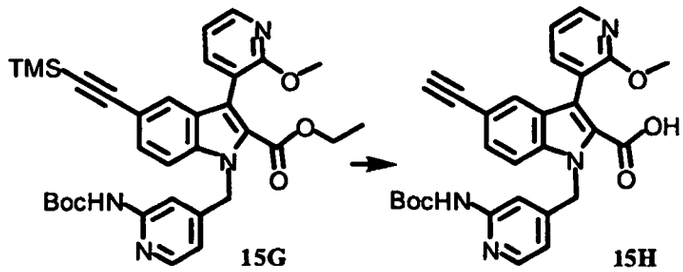
was washed with aqueous 1N sodium carbonate solution (2 x 50 mL). The separated aqueous solution was extracted with dichloromethane (100 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **15F** (1.55 g, 80% yield). M.S. found for C29H29F3N4O8S: 651.5 $(M+H)^+$.

Step 6:



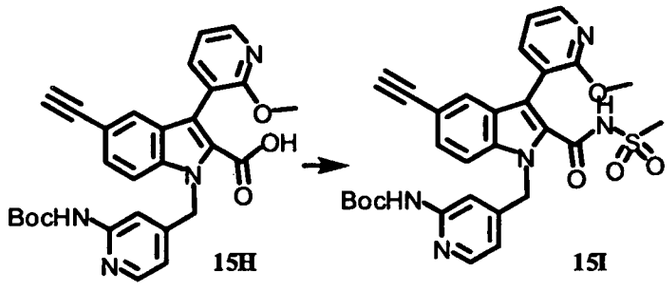
To a solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-3-(2-methoxy-pyridin-3-yl)-5-trifluoromethanesulfonyloxy-1H-indole-2-carboxylic acid ethyl ester, **15F** (600 mg, 0.92 mmol), TMS acetylene (0.65 mL, 4.69 mmol) and $nBu_4N^+\Gamma$ (409 mg, 1.11 mmol) in DMF (20 mL) were added $PdCl_2(PPh_3)_2$ (65 mg, 0.09 mmol), CuI (53 mg, 0.28 mmol) and triethyl amine (0.65 mL, 4.66 mmol). The resulting reaction mixture was stirred in a sealed tube at 65 °C for 18 hours. The mixture was cooled down to room temperature, and was diluted with water (90 mL) and EtOAc (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 90 mL). The combined organic layer was washed with water (2 x 50 mL) before it was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **15G** (514 mg, 93% yield). M.S. found for C33H38N4O5Si: 599.5 $(M+H)^+$.

Step 7:



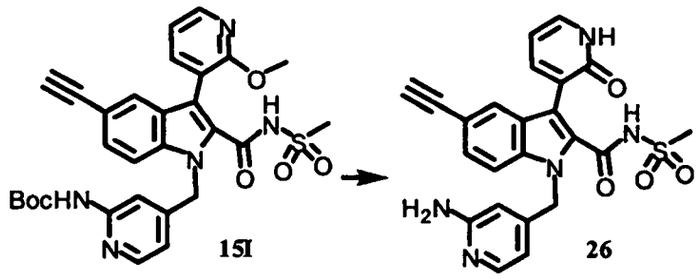
To a solution of 1-(2-tert-butoxycarbonylamino-pyridin-4-ylmethyl)-3-(2-methoxy-pyridin-3-yl)-5-trimethylsilanylethynyl-1H-indole-2-carboxylic acid ethyl ester, **15G** (251 mg, 0.42 mmol) in water (3 mL) and THF (3 mL) was added aqueous 1 N lithium hydroxide solution (1.3 mL). The resulting suspension was allowed to stir at 70 °C for 18 hours. The mixture was cooled to room temperature, and the aqueous layer was acidified to pH=2 by adding aqueous 1N HCl solution. The mixture was diluted with ethyl acetate (50 mL) and water (30 mL), and the layers were separated. The aqueous layer was extracted twice with 50 mL of THF/ethyl acetate (1:1). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **15H** (191 mg, 91% yield). M.S. found for C28H26N4O5: 499.4 $(M+H)^+$.

Step 8:



1-(2-tert-Butoxycarbonylamino-pyridin-4-ylmethyl)-5-ethynyl-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid, **15H** (128 mg, 0.26 mmol) was dissolved into tetrahydrofuran (5 mL) at room temperature. To the mixture was added carbonyl diimidazole (50 mg, 0.31 mmol). The resulting suspension was refluxed at 75 °C for 1 hour, and then cooled down to room temperature before methylsulfonamide (49 mg, 0.52 mmol) and 1,8-diazabicyclo(5.4.0)undec-7-ene (0.08 mL, 0.52 mmol) were added. The resulting reaction mixture was allowed to stir at room temperature for 24 hours. Ethyl acetate (50 mL), tetrahydrofuran (10 mL) and 1% aqueous phosphoric acid (15 mL) were added to the reaction mixture, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate/THF (3:1) (40 mL). The combined organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography to provide compound **15I** (80 mg, 54% yield). M.S. found for C29H29N5O6S: 576.20 $(M+H)^+$.

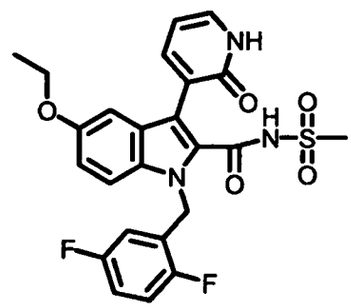
Step 9:



The solution of {4-[5-ethynyl-2-methanesulfonylaminocarbonyl-3-(2-methoxy-pyridin-3-yl)-indol-1-ylmethyl]-pyridin-2-yl}-carbamic acid tert-butyl ester, **151** (5 mg, 0.01 mmol) in chloroform was treated with TMSI (3.5 uL, 0.03 mmol). The reaction mixture was allowed to stir at 50 °C for 18 hours. The mixture was then cooled down to room temperature, and was quenched with MeOH (1 mL). The mixture was concentrated under reduced pressure to provide compound **26**. M.S. found for C23H19N5O4S: 462.3 $(M+H)^+$.

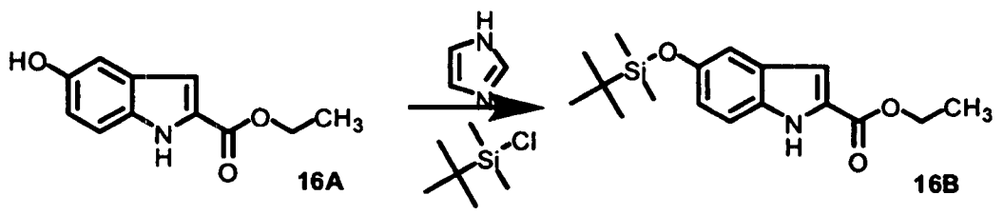
Example 16

Preparation of Compound **156**



156

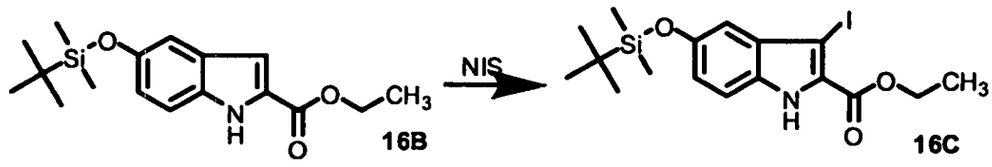
Step 1:



A solution of ethyl 5-hydroxy-1H-indole-2-carboxylate **16A** (10.0 g; 48.73 mmol) in 300 mL of dichloromethane was treated with imidazole (4.0 eq, 13.27 g) and tert-butyldimethylsilyl chloride (2.0 eq, 14.69 g). The reaction was allowed to stir at room temp for 3 hours. A small sample (1 mL) was taken from reaction mixture, diluted with

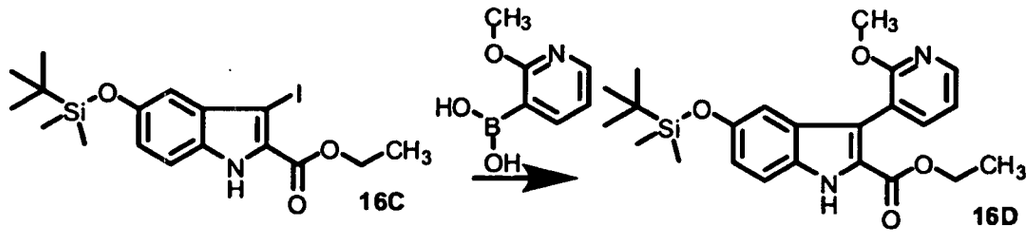
dichloromethane (10 mL) and washed with water. Evaporation of the solvent and NMR analysis showed all starting material had been consumed. The reaction mixture was diluted with dichloromethane (300 mL) and washed with water (2 x 200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **16B** (15.75 g) as a white solid.

Step 2:



A solution of ethyl 5-tert-butyldimethylsilyloxy-1H-indole-2-carboxylate **16B** (15.6 g) in 500 mL of chloroform was ice-cooled and treated with N-iodosuccinimide (1.1 eq, 12.06 g). The mixture was allowed to stir at 0 °C for 10 min and then at room temp for 2 hours. NMR analysis of a small aliquot showed complete conversion of starting material. The reaction mixture was diluted with dichloromethane (300 mL) and washed with aq saturated sodium thiosulfate (200 mL), aq saturated sodium bicarbonate (200 mL) and brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to provide compound **16C** (19.47 g; 90 %) as a white solid. M.S. found for C17H24INO3Si: 446.36 $(M+H)^+$.

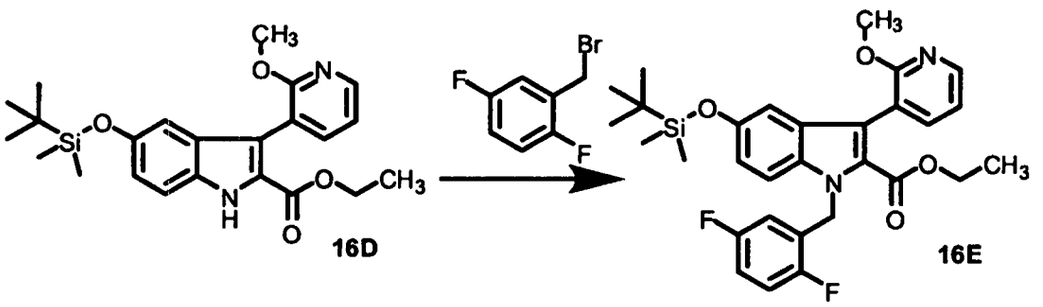
Step 3:



The 2-methoxy-3-pyridine boronic acid (1.05 eq, 6.99 g) was added to a solution of **16C** (19.4 g; 43.55 mmol) in 500 mL of 1,2-dimethoxyethane. The mixture was degassed (vaccum/argon flush) and $PdCl_2(dppf)_2$ (5 mol%, 1.78 g) was added and the resulting orange solution was allowed to stir for 30 min at room temp. A solution of potassium carbonate (4.0

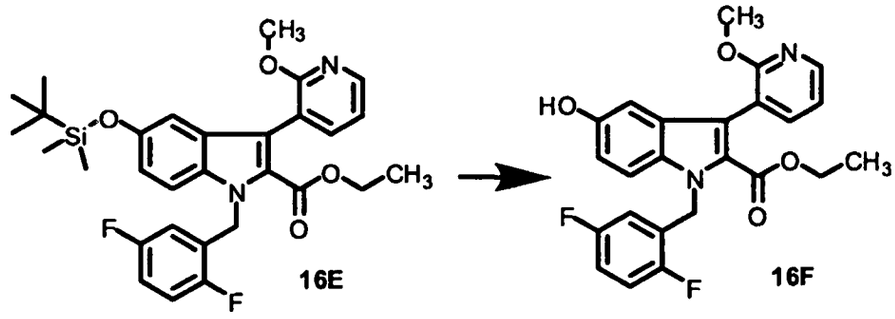
eq, 174 mL of aq 1M soln) was added and the resulting brown solution was allowed to stir at 90 °C for 2 hours. The reaction mixture was cooled to room temperature and concentrated. The residue was diluted with ethyl acetate (1 L) and washed with brine (200 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was divided into two equal portions and each was purified using silica gel chromatography (Biotage 75-M column; gradient: 0 to 35 % ethyl acetate in hexanes) to provide compound **16D** as a white solid (14.5 g; 80 %). M.S. found for C23H30N2O4Si: 427.56 $(M+H)^+$.

Step 4:



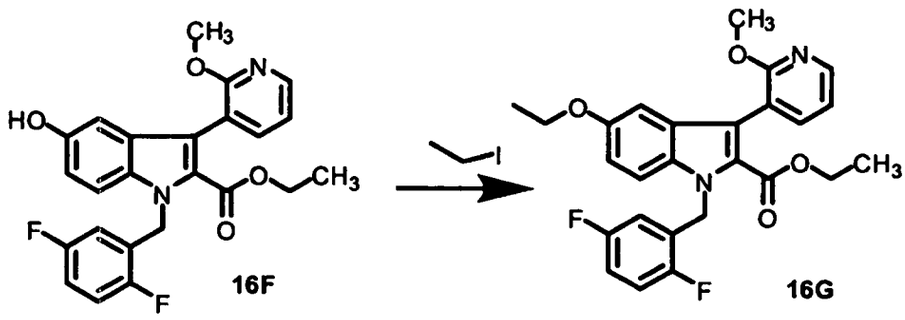
A solution of indole derivative **16D** (4.0 g, 9.376 mmol) in 90 mL of dry DMF was ice-cooled and treated with 2,5-difluorobenzyl bromide (1.1 eq, 1.32 mL, d 1.613) and cesium carbonate (3.0 eq, 9.16 g). The mixture turned yellow in color and the ice-water bath was removed. A catalytic amount of tetrabutylammonium iodide (approx 20 mg) was added. The reaction mixture was allowed to stir for 30 min where it became green in color and TLC (20% ethyl acetate in hexanes) showed no more starting materials left. The reaction was quenched by addition of water (10 mL) and the mixture was diluted with ethyl acetate (400 mL). The organic layer was washed with water (3 x 80 mL) and brine (80 mL), dried over magnesium sulfate, filtered and concentrated to provide the crude product **16E**. The crude mixture was used for next reaction without further any further purification.

Step 5:



A solution of crude silylether **16E** (9.376 mmol) in 100 mL of THF was ice-cooled and treated with ca 1.0 eq of TBAF (9.3 mL of 1.0M soln in THF). The mixture immediately turned yellow-green in color and TLC after 5 min (20% ethyl acetate in hexanes) showed no more starting material left. The mixture was diluted with ethyl acetate (400 mL) and washed with water (100 mL), aq saturated sodium bicarbonate (100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 75-M column; gradient: 10 to 50 % ethyl acetate in hexanes) to provide compound **16F** as a white solid (3.81 g; 94%). ^{1}H NMR (400 MHz, d_6-DMSO): δ 9.12 (s, 1H), 8.18 & 8.17 (dd, J = 1.46 & 5.13 Hz, 1H), 7.74 & 7.72 (dd, J = 2.20 & 7.32 Hz, 1H), 7.46 (d, J = 9.52 Hz, 1H), 7.31-7.25 (m, 1H), 7.16-7.07 (m, 1H), 6.87 (d, J = 8.79 Hz, 1H), 6.67 (s, 1H), 6.40-6.35 (m, 1H), 5.80 (s, 2H), 3.99 (q, J = 7.32 Hz, 2H), 3.75 (s, 3H), 0.845 (t, J = 7.32 Hz, 3H).

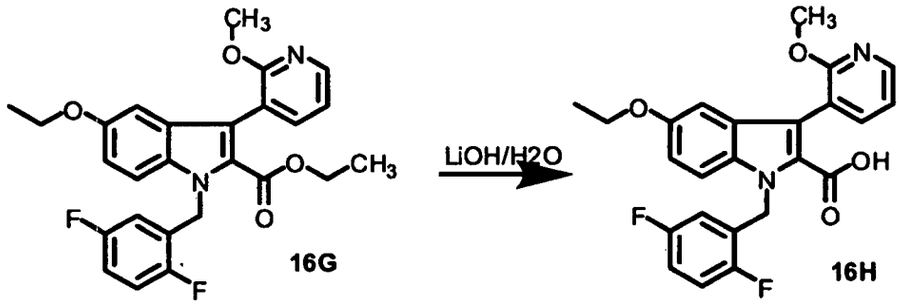
Step 6:



A solution of 1-(2,5-Difluoro-benzyl)-5-hydroxy-3-(2-methoxy-pyridin-3-yl)-1H-indole-2-carboxylic acid ethyl ester **16F** (600 mg; 1.368 mmol) in 10 mL of dry DMF was ice cooled and treated with iodoethane (3.0 eq, 0.34 mL, d 1.950) and cesium carbonate (2.5 eq, 1.11 g). The resulting yellow solution was allowed to stir at 50 ° C for 30 min at which time TLC (20% ethyl acetate in hexanes) showed no more starting material left and the mixture was

diluted with ethyl acetate (100 mL) and washed with water (3 x 20 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified using silica gel chromatography (Biotage 25-M column; gradient: 0 to 20% ethyl acetate in hexanes) to provide compound **16G** (530 mg; 87 %) as a white solid. MS found for C26H24F2N2O4: 467.13 $(M+H)^+$.

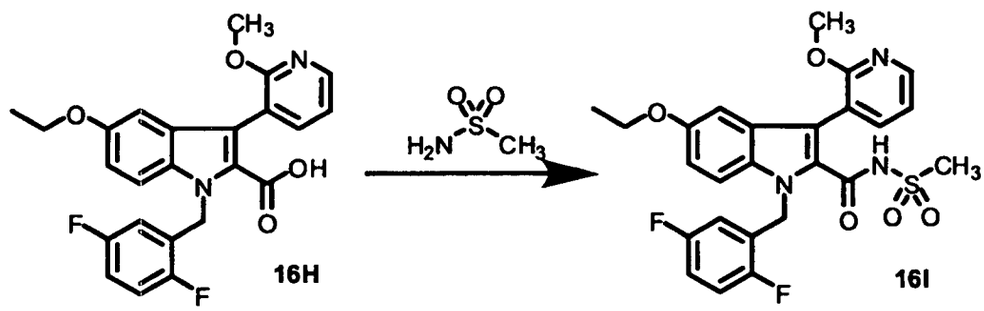
Step 7:



16G **16H**

A solution of **16G** (530 mg; 1.136 mmol) in 12 mL of a 4:1:1 THF/water/methanol mixture was treated with lithium hydroxide monohydrate (5.0 eq, 238 mg). The mixture was heated to 60 °C for 5 hours. TLC (20% ethyl acetate in hexanes) showed complete consumption of the starting material. The mixture was diluted with aq 1M HCl (50 mL) and the product was taken into dichloromethane (3 x 40 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to provide compound **16H** (0.912 mmol; 80 %) as a white solid. MS found for C24H20F2N2O4: 439.02 $(M+H)^+$.

Step 8:

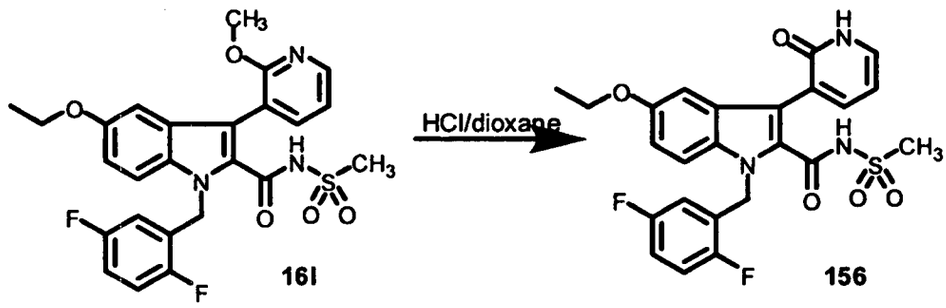


16H **16I**

A solution of **16H** (150 mg; 0342 mmol) in 3 mL of dry THF was treated with carbonyl dimidazole (1.2 eq, 67 mg). The mixture was heated to 70 °C for 2 h and then cooled to room temp. Methanesulfonamide (1.3 eq, 43 mg) and DBU (1.3 eq, 0.079 mL, d 1.018) were added

and the mixture was heated to 70 °C overnight. The mixture was diluted with ethyl acetate (100 mL) and washed with aq 1M HCl (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified using silica gel chromatography (Biotage 25-S silica gel column, gradient: 0 to 20% acetone in dichloromethane) to provide compound **16I** (0.242 mmol; 71 %) as a white solid. M.S. found for C25H23F2N3O5S: 516.02 $(M+H)^+$.

Step 9:



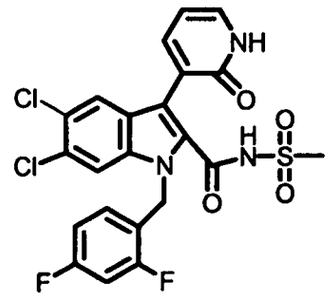
16I **156**

Compound **16I** (115 mg, 0.230 mmol) was dissolved in 4 mL of 4M HCl soln in dioxane. Methanol was added (3 mL) and the solution was heated at 90 °C in a sealed tube for 3 hours. The reaction mixture was cooled and concentrated to provide the crude product as a white solid. HPLC separation was utilized to recover product. The fraction containing the product according to MS analysis was concentrated to provide compound **156**(0.175 mmol, 76%) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 7.82 (d, J = 6.59 Hz, 1H), 7.63 (bs, 1H), 7.51 (d, J = 8.79 Hz, 1H), 7.31-7.25 (m, 1H), 7.17-7.11 (m, 1H), 7.00 (d, J = 8.79 Hz, 1H), 6.82 (s, 1H), 6.60-6.54 (m, 2H), 5.68 (s, 2H), 3.69 (q, J = 6.59 & 7.32 Hz, 2H), 3.24 (s, 3H), 1.29 (t, J = 6.59 Hz, 3H). M.S. found for C24H21F2N3O5S: 502.04 $(M+H)^+$.

Example 17

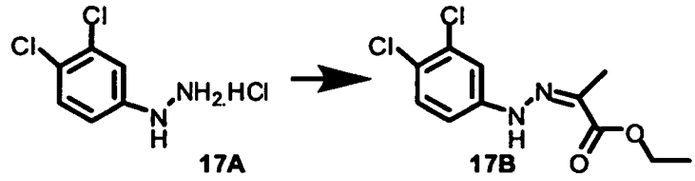
Preparation of Compound **257**

276



257

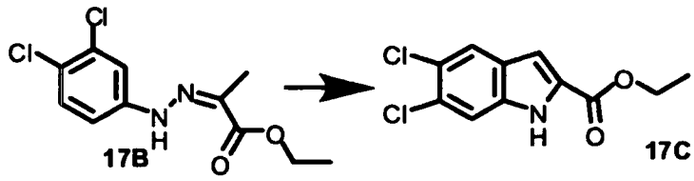
Step 1:



17A 17B

Compound **17A** (15.72g, 90% purity, 67 mmol) was dissolved into ethanol (100 mL) at room temperature. To the solution were added ethyl pyruvate (11 mL) and acetic acid (1 mL). The reaction mixture was refluxed for 2 hours. After being cooled to room temperature, the mixture was concentrated under reduced pressure. The crude product was purified using silica gel chromatography (EtOAc/Hexane=1/10) to provide product **17B** as a yellow solid (7.43 g). ^{1}H NMR (500 MHz, d_6-DMSO): δ 10.06 (s, 1H), 7.49 (d, J = 8.79 Hz, 1H), 7.41 (d, J = 2.20 Hz, 1H), 7.22 & 7.20 (dd, J = 2.20 & 8.79 Hz, 1H), 4.18 (q, J = 7.32 Hz, 2H), 2.04 (s, 3H), 1.24 (t, J = 7.32 Hz, 3H).

Step 2:

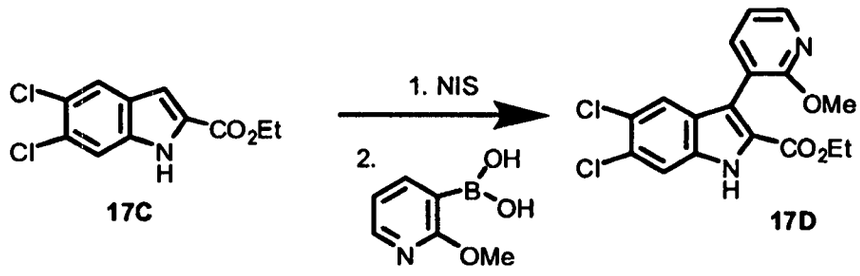


17B 17C

Compound **17B** (7.22 g) was ground into a powder before being mixed with polyphosphoric acid (50 g). The biphasic mixture was vigorously stirred at 120 °C for 2 hours. After cooling to room temperature, the reaction mixture was partitioned between EtOAc and water. The combined organic layer was dried (magnesium sulfate), filtered and concentrated *in vacuo*. The crude product was purified using flash chromatography (0-50% EtOAc/hexane) to provide a mixture of 5,6-dichloroindole **17C** and the undesired 4,5-dichloroindole. ^{1}H NMR

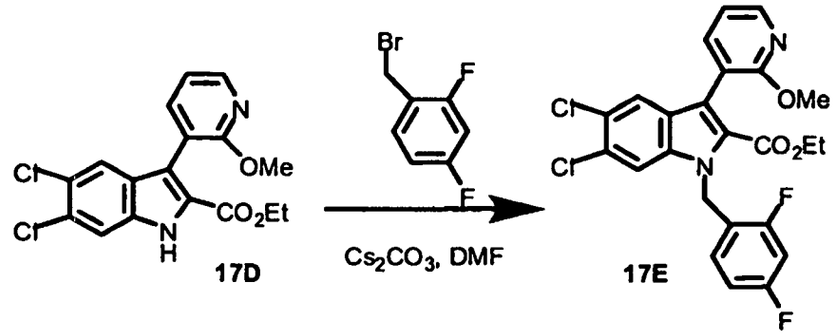
(500 MHz, d_6-DMSO): δ12.19 (s, 1H), 7.95 (s, 1H), 7.62 (s, 1H), 7.14 (s, 1H), 4.33 (q, J = 7.32 Hz, 2H), 1.32 (t, J = 7.32 Hz, 3H).

Step 3:



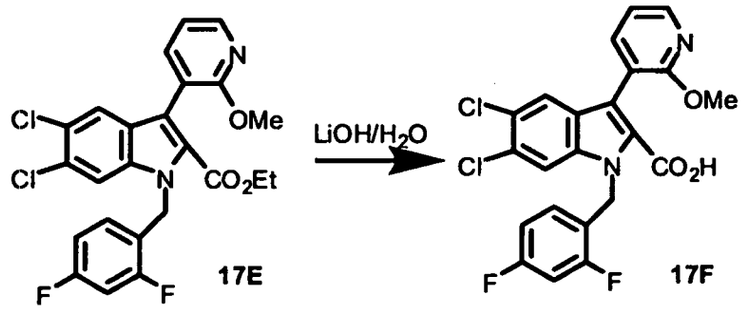
The N-iodosuccinimide (0.5 g) was added to a stirred CH_2Cl_2 (10 mL) solution of the Indole **17C** (0.57 g) at room temperature over night under an atmosphere of nitrogen. The reaction was partitioned between EtOAc and diluted aq. sodium thiosulfate. The organic phase was separated, washed with 10% aq. sodium bicarbonate, water, dried ($MgSO_4$) and concentrated to provide the desired crude iodoindole (0.828 g) which was added to the DME (4 mL). $PdCl_2(dPPF)_2$ (176 mg, 0.1 eq) was added to the mixture and was heated to 100° C (oil bath temperature) for a period of 0.5 hour and a solution of the boronic acid (99 mg, 3 eq) and potassium carbonate (1.50 g, 5 eq) in H_2O/DME (1.5 mL/1.5mL) was added dropwise. When the addition was complete the reaction mixture was heated to 100° C (oil bath) for 3 hours. After cooling, 3% aq. 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 aq. 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=3:7) to provide compound **17D** as a yellow solid (0.522 g). M.S. found for C17H14Cl2N2O3: 365.10 $(M+H)^+$.

Step 4:



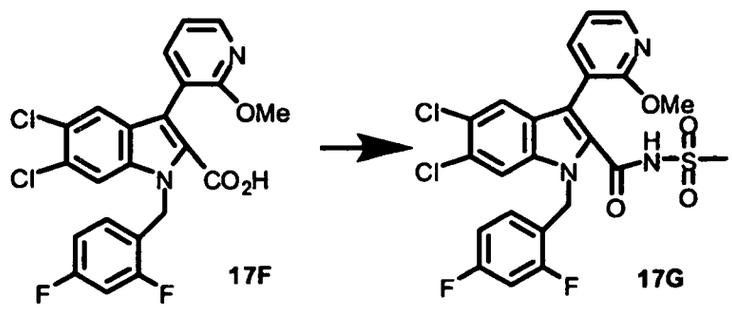
2, 4-difluorobenzylbromide (53 uL, 1.5 eq) was added drop wise to a stirred mixture of the indole **17D** (100 mg, 1 eq) and Cs_2CO_3 (134 mg, 1.5 eq) in DMF at room temperature under an atmosphere of nitrogen. After 16 hours, the reaction mixture was partitioned between EtOAc and water. The aq. phase was separated, washed with water three times, dried ($MgSO_4$) and concentrated. The residue was purified using silica gel column chromatography (EtOAc:Hexane=1:10) to to provide compound **17E** (0.105 g) as a white solid. M.S. found for C24H18Cl2F2N2O3: 490.98 $(M+H)^+$.

Step 5:



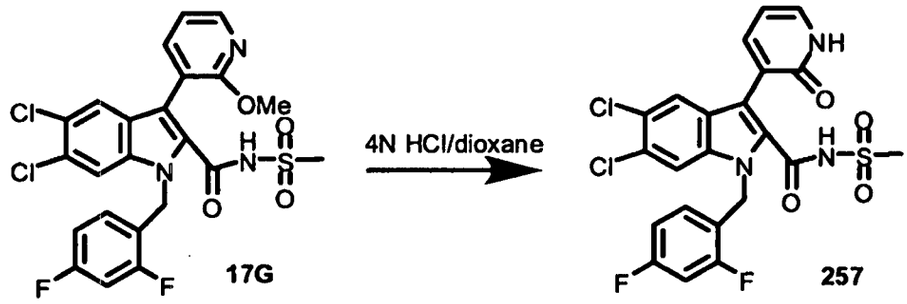
Lithium hydroxide (26 mg, 3 eq) was added to a stirred solution of the ethylester **17E** (100 mg, 1 eq) in THF/H_2O (7 mL / 3 mL) under an atmosphere of nitrogen. The resulting reaction mixture was heated to reflux over night. After cooling, the reaction was partitioned between EtOAc and diluted aq.1N HCl. The organic phases were separated. The organic phase was dried ($MgSO_4$) and concentrated to provide the crude product **17F** (100 mg). M.S. found for C22H14Cl2F2N2O3: 462.97 $(M+H)^+$.

Step 6:



A solution of acid **17F** (58 mg, 1 eq) in THF (3 mL) was treated with carbonyldiimidazole (22 mg, 1.1 eq) and heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and treated with methylsulfonamide (18 mg, 1.5 eq), and DBU (23 mg, 1.2 eq) and stirred overnight at room temperature. The mixture was concentrated and added EtOAc and washed with 1N HCl and water. The solvent was removed under reduced pressure and the crude material was purified using silica gel chromatography ($MeOH/CH_2Cl_2$=5%) to provide a pure colorless product **17G** (9 mg). M.S. found for C23H17Cl2F2N3O4S: 540.24 $(M)^+$.

Step 7:

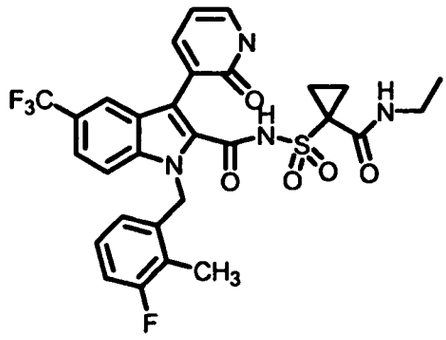


17G **257**

HCl (4N in dioxane, 2 mL) was added to **17G** (9 mg) in a sealed tube and the resulting suspension was heated to 105° C (oil bath) for 3 hours. After cooling, the solvent was removed under reduced pressure. Ether was added and the solid was collected to to provide compound **257** (8 mg). M.S. found for C22H15Cl2F2N3O4S: 527.96 $(M+H)^+$.

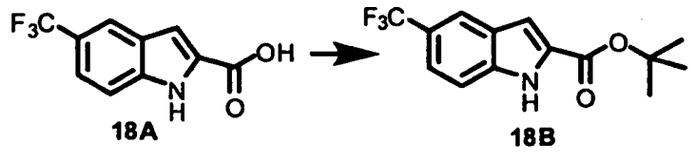
Example 18

Preparation of Compound **498**



498

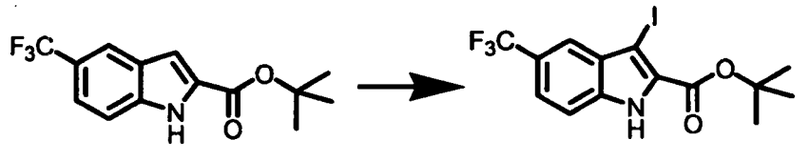
Step 1:



18A 18B

To a solution of the indole **18A** (1.6 g, 6.9 mmol) in toluene (5.0 mL) was added *N,N*-dimethylformamide di-tert butyl acetal (5 mL), and heated to 90 °C for 12h, cooled to room temperature, another aliquot of *N,N*-dimethylformamide di-tert butyl acetal (5 mL) was added and the reaction mixture was heated to 90 °C for 12h, cooled to room temperature, diluted with ethyl acetate (10.0 mL), washed with water (2 X 10.0 mL), brine, dried over $MgSO_4$, filtered and concentrated to provide compound **18B** (1.2 g, 60%) as a white solid. ^{1}H NMR (400 MHz, CDCl3); δ 9.17 (s, 1H), 7.97 (s, 1H), 7.51 (s, 2H), 7.21 (s, 1H), 1.63 (s, 9H).

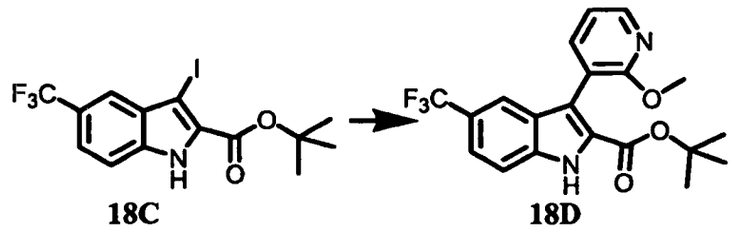
Step 2:



18B **18C**

To a solution of **18B** (1.2 g, 4.2 mmol) in $CHCl_3$ (25 mL) was added *N*-iodosuccinimide (946 mg, 4.2 mmol) and the reaction allowed to stir at room temperature for 12 hours. The reaction mixture concentrated *in vacuo*, diluted with water and extracted in EtOAc (200 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 **18C** was separated out as a brown solid which was filtered, and dried *in vacuo*. (1.23 g, 72% yield). ^{1}H NMR (400 MHz, CDCl3); δ 9.34 (s, 1H), 7.87 (s, 1H), 7.57 (d, J= 8.06 Hz, 1H), 7.49 (d, J= 8.79 Hz, 1H), 1.68 (s, 9H).

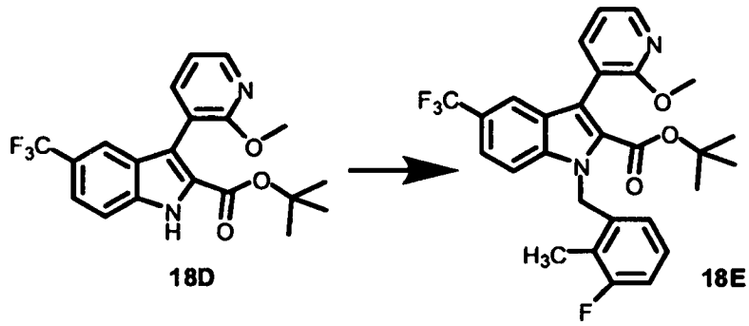
Step 3:



18C **18D**

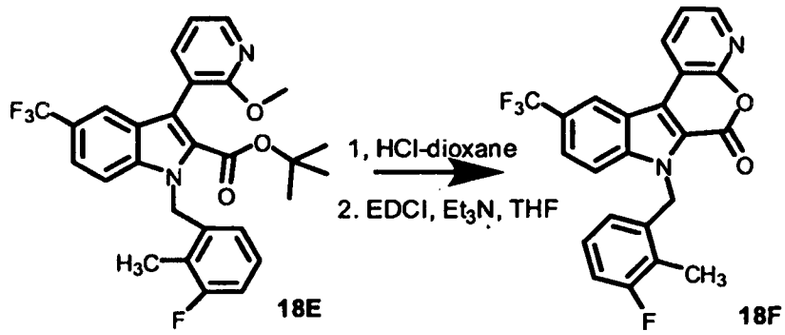
To a solution of compound **18C** (1.23 g, 3.0 mmol) in DME (30 mL) under nitrogen atmosphere was added with 2-methoxy-3-pyridyl boronic acid (0.482 g, 3.15 mmol) and Pd $(dppf)_2Cl_2$ (245 mg, 0.3 mmol) and the resulting reaction was allowed to stir at room temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (1.6 g, 12 mmol) in water (12 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 (200 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 30% EtOAc) to provide compound **18D** as a solid (820.0 mg). M.S. found for C20H19F3N2O3: 393.2 $(M+H)^+$.

Step 4:



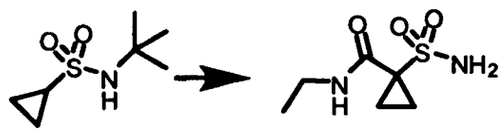
To a solution of indole **18D** (10.0 g, 25.4 mmol) in DMF (100 mL) was added cesium carbonate (9.93g, 30.5 mmol) and 3-fluoro-3-methylbenzyl bromide (3.57 mL, 30.5 mmol) and allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (500 mL), washed with water (3x100 mL) and 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 **18E** as a colorless solid.

Step 5:



A solution of compound **18E** (1.0 g, 1.94 mmol) was dissolved in 4N HCl in dioxane (20 mL) and heated at 80 ^{0}C overnight. After cooling the volatiles were removed under reduced pressure to provide the crude product, which was used directly in the next step. The residue from the first step was dissolved in anhydrous THF (10.0 mL) and EDCI (3.8 mmol, 746 mg) and Et_3N (2.55 mL, 19.0 mmol) were added to it. The reaction mixture was allowed to stir at room temperature for 12 hours, washed with 1N HCl and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated to provide compound **18F** (724 mg). M.S. found for C23H14F4N2O2: 427.2 $(M+H)^+$.

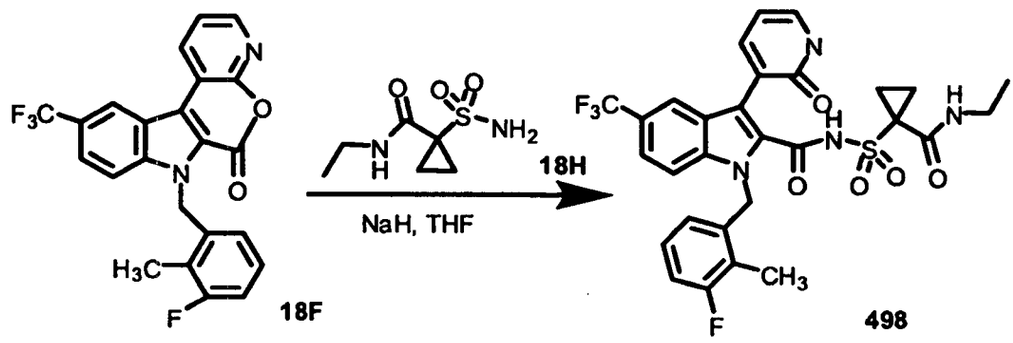
Step 6:



18G **18H**

To a cooled solution of **18G** (Prepared as described in International Publication No. WO 2004/043339) in THF (7.0 mL) was added BuLi (1.6 M in hexanes) dropwise. The reaction mixture was allowed to stir for 1 hour, ethyl isocyanate was added to it and then allowed to warm to room temperature overnight. The reaction mixture was acidified using 1N HCl and extracted with ethyl acetate (3 x 20 mL). The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel 10 % EtOAc/Hexane (0 to 60%) to provide the intermediate as an oily residue (110.0 mg). The oily residue was stirred overnight in 4N HCl in dioxane, and then concentrated to provide compound **18H** (46.0 mg).

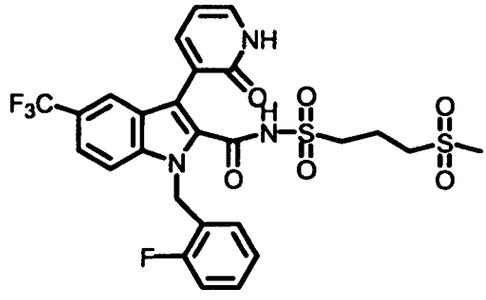
Step 7:



To a solution of compound **18F** (25.0 mg, 0.06 mmol) in THF (2.0 mL) was added sulfonamide **18H** and NaH (11.5 mg, 0.48 mg). The resulting reaction mixture was allowed to stir at room temperature for 30 minutes., then diluted with EtOAc (10 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 the resulting residue was purified using flash column chromatography on silica gel 10 % $MeOH/CH_2Cl_2$ (0 to 90%) to provide compound **498** (20 mg). ^1H NMR (400 MHz, d_6-DMSO) δ 8.30 (bs, 1H), 7.70 (s, 1H), 7.63-7.54 (m, 2H), 7.50-7.43 (m, 2H), 7.15 (t, J = 7.56 Hz, 1H), 6.91 (t, J = 7.56 Hz, 1H), 6.65 (t, J = 7.56 Hz, 1H), 6.28 (s, 1H), 5.86 (s, 2H), 3.00 (t, J = 6.94 Hz, 2H), 2.25 (s, 3H), 1.37-1.24 (m, 2H), 1.17-1.07 (m, 2H), 0.90 (t, J = 6.94 Hz, 3H).

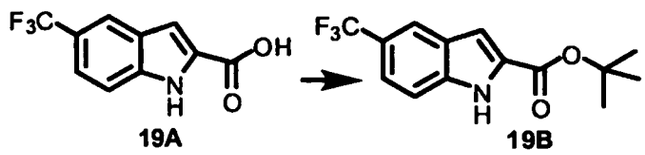
Example 19

Preparation of Compound **489**



489

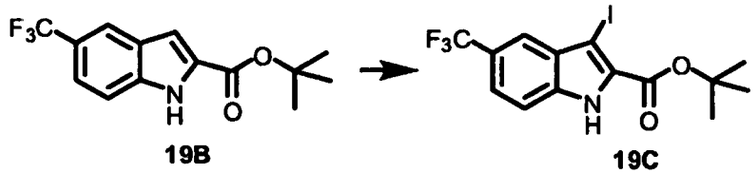
Step 1:



19A 19B

To a solution of the indole **19A** (1.6 g, 6.9 mmol) in toluene (5.0 mL) was added *N,N*-dimethylformamide di-tert butyl acetal (5 mL), and heated to 90 °C for 12h, cooled to room temperature, another aliquot of *N,N*-dimethylformamide di-tert butyl acetal (5 mL) was added and the reaction mixture was heated to 90 °C for 12h, cooled to room temperature, diluted with ethyl acetate (10.0 mL), washed with water (2 X 10.0 mL), brine, dried over $MgSO_4$, filtered and concentrated to provide compound **19B** (1.2 g, 60%) as a white solid.

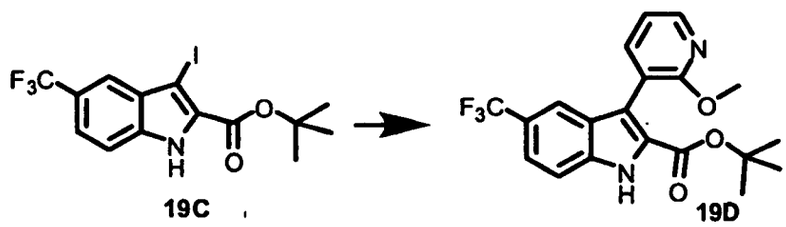
Step 2:



19B 19C

To a solution of compound **19B** (1.2 g, 4.2 mmol) in $CHCl_3$ (25 mL) was added *N*-iodosuccinimide (946 mg, 4.2 mmol) and the reaction allowed to stir at room temperature for 12 hours. The reaction mixture concentrated *in vacuo*, diluted with water and extracted in EtOAc (200 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. The product **19C** was separated out as a brown solid which was filtered, and dried *in vacuo*. (1.23 g, 72% yield)

Step 3:

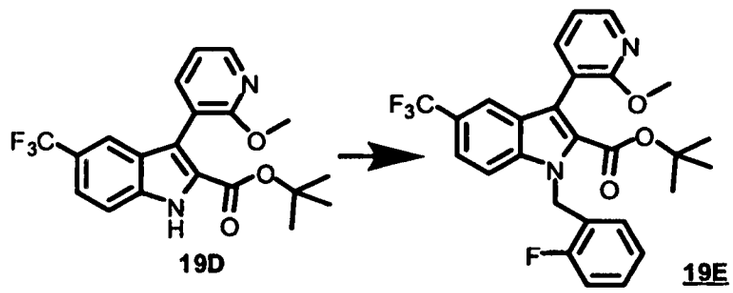


19C 19D

To a solution of compound **19C** (1.23 g, 3.0 mmol) in DME (30 mL) under nitrogen atmosphere was added with 2-methoxy-3-pyridyl boronic acid (0.482 g, 3.15 mmol) and Pd $(dppf)_2Cl_2$ (245 mg, 0.3 mmol) and the resulting reaction was allowed to stir at room

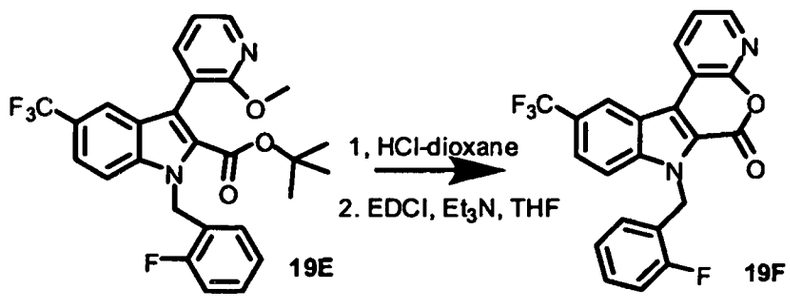
temperature under nitrogen for 0.5 hours. The reaction mixture was then treated with a solution of potassium carbonate (1.6 g, 12 mmol) in water (12 mL) and the resulting solution was heated to 90 °C and allowed to stir at this temperature for 1 hour. The reaction mixture was then diluted with EtOAc (200 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 30% EtOAc) to provide compound **19D** as a solid (820.0 mg).

Step 4:



To a solution of indole **19D** (10.0 g, 25.4 mmol) in DMF (100 mL) was added cesium carbonate (9.93g, 30.5 mmol) and 2-fluorobenzyl bromide (3.57 mL, 30.5 mmol) and allowed to stir at room temperature for 12 hours. The reaction mixture was diluted with EtOAc (500 mL), washed with water (3x100 mL) and 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 **19E** as a colorless solid.

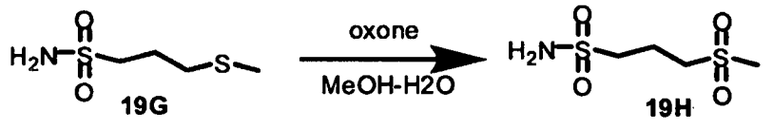
Step 5:



4N HCl in dioxane (20 mL) was added to compound **19E** (1.30 g) in a sealed tube and heated to 80° C (oil bath) overnight. After cooling to room temperature, the solvents were removed under reduced pressure to provide a crude product which was dissolved in anhydrous THF (20 mL) and EDCI (1.15 g) followed by Et3N (4.10 mL) were added and the resulting

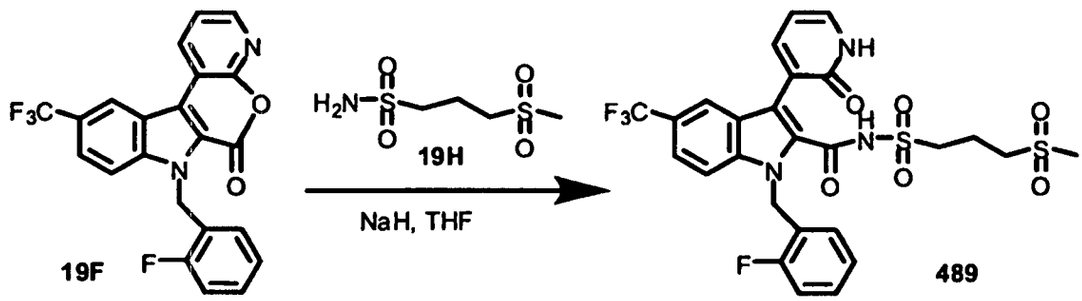
reaction mixture was stirred overnight at room temperature. The reaction mixture was partitioned between diluted aq. HCl (~10%) and CH_2Cl_2. The organic phase was separated, extracted with CH_2Cl_2 two times. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated to provide the lactone **19F** as a light brown solid (0.991 g). ^1H NMR (400 MHz, d_6-DMSO) δ 9.13 & 9.11 (dd, J = 1.46 & 8.06 Hz, 1H), 8.94 (s, 1H), 8.48 & 8.46 (dd, J = 1.46 & 5.13 Hz, 1H), 7.99 (d, J = 8.79 Hz, 1H), 7.89 (d, J = 8.79 Hz, 1H), 7.57 (dd, J = 4.39 & 8.06 Hz, 1H), 7.33-7.21 (m, 2H), 7.01 (t, J = 7.32 Hz, 1H), 6.77 (t, J = 7.32 Hz, 1H), 6.12 (s, 2H). M.S. found for C22H12F4N2O2: 412.93 $(M+H)^+$.

Step 6:



An aq. solution of oxone (1.82 g, 3 mL water) was added to the methanol (3 mL) solution of the sulfide **19G** (0.1 g) at room temperature and the resulting reaction mixture was stirred overnight at room temperature. The methanol was removed under reduce pressure and the residue was partitioned between CH_2Cl_2 and water. The organic phases were washed with water, dried ($MgSO_4$) and concentrated to provide the sulfone **19H** (25.6 mg). ^1H NMR (400 MHz, d_6-DMSO) δ 6.90 (s, 2 H), 3.25 (t, J = 7.32 Hz, 2H), 3.10 (t, J = 7.32 Hz, 2H), 2.97 (s, 3H), 2.13-2.05 (m, 2H).

Step 7:

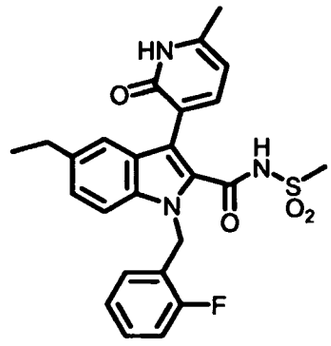


NaH (3.5 mg, 1.2 eq) was added in one portion to the stirred solution of the lactone **19F** (50 mg, 0.12 mmol) and sulfonamide **19H** (25 mg, 0.12 mmol) at room temperature under an atmosphere of nitrogen. The reaction mixture was allowed to stir for 4 hours at room temperature. The crude reaction product was purified using silica gel column chromatography

(CH_2Cl_2/MeOH=99:1 – 20:1) to to provide compound **489** (22. 6 mg) as a white solid. ^1H NMR (400 MHz, d_6-DMSO) δ 7.87 (d, J = 8.30 Hz, 1H), 7.82 (d, J = 6.35 Hz, 1H), 7.78 (s, 1H), 7.65-7.64 (m, 2H), 7.32 (q, J = 6.35 Hz, 1H), 7.22 (t, J = 8.79 Hz, 1H), 7.10 (t, J = 7.32 Hz, 1H), 6.93 (t, J = 7.32 Hz, 1H), 6.58 (bs, 1H), 5.83 (s, 2H), 3.54 (s, 2H), 3.26 (t, J =7.81 Hz, 2H), 2.97 (s, 3H), 2.06 (quintet, J = 7.32 Hz, 2H). M.S. found for C26H23F4N3O6S2: 614.3 $(M+H)^+$.

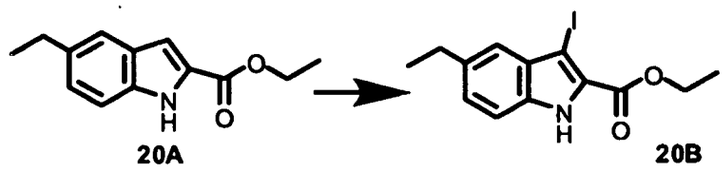
Example 20

Preparation of Compound **71**



71

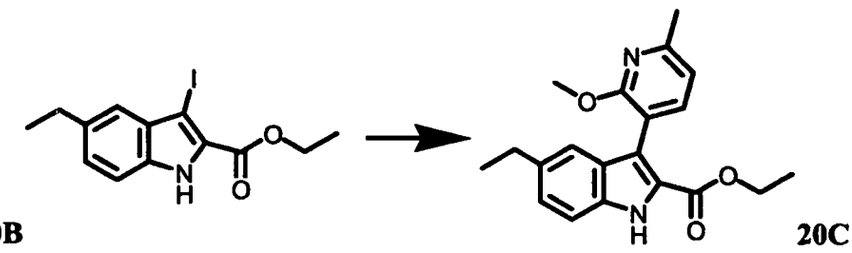
Step 1:



20A **20B**

The starting materials **20A** (15.0 g, 69.04 mmol) and THF (100 mL) were added to a 1000 ml round-bottomed flask. The resulting solution was cooled with a water bath. To this stirring solution, NIS (15.30 g, 68.80 mmol) was added slowly. The resulting solution was allowed to stir at room temperature for 5 hours before 700 ml of water was added. The resulting mixture was continued to stir at room temperature for 30 minutes and then filtered. The cake was washed with water (2X40 mL), air-dried, then dried under vacuum to provide compound **20B** as an off-white solid (23.0 g, 97%). M.S. found for $C_{13}H_{14}INO_2$: 344.2 $(M+H)^+$.

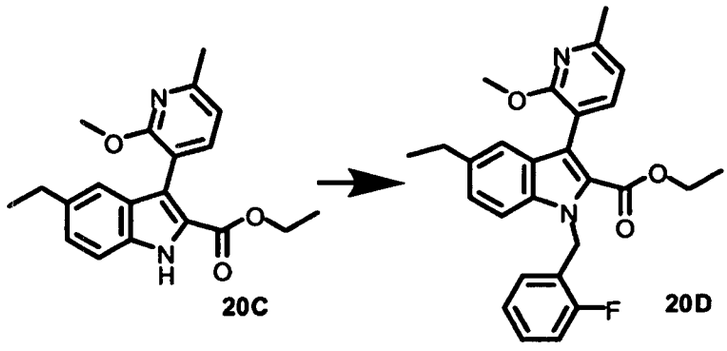
Step 2:



20B **20C**

A 200 ml round-bottomed flask was charged with **20B** (2.45 g, 7.14 mmol), 6-methyl-2-methoxypyridine-3-boronic acid (0.98 g, 5.87 mmol), [1,1' bis(diphenylphosphino) ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.58 g, 0.71 mmol), and DME (50 mL). To the stirring solution, a solution of sodium carbonate (10 ml of 1.5 M, 15.0 mmol) was added via a syringe. The reaction mixture was maintained reflux for 4 hours before cooled to room temperature. After concentration, the residue was taken up with ethyl acetate (200 mL), washed with water (3x100 mL), and dried over sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified using Combiflash chromatography on silica gel using 0-10 % ethyl acetate in hexanes as the solvent to provide compound **20C** as a white solid (1.51 g, 76%). M.S. found for $C_{20}H_{22}N_2O_3$: 339.2 $(M+H)^+$.

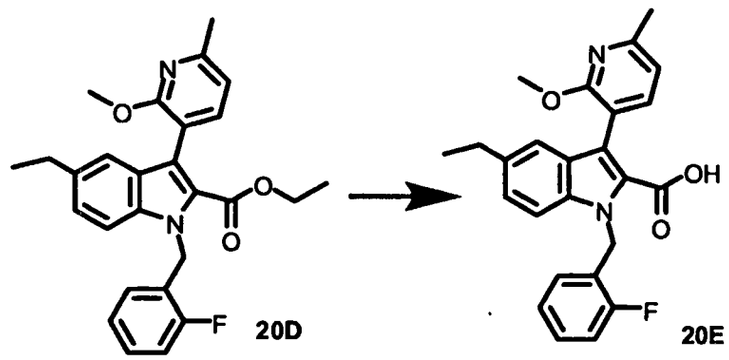
Step 3:



20C **20D**

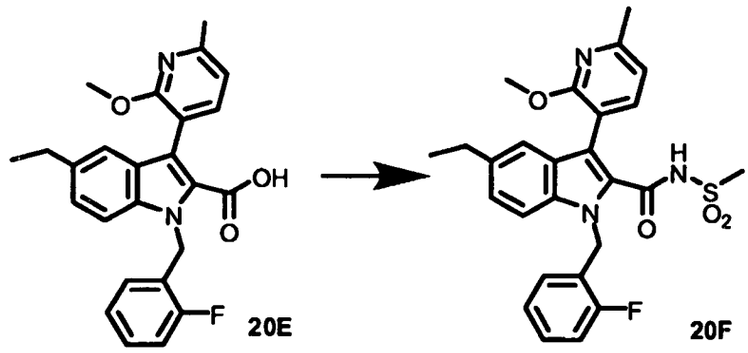
The reaction materials **20C** (200 mg, 0.59 mmol), 2-fluorobenzylchloride (170 mg, 1.76 mmol), cesium carbonate (700 mg, 2.16 mmol), and DMF (3 mL) were added to a 100 ml round-bottomed flask. The resulting suspension was allowed to stir at room temperature for 16 hours, diluted with ethyl acetate (100 mL), and washed with water (3X40 mL). The organic solution was dried over sodium sulfate and concentrated. The residue was purified using Combiflash chromatography on silica gel using 0-10% ethyl acetate in hexanes as the eluent to provide compound **20D** as a gel (205 mg, 78%).

Step 4:



To the stirring mixture of **20D** (200 mg, 0.45 mmol) in THF (5 mL) in a 100 ml round-bottomed flask was added with a solution of lithium hydroxide (2.5 ml of 1 M, 2.5 mmol). The resulting solution was maintained at reflux for 4 days before cooled to room temperature. After concentration *in vacuo*, the residue was dissolved in methanol (5 mL), neutralized with 1.0 M HCl aqueous solution (2.5 mL, 2.5 mmol) and then concentrated again. The residue was extracted with ethyl acetate (3x40 mL). The combined organic solutions were concentrated and dried on house vacuum to provide compound **20E** as a white wax (190 mg, ~100%). M.S. found for $C_{27}H_{25}ClFN_2O_3S$: 542.3 $(M+H)^+$.

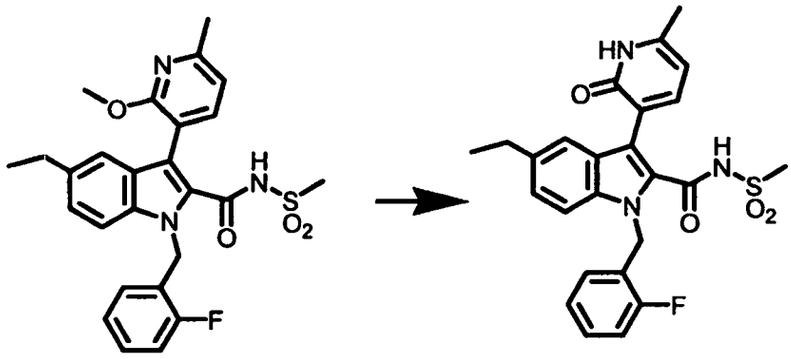
Step 5:



A solution of **20E** (65 mg, 0.16 mmol) and 1,1'-carbonyldiimidazole (37 mg, 0.23 mmol) in THF (5 mL) in a 50 ml round-bottomed flask was refluxed for 1 hour before cooled to room temperature. Methylsulfonamide (35 mg, 0.37 mmol) followed by DBU (55 mg, 0.36 mmol) were added. The resulting reaction mixture was allowed to reflux for 3 hours before cooled to room temperature and concentrated *in vacuo*. The residue was purified using Combiflash chromatography on silica gel using 0-2% methanol in dichloromethane as the

eluent to provide compound **20F** as a white wax (70 mg, 91%). M.S. found for $C_{26}H_{26}FN_3O_4S$: 496.3 $(M+H)^+$.

Step 6:

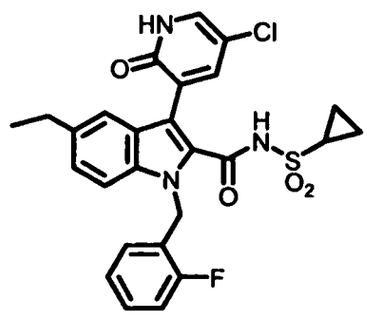


20F **71**

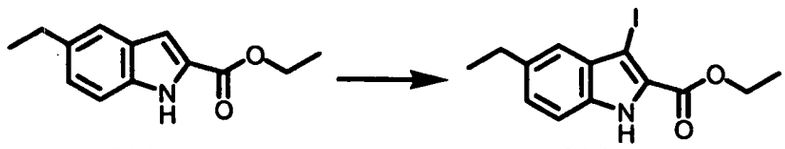
The starting material **20F** (60 mg, 0.12 mmol) and 4.0 M HCl in 1,4-dioxane (3.0 mL, 12.0 mmol) were added to a 15 ml pressure vessel. The resulting solution was allowed to stir at 90 °C for 1 hour before cooled to room temperature. The mixture was transferred to a 25 ml round-bottomed flask and concentrated on rotavapor. The residue was purified using preparative TLC on silica gel with 5% methanol in dichloromethane as the developing solvent to provide compound **71** as a white solid (25 mg, 43%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.72 (s, 1H), 7.33 (s, 1H), 7.30-7.25 (m, 1H), 7.25-7.18 (m, 1H), 7.18-7.11 (m, 1H), 7.09-7.05 (m, 1H), 7.00-6.94 (m, 1H), 6.94-6.84 (m, 1H), 6.33 (s, 1H), 5.78 (s, 2H), 2.95 (s, 3H), 2.72 (q, J = 7.57 Hz, 2H), 2.26 (s, 3H), 1.26 (t, J = 7.57 Hz, 3H). M.S. found for $C_{25}H_{24}FN_3O_4S$: 482.3 $(M+H)^+$.

Example 21

Preparation of Compound **263**



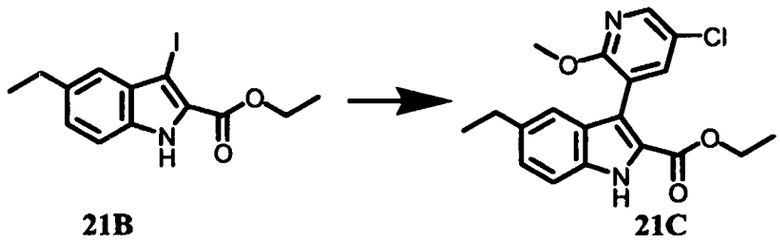
Step 1:



21A **21B**

The starting materials **21A** (15.0 g, 69.04 mmol) and THF (100 mL) were added to a 1000 ml round-bottomed flask. The resulting solution was cooled with a water bath. To this stirring solution, NIS (15.30 g, 68.80 mmol) was added slowly. The resulting solution was allowed to stir at room temperature for 5 hours before 700 ml of water was added. The resulting mixture was continued to stir at room temperature for 30 min and then filtered. The cake was washed with water (2 X 40 mL), dried by air and then on house vacuum to provide compound **21B** as an off-white solid (23.0 g, 97%). MS found 344.2 for $C_{13}H_{14}INO_2 + H^+$.

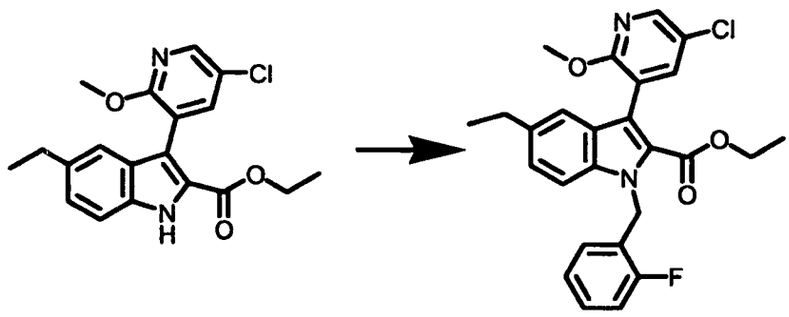
Step 2:



21B **21C**

A 250 ml round-bottomed flask was charged with **21B** (3.60 g, 10.49 mmol), 5-chloro-2-methoxypyridine-3-boronic acid (2.0 g, 10.67 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.87 g, 1.06 mmol), and DME (50 mL). To the stirring solution, a solution of sodium carbonate (10 ml of 1.5 M, 15.0 mmol) was added via a syringe. The reaction mixture was maintained at reflux for 6 hours before cooled to room temperature. After concentration, the residue was taken up with ethyl acetate (200 mL), washed with water (100 mL), and dried over sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified using Combiflash chromatography on silica gel using 0-10 % ethyl acetate in hexanes as the solvent to provide compound **21C** as a white solid (2.4 g, 64%). M.S. found for $C_{19}H_{19}ClN_2O_3$: 359.2 $(M+H)^+$.

Step 3:

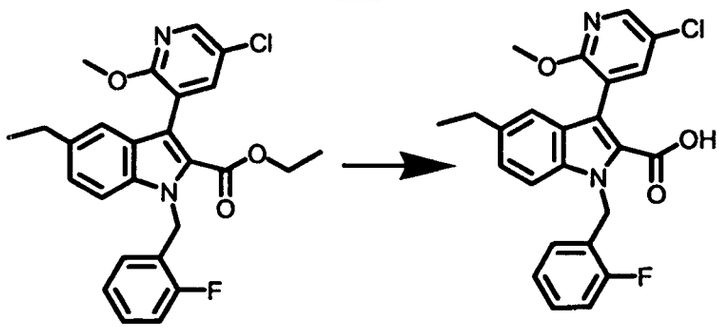


21C **21D**

A suspension of **21C** (280 mg, 0.78 mmol), 2-fluorobenzylchloride (300 mg, 2.07 mmol), cesium carbonate (400 mg, 1.23 mmol) and DMF (3 mL) was allowed to stir at room temperature for 19 hours, diluted with ethyl acetate (100 mL), and washed with water (3X50 mL). The organic solution was dried over sodium sulfate and concentrated. The residue was purified using Combiflash chromatography on silica gel using 0-5% ethyl acetate in hexanes as the eluent to provide compound **21D** as a gel (318 mg, 87%).

Step 4:

21D

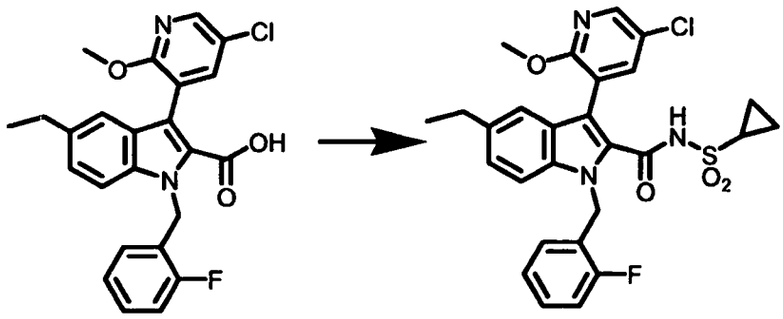


21D **21E**

To the stirring mixture of **21D** (318 mg, 0.68 mmol) in THF (10 mL) in a 100 ml round-bottomed flask was added with a solution of lithium hydroxide (2.0 ml of 1 M, 2.0 mmol). The resulting solution was maintained at reflux for 5 days before cooled to room temperature. After concentration *in vacuo*, the residue was dissolved in methanol (5 mL), neutralized with 1.0 M HCl aqueous solution (2.0 mL, 2.0 mmol) and then concentrated again. The residue was extracted with ethyl acetate (3x40 mL). The combined organic solutions were

concentrated and dried on house vacuum to provide compound **21E** as a white solid (280 mg, 94%). M.S. found for $C_{24}H_{20}ClFN_2O_3$: 439.2 $(M+H)^+$.

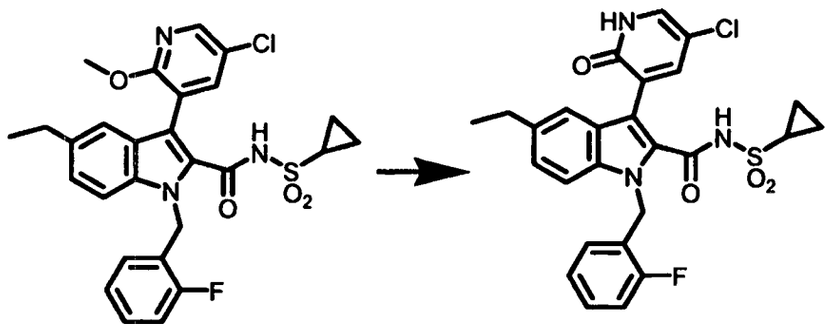
Step 5:



21E **21F**

A solution of **21E** (70 mg, 0.16 mmol) and 1,1'-carbonyldiimidazole (40 mg, 0.25 mmol) in THF (3 mL) in a 50 ml round-bottomed flask was refluxed for 1.5 hour before cooled to room temperature. Cyclopropylsulfonamide (40 mg, 0.33 mmol) followed by DBU (80 mg, 0.53 mmol) were added. The resulting reaction mixture was allowed to reflux for 4 hours before cooled to room temperature and concentrated on rotavapor. The residue was purified using Combiflash chromatography on silica gel using 0-4% methanol in dichloromethane as the eluent to provide compound **21F** as a gel (45 mg, 52%). M.S. found for $C_{27}H_{25}ClFN_3O_4S$: 542.3 $(M+H)^+$.

Step 6:



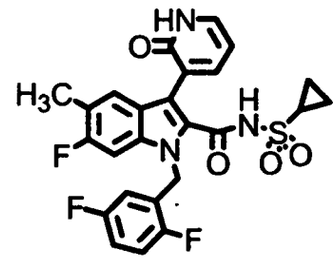
21F **263**

The starting material **21F** (40 mg, 0.073 mmol) and 4.0 M HCl in 1,4-dioxane (5.0 mL, 20.0 mmol) were added to a 15 ml pressure vessel. The resulting solution was allowed to stir at 90 °C for 2 hours before cooled to room temperature. The mixture was transferred to a 25

ml round-bottomed flask and concentrated *in vacuo*. The residue was purified using preparative TLC on silica gel with 5% methanol in dichloromethane as the developing solvent to provide compound **263** as a white solid (25 mg, 65%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.80 (s, 1H), 7.69 (s, 1H), 7.46 (d, J = 8.51 Hz, 1H), 7.34 (s, 1H), 7.29-7.24 (m, 2H), 7.10 (t, J = 9.14 Hz, 1H), 7.04 (t, J = 7.25 Hz, 1H), 6.90 (t, J = 6.62 Hz, 1H), 5.79 (s, 2H), 2.94 (bs, 1H), 2.74 (q, J = 7.57 Hz, 2H), 1.26 (t, J = 7.57 Hz, 3H), 1.16 (bs, 2H), 1.04 (bs, 2H). M.S. found for $C_{26}H_{23}ClFN_3O_4S$: 528.3 $(M+H)^+$.

Example 22

Preparation of Compound **213**

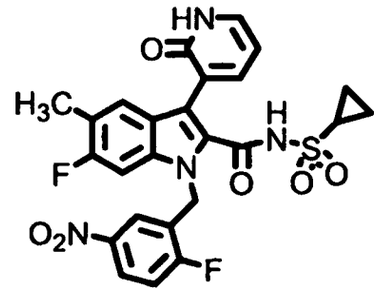


213

Using the method described in Example 1, Step 7, and subsituting 2,5-difluorobenzyl bromide for 3-bromomethyl-4-fluoro-benzonitrile, compound **213** was prepared. M.S. found for C25H20F3N3O4S: 516.3 $(M+H)^+$.

Example 23

Preparation of Compound **317**



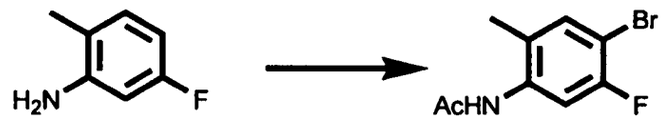
317

Using the method described in Example 1, Step 7, and subsituting 3-bromomethyl-4-fluoro-nitrobenzene for 3-bromomethyl-4-fluoro-benzonitrile, compound **317** was prepared. M.S. found for C25H20F2N4O6S: 543.3 $(M+H)^+$.

Example 24

Preparation of Intermediate Compound **24G**

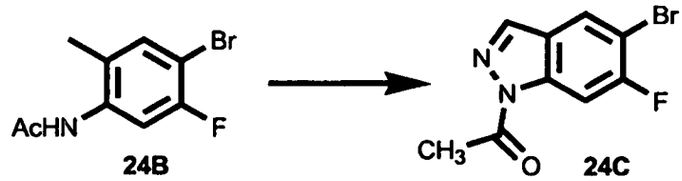
Step A – Synthesis of Compound 24B



24A **24B**

A solution of 5-fluoro-2-methylaniline (**24A**, 25 g, 200 mmol) in toluene (250 mL) was treated with acetic anhydride (25 mL. 226 mmol) heated at reflux for 1 hour. The reaction mixture was cooled when a colorless solid precipitated out which was filtered and washed with a mixture of ether and hexanes. The colorless solid was taken in acetic acid (150 mL) and treated dropwise with a solution of bromine (9.6 mL, 186 mmol) in acetic acid (20 mL) and stirred at room temperature. for 12 hours. The solution was diluted with water and the solid separating out was filtered and washed to provide N-(4-bromo-5-fluoro-2-methylphenyl)acetamide (**24B**, 40 g) as a colorless solid.

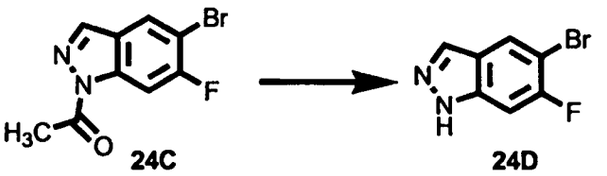
Step B – Synthesis of Compound 29C



24B **24C**

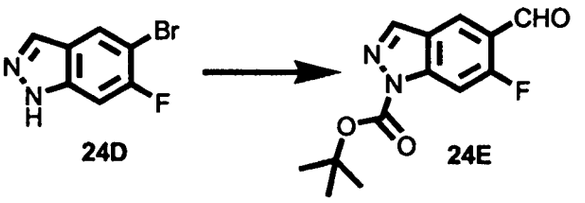
A solution of N-(4-bromo-5-fluoro-2-methylphenyl)acetamide (**24B**, 10.00 g, 40.64 mmol) in chloroform (100 mL) was treated with acetic anhydride (11.5 mL, 122.0 mmol), potassium acetate (8.00 g, 81.5 mmol), and 18-Crown-6 (540.00 mg, 2.0430 mmol) and then with isoamyl nitrite (12.3 mL, 871 mmol) and heated at 65 °C for 12 hours. The reaction mixture was cooled to room temperature and treated with EtOAc (500 mL), washed with water, dried ($MgSO_4$), filtered, and then concentrated *in vacuo* . A pale yellow solid of 1-(5-bromo-6-fluoro-1H-indazol-1-yl)ethanone (**29C**) precipitated out. The initial filtrate was concentrated and the residue was purified using chromatography (SiO_2, EtOAc/Hexanes) to provide more of product **24C**.

Step C– Synthesis of Compound 24D



A solution of 1-(5-bromo-6-fluoro-1H-indazol-1-yl)ethanone (**24C**, 5.0 g, 19.5 mmol) was treated with aq HCl (3M soln., 100 mL) and methanol (20 mL) and heated at 90 °C for 3h, when the reaction turns homogenous. The reaction mixture was cooled to room temperature and basified with aq. NaOH. A colorless solid precipitated out which was filtered and dried to provide 5-bromo-6-fluoro-1H-indazole (**24D**)

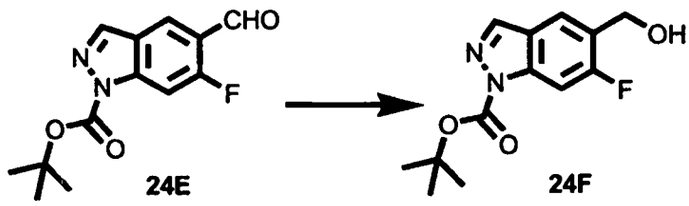
Step D – Synthesis of Compound 24E



A solution of 5-bromo-6-fluoro-1H-indazole (**24D**, 3.50 g, 16.28 mmol) in tetrahydrofuran (200.00 mL) was treated with sodium hydride (60% in mineral oil, 1.172 g) at 0 °C and stirred at room temperature. for 20 minutes. The reaction mixture was cooled to -78 °C (dry ice and acetone) and treated with 2.5 M of n-butyl lithium in hexane (8.2 mL, 20.3 mmol) dropwise. The reaction mixture was allowed to stir at that temperature for 20 min and treated with DMF (5.06 mL, 65.11 mmol). The reaction mixture was slowly warmed to room temperature when the viscous solution turn fluidic and stirring was efficient. Analysis of TLC (40% EtOAc/Hexanes) indicated complete conversion of starting material to product. The reaction mixture was acidified with aq. HCl taken up in EtOAc (500 mL) washed with aq. HCl (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo* and used as it is in next step. A solution of product 6-fluoro-1H-indazole-5-carbaldehyde (2.3 g) in THF (100 mL) was treated with di-*tert*-butyldicarbonate (3.56 g, 16.28 mmol) and DMAP (300 mg) and stirred at room temperature for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified using chromatography (SiO_2, EtOAc/Hexanes gradient 0-40%) to

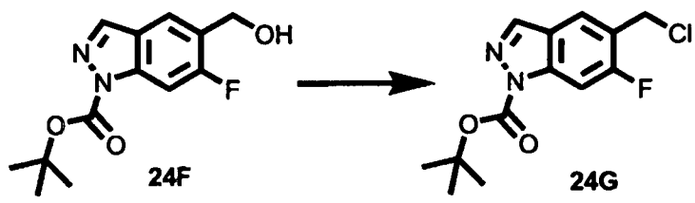
provide [2e] *tert*-butyl 6-fluoro-5-formyl-1H-indazole-1-carboxylate (**24E**, 3.5 g; Yield = 81%) as a colorless solid.

Step E – Synthesis of Compound 24F



A solution of *tert*-butyl 6-fluoro-5-formyl-1H-indazole-1-carboxylate (**29E**, 3.55 g, 13.4 mmol) in methanol (50.00 mL) was treated with $NaBH_4$ (1.02 g, 26.9 mmol) at 0 °C and allowed to stir for 1h. The reaction mixture was diluted with water and EtOAc (500 mL). The organic layer was separated and washed with aq. HCl (1M, 200 mL), aq. NaOH (1M, 200 mL) brine (200 mL) dried ($MgSO_4$), filtered, concentrated in *vacuo* and residue was purified using chromatography (SiO_2, EtOAc/hexanes) to provide *tert*-butyl 5-(hydroxymethyl)-6-fluoro-1H-indazole-1-carboxylate (**29F**, 3.00 g; Yield = 83.9%) as a colorless solid.

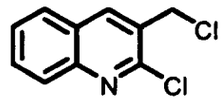
Step F – Synthesis of Compound 24G



A solution of *tert*-butyl 5-(hydroxymethyl)-6-fluoro-1H-indazole-1-carboxylate (**29F**, 3.0g, 11.27 mmol) in methylene chloride (50.00 mL, 780.0 mmol) at room temperature. was treated with pyridine (4.56 mL, 56.33 mmol) and methanesulfonyl chloride (1.31 mL) and stirred at room temperature for 16 hours. The reaction mixture was concentrated in *vacuo* and the residue was dissolved in EtOAc (300 mL) washed with aq HCl (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, concentrated in *vacuo*, and purified using chromatography (SiO_2, EtOAc/Hexanes) to provide *tert*-butyl 5-(chloromethyl)-6-fluoro-1H-indazole-1-carboxylate (**24G**, 1.9 g; Yield = 59%)

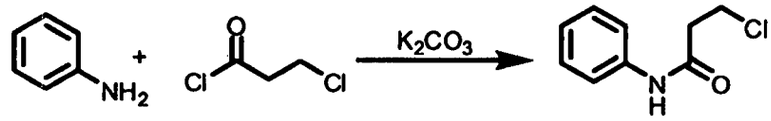
Example 25

Preparation of Intermediate Compound **25B**



25B

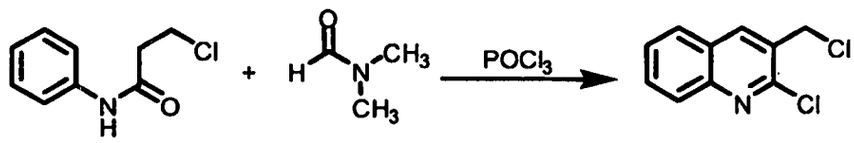
Step A – Synthesis of Compound 6A



25A

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 **25A**, which was used without purification (114.5 g, 87%).

Step B – Synthesis of Compound 25B

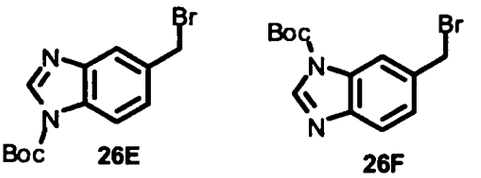


25A **25B**

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 allowed to stir at that temperature for 10 min and treated with 3-Chloro-N-phenylpropanamide **25A** (50.00 g, 272.3 mmol) and stirred at room temperaturefor 30 minutes. 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 **25B** (20 g).

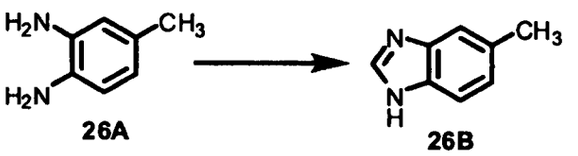
Example 26

Preparation of Intermediate Compounds **26E** and **26F**



26E **26F**

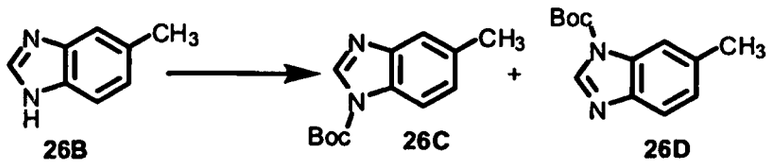
Step A – Synthesis of Compound 26B



26A **26B**

A solution of compound **26A** (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 **26B** (3.65 g), which was used without further purification. M.S. found for $C_8H_8N_2$: 133.2 $(M+H)^+$.

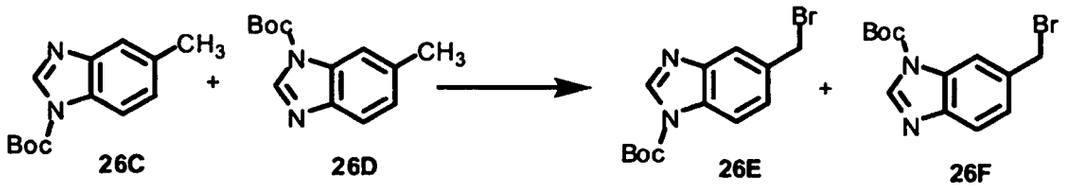
Step B – Synthesis of Compounds 26C and 26D



26B **26C** **26D**

To a solution of compound **26B** (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 **26C** and **26D** (5.38 g, 94.3% yield over steps A and B).

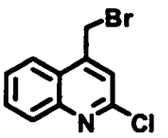
Step C – Synthesis of Compounds 26E and 26F



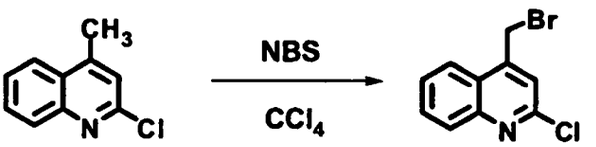
To a solution of compounds **26C** and **26D** (2 g, 8.61 mmol) in carbon tetrachloride (40 mL) was added N-bromosuccinimide (1.6 g, 9.04 mmol) and dibenzoyl peroxide (41.7 mg, 0.1722 mmol) and the resulting reaction was heated to 90 °C and allowed to stir at this temperature for 12 hours. The reaction 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 **26E** and **26F** (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 27

Preparation of Intermediate Compound **27B**



27B

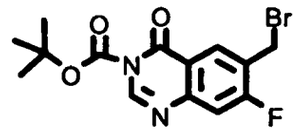


27A **27B**

A mixture of compound **27A** (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 **27B**, and was used without further purification.

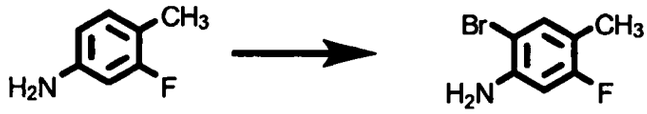
Example 28

Preparation of Intermediate Compound **28G**



28G

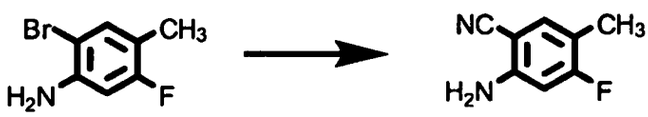
Step A – Synthesis of Compound 9B



28A **28B**

A mixture of compound **28A** (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 **28B** (11.0 g, quant.), which was used without further purification.

Step B – Synthesis of Compound 28C

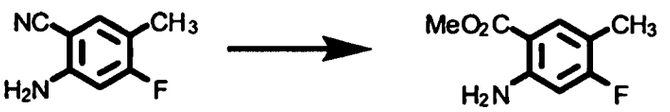


28B **28C**

Compound **28B** 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 allowed to stir 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

28C (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 28D



28C **28D**

To a solution of **28C** (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 allowed to stir 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 **28D** (1.0 g, 41 %) and some recovered **28C**. ^{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).

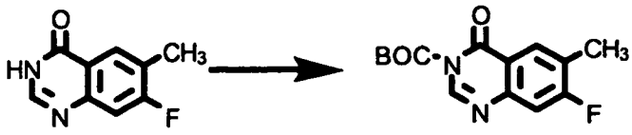
Step D – Synthesis of Compound 28E



28D **28E**

The solution of compound **28D** (500 mg, 2.73 mmol) in formamide (6.0 mL) was heated to 150 °C in an oil bath and allowed to stir 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 **28E** (0.50 g, quant.) which, was used without further purification. MS found for $C_9H_7FN_2O$: 179.0 $(M+H)^+$.

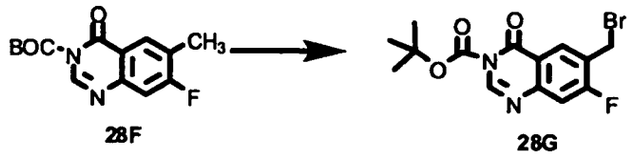
Step E – Synthesis of Compound 28F



28E 28F

To a solution of **28E** (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 allowed to stir 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 **28F** (285 mg, 36 %). MS found for $C_{14}H_{15}FN_2O_3$: 179.0 $(M+H-100)^+$.

Step F – Synthesis of Compound 28G

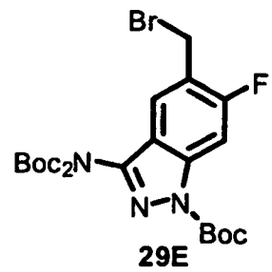


28F 28G

The mixture of **28F** (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 allowed to stir 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 **28G** (453 mg, quant.) which, was used without further purification.

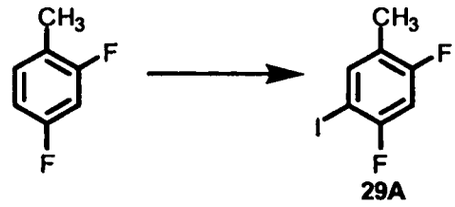
Example 29

Preparation of Intermediate Compound **29E**



29E

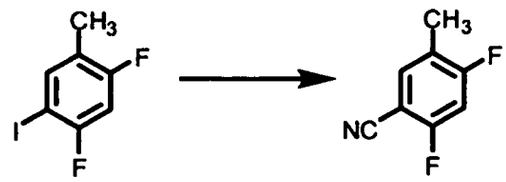
Step A – Synthesis of Compound 29A



29A

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 **29A** (7.2 g, 77%) as a colorless oil.

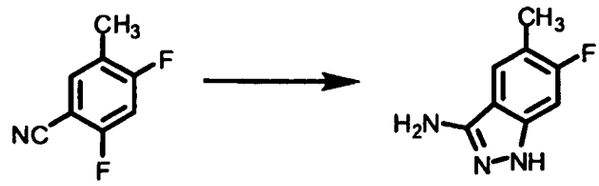
Step B – Synthesis of Compound 29B



29A **29B**

A solution of compound **29A** (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 **29B** (1.8 g; Yield = 42%).

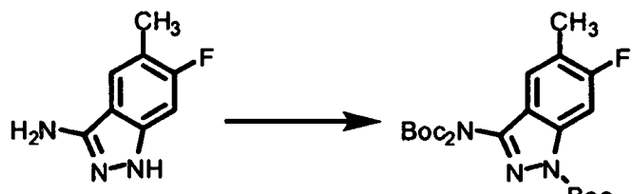
Step C – Synthesis of Compound 29C



29B **29C**

A solution of compound **29B** (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 **29C** (330 mg, 22%).

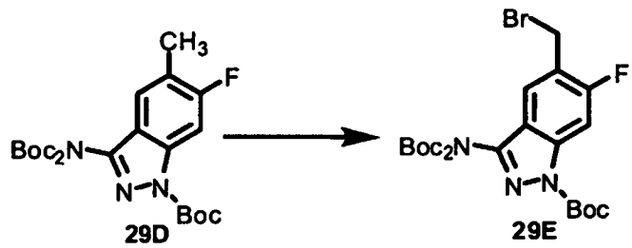
Step D – Synthesis of Compound 29D



29C **29D**

A solution of compound **29C** (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 **29D** (640.00 mg, 68%) as a colorless oil.

Step E - Synthesis of Compound 29E



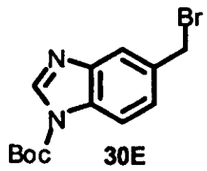
29D **29E**

A solution of compound **29D** (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

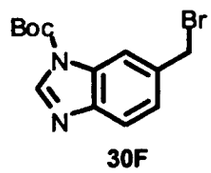
mixture was cooled to room temperature, concentrated *in vacuo* and the residue obtained was dissolved in EtOAc (300 mL). The resulting solution was washed with aqueous sodium thiosulfate (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue obtained was purified using flash column chromatography (SiO_2, EtOAc/Hexanes) to provide compound **29E** as a colorless oil.

Example 30

Preparation of Intermediate Compounds **30E** and **30F**

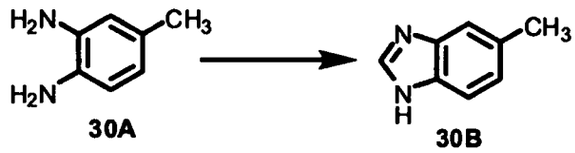


30E



30F

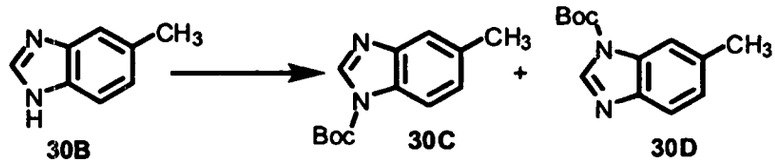
Step A – Synthesis of Compound 30B



30A **30B**

A solution of compound **8A** (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 **8B** (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 30C and 30D

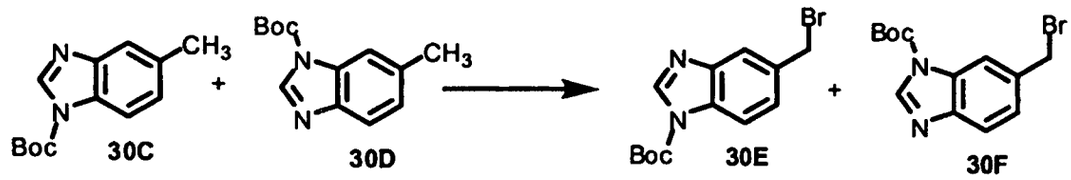


30B **30C** **30D**

To a solution of compound **30B** (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 **30C** and **30D** (5.38 g, 94.3% yield over steps A and B).

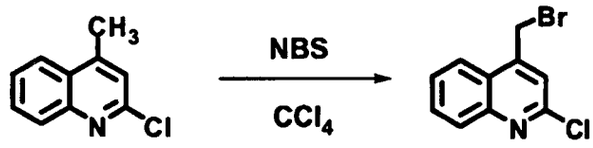
Step C – Synthesis of Compounds 30E and 30F



To a solution of compounds **30C** and **30D** (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 **30E** and **30F** (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 31

Preparation of Intermediate Compound **31B**



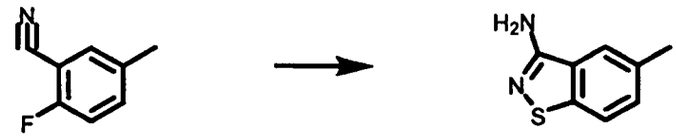
31A **31B**

A mixture of compound **31A** (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 **31B**, and was used without further purification.

Example 32

Preparation of Intermediate Compound **32D**

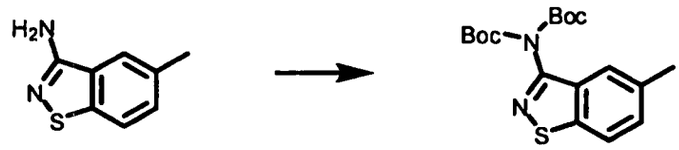
Step A – Synthesis of Compound 32B



32A 32B

A mixture of 2-fluoro-5-methylbenzonitrile (**32A**, 2.0 g; 14.799 mmol) and sodium sulfide (1.0 eq, 1.15 g) was dissolved in 150 mL of DMSO and heated at 70 °C overnight. The mixture was placed in an ice-water bath and treated with concentrated aqueous ammonium hydroxide (20 mL) and aqueous sodium hypochlorite (20 mL). The reaction mixture was allowed to warm to room temperature and allowed to stir for 5 hours. The mixture was diluted with ethyl acetate (300 mL) and washed with water (2 x 60 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-M silica gel column (gradient: 0 to 30 % acetone in hexanes) to provide compound **32B** (860 mg; 36 %) as a white solid. ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.68 (1H, d, J = 8.54 Hz), 7.48 (1H, s), 7.33 (1H, d, J = 8.54 Hz), 4.89 (2H, broad s), 2.50 (3H, s).

Step B – Synthesis of Compound 32C



32B 32C

A solution of 5-methylbenzo[d]isothiazol-3-ylamine, (**10B**, 850 mg; 5.176 mmol) in dry acetonitrile (50 mL) was treated with Boc-anhydride (2.1 eq, 2.37 g) and heated to 50 °C. All starting material had been consumed after 2 h and the mixture was concentrated *in vacuo* to one third of its volume. The residue was dissolved in ethyl acetate (100 mL) and washed with aqueous sodium hydrogen sulfate (20 mL), and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-M silica gel column (gradient: 0 to 10 % ethyl acetate in hexanes) to provide compound **10C** (1.7 g; 91 %) as a white powder. ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.77 (1H, d, J = 8.54 Hz), 7.55 (1H, s), 7.38 (1H, dd, J = 1.83, 8.54 Hz), 2.51 (3H, s), 1.36 (18H, s). LR-MS (ESI): caldc for $C_{18}H_{25}N_2O_4S$ $[M+H]^+$ 365.15; found 365.23.

Step C – Synthesis of Compound 32D



32C 32D

A solution of N,N-bis-Boc-5-methyl-benzo[d]isothiazol-3-ylamine (**32D**, 500 mg; 1.371 mmol) in 15 mL of carbon tetrachloride was treated N-bromosuccinimide (1.05 eq, 256 mg) and benzoyl peroxide (10 mol%; 33 mg). The solution was degassed (vacuum/argon flush) and then heated to 75 °C for 5 hours. The reaction mixture was concentrated to one third of its volume *in vacuo* and the residue was dissolved in ethyl acetate (50 mL). The solution was washed with aqueous saturated sodium bicarbonate soln (2 x 10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a Biotage 40-S silica gel column (gradient: hexanes then 0 to 10 % ethyl acetate in hexanes) to provide compound **32D** (396 mg; 69 %) as a white solid. ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 7.87 (1H, d, J = 8.54 Hz), 7.78 (1H, s), 7.58 (1H, dd, J = 1.83, 8.54 Hz), 4.63 (2H, s), 1.37 (18H, s). LR-MS (ESI): caldc for $C_{18}H_{24}BrN_2O_4S$ $[M+H]^+$ 445.06; found 445.24.

Example 33

Preparation of Intermediate Compound **33D**

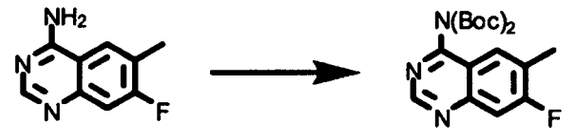
Step A – Synthesis of Compound 33B



33A 33B

A solution of **33A** (0.20 g, 1.33 mmol) in formamide (15 mL) was heated to 150 °C and allowed to stir for 18 hours. After cooled to room temperature, ethyl acetate (60 mL) and water (30 mL) were added and the layers were separated. The organic solution was washed with water (3x20 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo* to provide the crude product **33B** (0.22 g, 93 %). MS found for $C_9H_8FN_3$: 178.2 $(M+H)^+$.

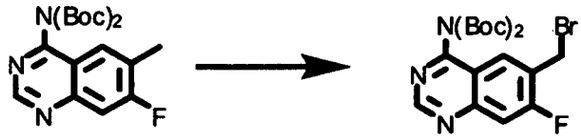
Step B – Synthesis of Compound 11C



33B 33C

33B was treated with 3.0 equivalent of $(Boc)_2O$ to provide **33C**. MS found for $C_{19}H_{24}FN_3O_4$: 378.4 $(M+H)^+$.

Step C – Synthesis of Compound 33D



33B 33C

Bromination of **33C** understandard N-bromo succinimide conditions afforded **33D**. MS found for $C_{19}H_{23}BrFN_3O_4$: 458.3 $(M+H)^+$.

Example 34

Preparation of Intermediate Compound **34F**

Step A – Synthesis of Compound 34B



34A 34B

N-iodosuccinimide (1.1 eq; 17.1 g) was added to a solution of 2,4-difluoro toluene (**34A**, 10.0 g; 69.17 mmol; Alfa Aesar) in trifluoroacetic acid (46 mL). The reaction was set to stir for 12 hours. The volatiles were removed under reduced pressure; the remaining slurry was diluted with ether (400 mL) and washed with 5% aq sodium thiosulfate (5x40 mL), water (2x30 mL), and brine (40 mL). The organic layer was collected, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The reaction was purified via bulb to bulb distillation to provide product **34B** as a colorless liquid (17 g; 91%)

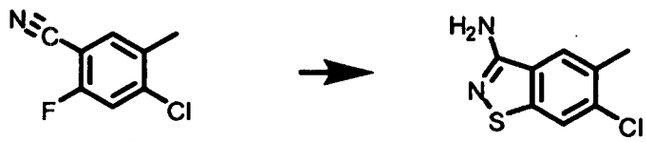
Step B – Synthesis of Compound 34C



34B 34C

A solution of intermediate **34B** (13.0 g; 48.06 mmol) and zinc cyanide (1 eq; 5.644 g) in N,N-dimethlyformamide (50 mL) was treated with tetrakis (triphenylphosphine) palladium(0) (0.1 eq; 5.55 g) and heated at 90 °C for 12 hours. The reaction mixture was diluted with ether (600 mL) and ammonium hydroxide (1:1 concentrated ammonium hydroxide: water 200 mL). The organic layer was separated and washed with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, and purified over silica gel first eluting with hexanes, then with 20% ethyl acetate/hexanes. Product 34C (4.48 g; 33%) was afforded as a clear oil.

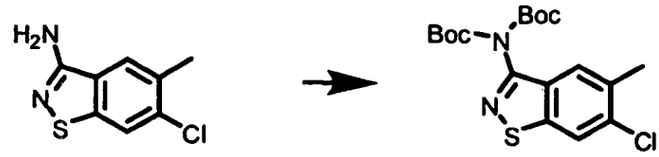
Step C – Synthesis of Compound 34D



34C 34D

A solution of **34C** (2.25 g; 13.27 mmol) and sodium sulfide (1 eq; 1.035 g) was prepared in DMSO (130 mL) and heated at 70 °C overnight. The mixture was placed in an ice water bath and treated with concentrated aqueous ammonium hydroxide (30 mL) and aqueous sodium hypochlorite (30 mL). The reaction mixture was allowed to stir for 5 h (temp from 0 to 25 °C). The mixture was diluted with ethyl acetate (400 mL) and washed with water (2x40 mL) and brine (50 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on an ISCO 330G column (gradient: 0-30% acetone in hexanes), affording product **34D** (800 mg; 30.3%) as a white solid.

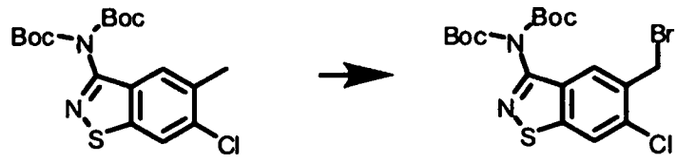
Step D – Synthesis of Compound 34E



34D 34E

A solution of intermediate **34D** (780 mg; 3.93 mmol) in dry acetonitrile (39 mL) was treated with Boc-anhydride (2.2 eq; 1.885 g) and heated to 50 °C. All starting material had been consumed after 2 h and the mixture was concentrated *in vacuo* to one third of its volume. The residue was dissolved in ethyl acetate (100 mL) and washed with aqueous sodium hydrogen sulfate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on a ISCO 80 gram column (gradient: 0 to 10% ethyl acetate in hexanes) to provide compound **34E** (1.03 g; 66% yield) as a white solid.

Step E – Synthesis of Compound 34F



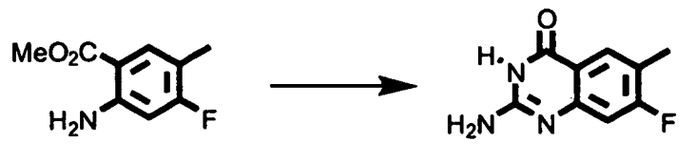
34E **34F**

A solution of intermediate **34E** (400 mg; 1.003 mmol), N-Bromosuccinimide (1.05 eq; 187.4 mg), and benzoyl peroxide (0.1 eq; 24.3 mg) in dry carbon tetrachloride (10 mL) was prepared and heated at reflux for 12 hours. TLC (30% ethyl acetate in hexanes) revealed the reaction had partially progressed. The reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium bicarbonate (25 mL) and brine (25 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was then diluted with dichloromethane, adsorbed onto silica gel, and purified on ISCO (25-M Column; 0-40% ethyl acetate in hexanes). The fractions containing product were concentrated under reduced pressure affording intermediate **34F** (278 mg; 58%) as a clear yellow oil.

Example 35

Preparation of Intermediate Compound **35C**

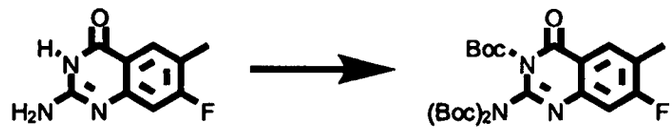
Step A – Synthesis of Compound 31A



35A

A solid mixture of methyl 2-amino-4-fluoro-5-methylbenzoate (2.66 g, 14.5 mmol), chloroformamidinium hydrochloride (2.6 g, 22.6 mmol) and methyl sulfone (8.5 g, 90.3 mmol) was heated to 150-160 °C in an oil bath with vigorous stirring. It became a clear solution after about 10 minutes. Heating was continued for a total of 2 hours.When cooled to room temperature, it became a solid. The material was taken up with water (200 mL), basified with commercial ammonium hydroxide. After stirred for 1 hour, the solid was collected through filtration. It was washed with water (20 mL) and dried under vacuum to provide crude product **35A** (2.93 g, quant.). MS found for $C_9H_8FN_3O$: 194.2 $(M+H)^+$.

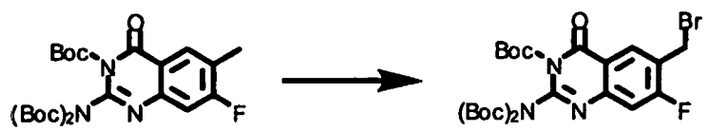
Step B – Synthesis of Compound 35B



35A **35B**

Compound **35B** was prepared from **35A** according the procedures described, and using 4 equivalents of $(Boc)_2O$. MS found for $C_{24}H_{32}FN_3O_7$: 394.3 $(M+H-100)^+$.

Step C – Synthesis of Compound 35C



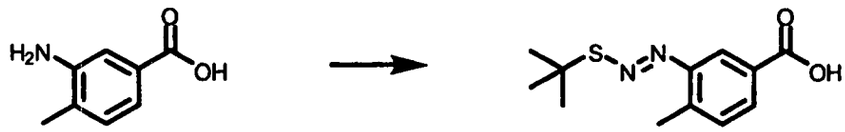
35B **35C**

A solution of compound **35B** (4.83 g, 9.8 mmol), N-bromosuccinimide (2.70 g, 15.2 mmol) and benzoyl peroxide (600 mg, 2.48 mmol) in carbon tetrachloride (300 mL) was heated to reflux and allowed to stir at this temperature for 18 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* to provide intemediate compound **35C**, which was used without further purification. MS found for $C_{24}H_{31}BrFN_3O_7$: 472.3 $(M+H-100)^+$.

Example 36

Preparation of Interemdiate Compound **36G**

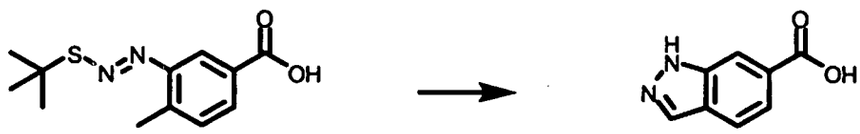
Step A – Synthesis of Compound 36B



36A **36B**

To a stirred solution of aqueous HCl (15 mL of conc HCl in 50 mL of water) was added 3-amino-4-methyl benzoic acid (**36 A**, 5.0 g; 33.0 mmol). The mixture was cooled in an ice-water bath followed by slow addition of a solution of sodium nitrite (1.1 eq, 2.50 g) in water (12 mL). The mixture was allowed to stir for 30 min at which point the mixture was a homogeneous dark solution. A saturated aqueous solution of sodium acetate was added until pH 6 was attained. Sodium t-butylthiolate (0.5 eq, 1.85 g) was added in one portion. The reaction was allowed to stir for 2 h and the resulting precipitate was collected by filtration (whatman #1), washed with water (20 mL) and dried under vacuum to provide compound **36B** (2.7 g; 64 %) as a tan solid.

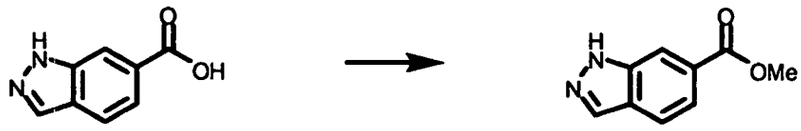
Step B – Synthesis of Compound 36C



36B **36C**

To a stirred solution of potassium tert-butoxide (10.0 eq, 12.0 g) in DMSO (50 mL) was added a solution of t-butyldiazaenyl benzoic acid **36B** (2.7 g; 10.70 mmol) in DMSO (30 mL). The mixture was allowed to stir for 6 h and then diluted with ice and acidified with aqueous 1 M HCl until pH 5-6 was attained. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were washed with water (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product **36C** as a slightly yellow solid which was used without further purification.

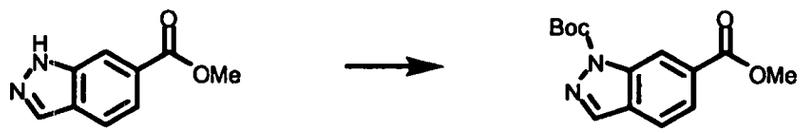
Step C – Synthesis of Compound 36D



36C 36D

A solution of 1H-indazole-6-carboxylic acid **36C** (1.73 g; 10.70 mmol) in toluene (80 mL) and methanol (30 mL) was treated with a solution of TMS-diazomethane (2 M soln in ether) until evolution of gas stopped. The reaction mixture was concentrated *in vacuo* and the residue was adsorbed on silica gel. The product was purified on a Biotage 40-M silica gel column (gradient: 0 to 20 % acetone in hexanes) to provide compound **36D** (950 mg; 50 % for two steps) as a yellow solid. ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 8.28 (1H, s), 8.16 (1H, s), 7.86 (1H, d, J = 8.54 Hz), 7.81 (1H, d, J = 8.54 Hz), 3.98 (3H, s). LR-MS (ESI): caldc for $C_9H_9N_2O_2$ $[M+H]^+$ 177.07; found 177.20.

Step D – Synthesis of Compound 36E



36D 36E

A solution of 1H-indazole-6-carboxylic acid methyl ester **36D** (840 mg; 4.76 mmol) in 25 mL of acetonitrile was treated with Boc-anhydride (1.05 eq, 1.09 g) and a catalytic amount of DMAP (tip of spatula). The mixture was allowed to stir at 60 °C for 3 hours. The mixture was concentrated to half its volume *in vacuo*, then diluted with ethyl acetate (100 mL) and washed with aqueous saturated sodium bicarbonate (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified on a Biotage 40-M silica gel column (gradient: 0 to 20 % ethyl acetate in hexanes) to provide compound **36E** (1.2 g; 93 %) as a colorless oil. ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 8.91 (1H, s), 8.22 (1H, s), 7.99 (1H, dd, J = 1.22, 8.54 Hz), 7.78 (1H, d, J = 8.54 Hz), 3.97 (3H, s), 1.74 (9H, s).

Step E – Synthesis of Compound 36F



36E 36F

A solution of indazole **36E** (460 mg; 1.66 mmol) in 16 mL of dry THF was cooled to -78 °C and treated with lithium triethylborohydride (2.5 eq, 4.15 mL of a 1 M soln in THF). The reaction mixture was allowed to stir at -78 °C and followed by TLC (25 % ethyl acetate in hexanes). The reaction was completed in about 1 h and quenched by addition of aqueous saturated sodium hydrogen sulfate (3 mL). The mixture was extracted with ethyl acetate (100 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to provide the crude product as a colorless oil. The residue was chromatographed on a Biotage 40-S silica gel column (0 to 40 % ethyl acetate in hexanes) to provide compound **36F** (160 mg; 40 %). ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 8.19 (1H, s), 8.13 (1H, s), 7.67 (1H, d, J = 7.93 Hz), 7.30 (1H, d, J = 7.93 Hz), 5.13 (2H, s), 1.71 (9H, s).

Step F – Synthesis of Compound 36G



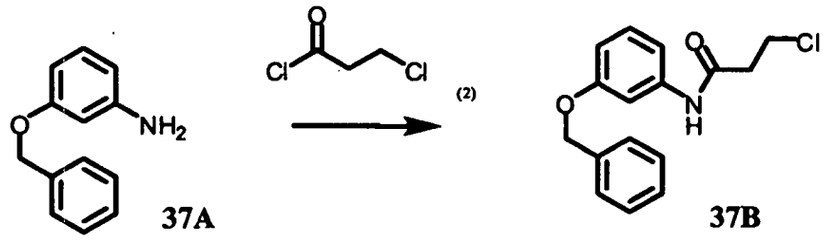
36F **36G**

A solution of alcohol **36F** (160 mg; 0.644 mmol) in dry chloroform (12 mL) was placed in an ice-water bath and treated with pyridine (4.0 eq, 0.208 mL, d 0.978) and a solution of thionyl bromide (1.2 eq, 0.060 mL, d 2.683) in 1 mL of chloroform. The ice-water bath was removed and the reaction mixture was allowed to stir at room temp for 30 minutes. TLC (30 % ethyl acetate in hexanes) showed about 40 % conversion and more thionyl bromide was added (0.2 eq). The mixture was heated to 70 °C for 10 minutes. Upon cooling the mixture was diluted with ethyl acetate (30 mL) and washed with aqueous saturated sodium bicarbonate (5 mL), aqueous sodium hydrogen sulfate (5 mL) and brine (5 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified on a Biotage 25-S silica gel column (gradient: 0 to 40 % ethyl acetate in hexanes) to provide compound **36G** (76 mg; 38 %) as a colorless oil along with unreacted starting material (25 mg; 24 %). ^{1}H-NMR ($CDCl_3$; 400 MHz): δ 8.23 (1H, s), 8.14 (1H, s), 7.72 (1H, d, J = 8.54 Hz), 7.32 (1H, dd, J = 1.22, 8.54 Hz), 5.21 (1H, d, J = 12.20 Hz), 5.09 (1H, d, J = 12.20 Hz), 1.71 (9H, s).

Example 37

Preparation of Intermediate Compound **37C**

Step A – Synthesis of Compound 37B



37A **37B**

Compound **37A** (commercially available) (10.0 g, 50.25 mmol) was dissolved in water at room temperature and to resulting suspension K_2CO_3 (3.8 g, 27.64 mmol) was added. 3-Chloro propionylchloride (7.0 g, 55.28 mmol) was added dropwise for 30 minutes and allowed to stir for 2 hours at room temperature . The precipitate was filtered and washed with water, 1 N HCl, dried at 50 ^{0}C under vacuum overnight to provide 7.2 g of compound **37B**.

Step B – Synthesis of Compound 37C



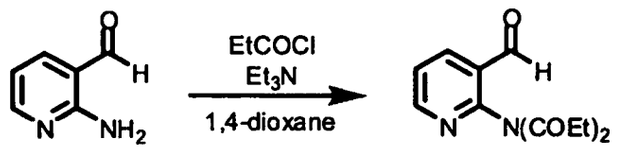
37B **37C**

To N,N-Dimethylformamide (3.6 g, 49.66 mmol) at 0 ^{0}C was added drop wise $POCl_3$ (26.6 g, 173.8 mmol) and allowed to stir for 60 minutes, during which time a white precipitate was formed. The 7.2 g of the compound **37B** was added by portion in reaction mixture and allowed to stir for 24 hours at room temperature. The reaction mixture was diluted with ethyl acetate and slowly added to a beaker with ice, after ice was melted, organic layer was separated and washed with 0.5 N NaOH and water, brine, dried over sodium sulfate, and concentrated *in vacuo*, purified using flash chromatography, to provide compound **37C** (5.5 g , 34 % after two steps). M.S. found: 318.04 $(M+H)^+$.

Example 38

Preparation of Intermediate Compound **38E**

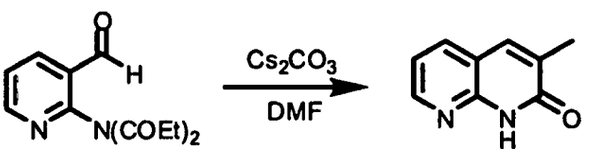
Step A – Synthesis of Compound 38B



38A **38B**

To a solution of **38A** (7.2 g, 58.8 mmol) in 1,4-dioxane (39 mL) at 0°C was added propionyl chloride (37.8 mL, 176.5 mmol) and Et_3N (24.6 mL, 176.5 mmol) with stirring. The reaction mixture was allowed to stir at room temperature for overnight. The solvent was removed under reduced pressure, and the resulting residue was taken up in EtOAc. The organic phase was washed with water, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to compound **38B**, which was used without further purification.

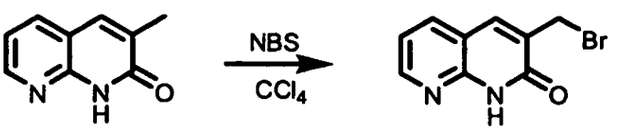
Step B– Synthesis of Compound 38C



38B **38C**

To a suspension of **38B** (crude residue from above) in DMF (60 mL) was added cesium carbonate (38 g, 117.6 mmol), and the resulting mixture was heated at 65°C for overnight. Reaction was cooled to room temperature, and the bulk of DMF was removed under reduced pressure. Water was then added to the crude residue and the mixture was filtered. The filter-cake was washed with water and EtOAc. 5.2 g of **38C** was collected as a pale yellow solid.

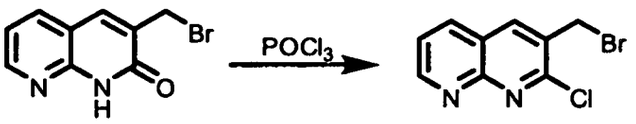
Step C – Synthesis of Compound 38D



38C **38D**

To a suspension of **38C** (0.8 g, 5 mmol) in CCl_4 (25 mL) was added NBS (38 g, 117.6 mmol), and benzoyl peroxide (61 mg, 0.25 mmol), and the resulting mixture was then heated at 90°C for 4 hours. Cooled the reaction to room temperature, and 300 mL of CH_2Cl_2 was added. The mixture was filtered, and filtrate was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide 2 g of compound **38D**, which was used without further purification.

Step D – Synthesis of Compound 38E



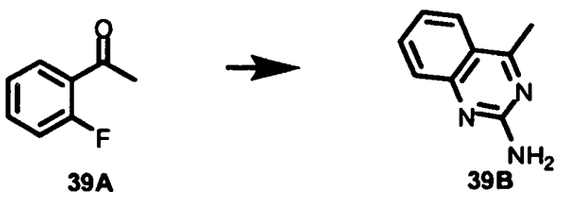
38D **38E**

$POCl_3$ was added to a 100 mL round bottom flask containing crude **38D**. The resulting suspension was then heated at 88°C for 4 hours. Cooled the reaction to room temperature, and then poured into a 1 liter beaker containing ice. The resulting solution was neutralized to ph 8 using 6 *N* NaOH solution. Solid that precipitated from the solution was collected to provide 0.82 g of crude residue which was purified using column chromatography on silica gel (ISCO Combi-Flash Rf; gradient: 5 to 50 % ethyl acetate in hexanes) to provide 330 mg of compound **38E**.

Example 39

Preparation of Intermediate Compound **39D**

Step A – Synthesis of Compound 39B

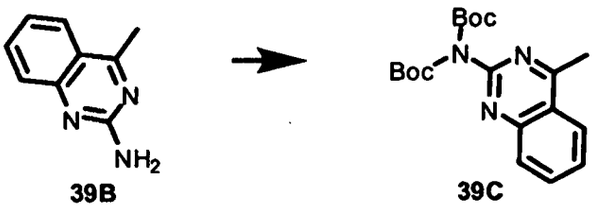


39A **39B**

A mixture of ortho-fluoroacetophenone (**39A**, 3.45 g; 25 mmol) and guanidine carbonate (2 eq; 9.0 g) was prepared in 250 mL of N,N-dimethyl acetamide, set to stir, and heated at 135 oC under nitrogen purge overnight. The solvent was removed under reduced pressure and diluted with ethyl acetate (600 mL). The solution was washed with water (2x100

mL) and brine (40 mL). The organic layer was separated, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The solid was dissolved in methylene dichloride, loaded on silica gel and dried under reduced pressure. The material was purified on ISCO (80 g column; 0-70% THF in Hexanes). Fractions containing product were collected and concentrated *in vacuo* to provide product **39B** as a crème colored solid (880 mg; 22%)

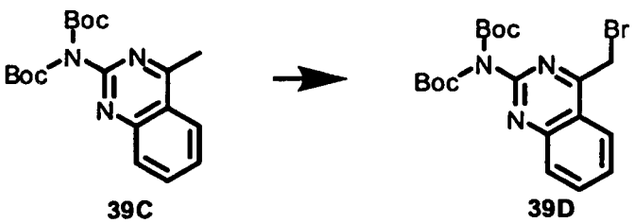
Step B – Synthesis of Compound 39C



39B **39C**

A solution of 4-Methyl-quinazolin-2-ylamine **39B** (640 mg; 4.02 mmol) in 10 mL of dry acetonitrile was treated with a solution of Boc-anhydride (2.5 eq; 2.19 g) in 10.0 mL of dry acetonitrile. The resulting solution was treated with DMAP (0.2 eq; 98.2 mg). The mixture was set to stir overnight. TLC (50% THF in hexanes) showed a complete reaction. The mixture was diluted with ethyl acetate (500 mL) and washed with water (3x30 mL), and Brine (40 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was adsorbed on silica gel and purified on an ISCO column (120 g) (0% to 60% THF in hexanes). The fractions with product were collected and concentrated *in vacuo* to provide product **39C** as a light yellow-white solid (1.3 g; 90%).

Step C – Synthesis of Compound 39D



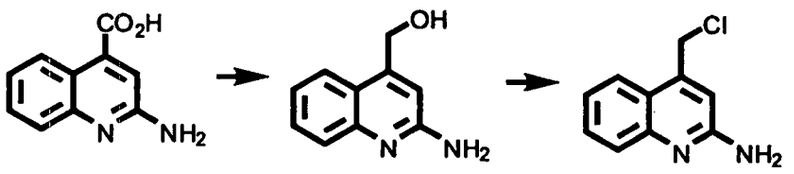
39C **39D**

Intermediate **39C** (1.11 g; 3.09 mmol), N-Bromosuccinimide (1.05 eq; 577 mg), and benzoyl peroxide (0.1 eq; 75 mg) were combined in round bottom and diluted with dry carbon tetrachloride (31 mL). The reaction was allowed to stir at room temperature for 10 minutes and then heated at reflux overnight. TLC (30% ethyl acetate in hexanes) revealed the reaction has partially progressed. The reaction mixture was concentrated under reduced pressure,

diluted with ethyl acetate (300 mL), and washed with sat. aqueous sodium bicarbonate (40 mL) and brine (40 mL), dried over magnesium sulfate, filtered, concentrated under reduced pressure, diluted with methylene dichloride, adsorbed onto silica gel, and purified on ISCO (25-M Column; 0-40% ethyl acetate in hexanes). The fractions containing product were concentrated under reduced pressure and afforded product as a clear oil in a 2:1 mixture of compound **39D** and starting material (Total : 440 mg; 33%).

Example 40

Preparation of Intermediate Compound **40C**



40A **40B** **40C**

The starting materials **40A** (2.0 g, 10.6 mmol), lithium aluminum hydride (2.0 g, 52.7 mmol), and THF (100 mL) were added to a 250 ml round-bottomed flask. The resulting suspension was allowed to stir at room temperature for 18 hours. The reaction was quenched with 10 ml of saturated ammonium chloride solution followed by 200 ml of ethyl acetate. After filtration, the organic layer was washed with brine (2x100 mL), dried over sodium sulfate, and concentrated under vacuum to provide **40B** as a yellowish solid (1.05 g, 59%).

A 250 ml round-bottomed flask was charged with **40B** (1.05 g, 6.03 mmol) and thionyl chloride (10 mL). The resulting mixture was allowed to stir at 60 °C for 4 hours before cooled to room temperature. After removal of excess of thionyl chloride, the residue was dried under vacuum to provide **40C** as an orange solid (1.45 g). This crude material was used without further purification.

Example 41

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). A soluble C-terminal 21-amino acid truncated NS5B enzyme form (NS5BDeltaCT21) 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 2,3-Substituted Indole Derivatives on the polymerase activity was evaluated by adding various concentrations of a 2,3-Substituted Indole Derivative, typically in 10 serial 2-fold dilutions, to the assay mixture. The starting concentrations of the indole derivatives 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 2,3-Substituted Indole Derivatives of the present invention was obtained using the above method and calculated IC_{50} values ranged from about 0.001 μM to about 14000 μM.

Example 42

Cell-based HCV Replicon Assay

To measure cell-based anti-HCV activity of the 2,3-Substituted Indole Derivatives of the present invention, replicon cells were seeded at 5000 cells/well in 96-well collagen I-coated

Nunc plates in the presence of the 2,3-Substituted Indole Derivative. Various concentrations of a 2,3-Substituted Indole Derivative, typically in 10 serial 2-fold dilutions, were added to the assay mixture, the starting concentration of the compound 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 minutes, 95°C for 10 minutes, 40 cycles of 95°C for 15 sec, 60°C for 1 minute. 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 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 2,3-Substituted Indole Derivatives of the present invention was obtained using the above method and calculated EC_{50} values ranged from about 1 μM to about 14000 μM.

Uses of the 2,3-Substituted Indole Derivatives

The 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Viral Infection

The 2,3-Substituted Indole Derivatives can be used to treat or prevent a viral infection. In one embodiment, the 2,3-Substituted Indole Derivatives can be inhibitors of viral replication. In a specific embodiment, the 2,3-Substituted Indole Derivatives can be inhibitors of HCV replication. Accordingly, the 2,3-Substituted Indole Derivatives 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 (HCV) 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 2,3-Substituted Indole Derivatives can be used to treat or prevent a virus-related disorder. Accordingly, the 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

Treatment or Prevention of a Disorder Related to HCV Infection

The 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative, 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 2,3-Substituted Indole Derivatives.

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 2,3-Substituted Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) at least one other antiviral agent that is other than a 2,3-Substituted Indole Derivative, 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative 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 nucleoside, 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 one embodiment, the other antiviral agent is a viral replication inhibitor, which is an HCV replicase 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.

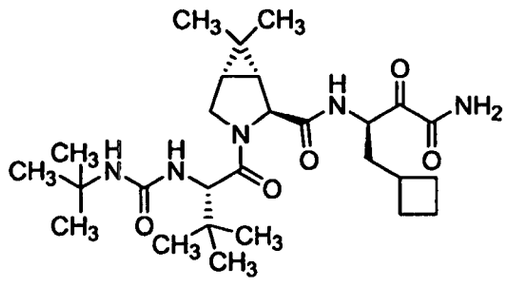
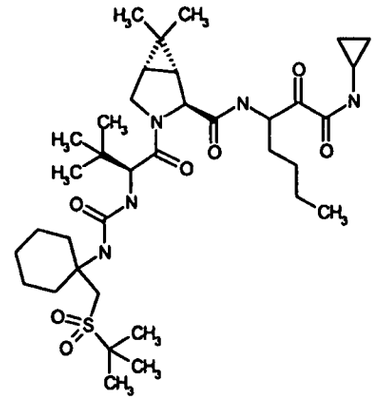
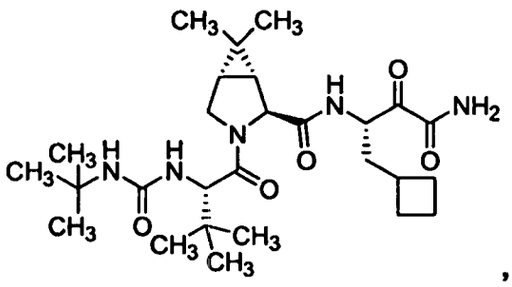
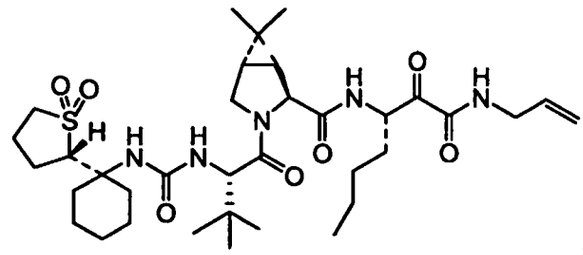
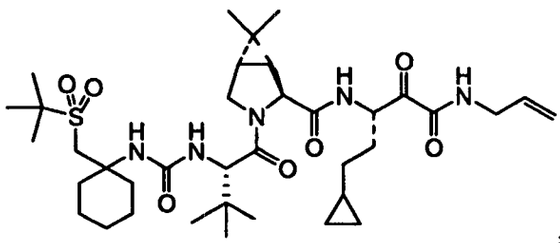
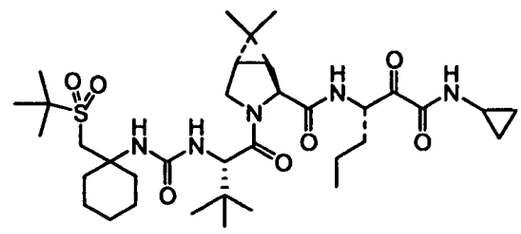
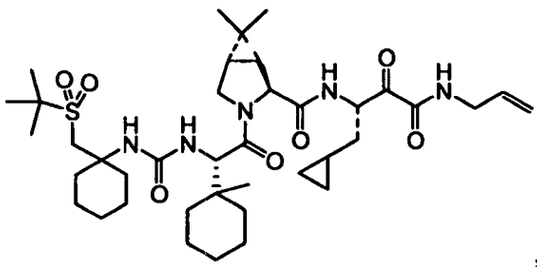
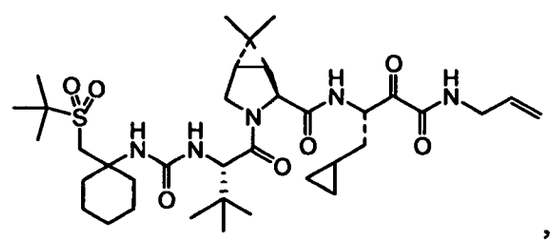
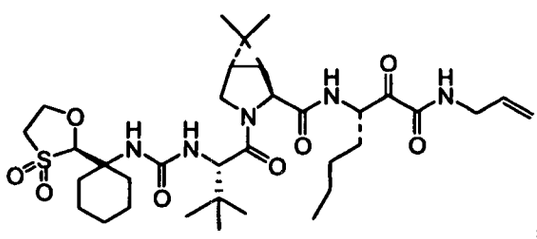
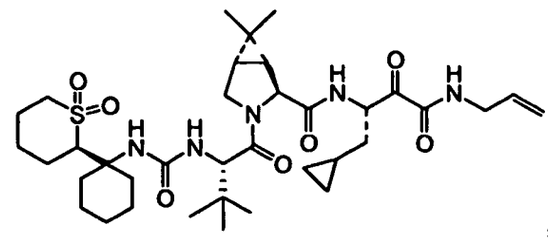
Viral replication inhibitors useful in the present methods and compositions include, but are not limited to, HCV replicase inhibitors, NS3 helicase inhibitors, NS5A inhibitors, ribavirin, viramidine, A-831 (Arrow Therapeutics); an antisense agent or a therapeutic vaccine.

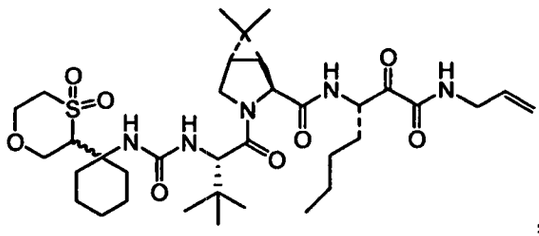
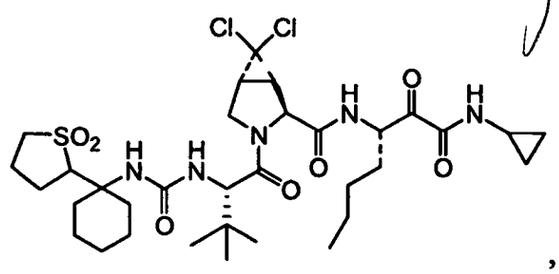
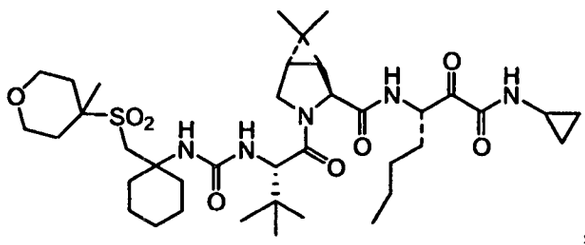
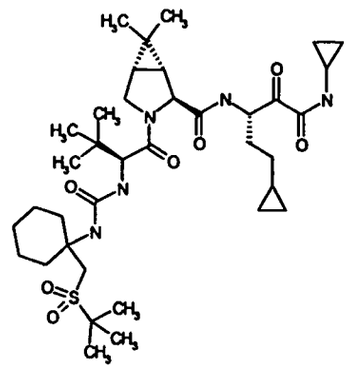
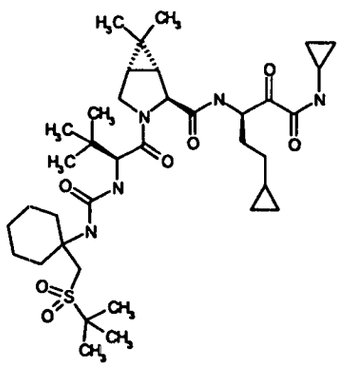
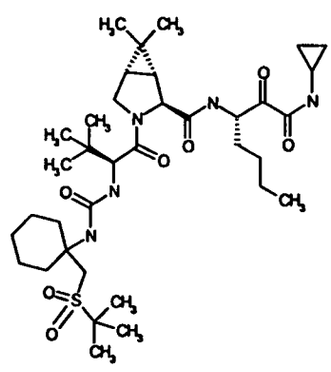
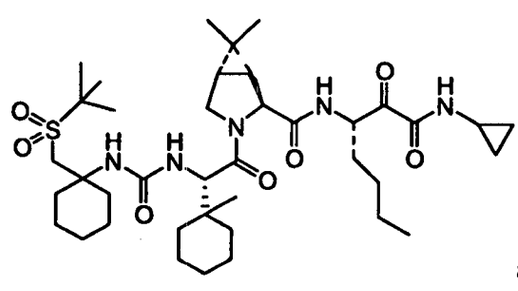
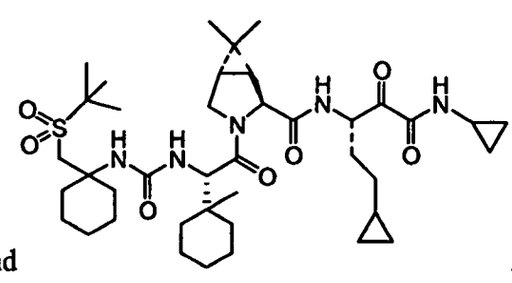
In one embodiment, viral replication inhibitors useful in the present methods and compositions include, but are not limited to, NS3 helicase inhibitors or NS5A inhibitors.

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); U.S. Patent Publication Nos. US2005/0249702 and US 2007/0274951; and International Publication Nos. WO 98/14181; WO 98/17679, WO 98/17679, WO 98/22496 and WO 99/07734 and WO 05/087731.

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


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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 2,3-Substituted Indole Derivative(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 2,3-Substituted Indole Derivative 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.

In one embodiment, one or more compounds of the present invention are adminstered with one or more additional therapeutic agents selected from an HCV protease inhibitor, an HCV replicase inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin. The combination therapies can include any combination of these additional therapeutic agents.

In another embodiment, one or more compounds of the present invention are adminstered with one additional therapeutic agent selected from an HCV protease inhibitor, an HCV replicase inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are adminstered with two additional therapeutic agents selected from an HCV protease inhibitor, an HCV replicase inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In still another embodiment, one or more compounds of the present invention are adminstered with two additional therapeutic agents selected from an HCV protease inhibitor, an HCV replicase inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin. In a specific embodiment, one or more compounds of the present invention are adminstered with an HCV protease inhibitor and ribavirin. In another specific embodiment, one or more compounds of the present invention are adminstered with a pegylated interferon and ribavirin.

In another embodiment, one or more compounds of the present invention are adminstered with three additional therapeutic agents selected from an HCV protease inhibitor, an HCV replicase inhibitor, a nucleoside, an interferon, a pegylated interferon and ribavirin.

In one embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, and a viral replication inhibitor. In another embodiment, one or more compounds of the present invention are administered with one or more additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, and ribavirin. In one embodiment, one compound of the present invention is administered with one additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, and a viral replication inhibitor. In another embodiment, one compound of the present invention is administered with two additional therapeutic agents selected from an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, and a viral replication inhibitor. In another embodiment, one compound of the present invention is administered with ribavirin. In still another embodiment, one compound of the present invention is administered with ribavirin and another therapeutic agent. In still another embodiment, one compound of the present invention is administered with ribavirin and another therapeutic agent, wherein the other therapeutic agent is selected from an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, and a viral replication inhibitor.

Compositions and Administration

Due to their activity, the 2,3-Substituted Indole Derivatives are useful in veterinary and

human medicine. As described above, the 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives are administered orally.

In another embodiment, the one or more 2,3-Substituted Indole Derivatives are administered intravenously.

In another embodiment, the one or more 2,3-Substituted Indole Derivatives are administered topically.

In still another embodiment, the one or more 2,3-Substituted Indole Derivatives are administered sublingually.

In one embodiment, a pharmaceutical preparation comprising at least one 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivative(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 2,3-Substituted Indole Derivative(s) by weight or volume.

The quantity of 2,3-Substituted Indole Derivative 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivatives 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 2,3-Substituted Indole Derivative or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; (ii) one or more additional therapeutic agents that are not a 2,3-Substituted Indole Derivative; 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 2,3-Substituted Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

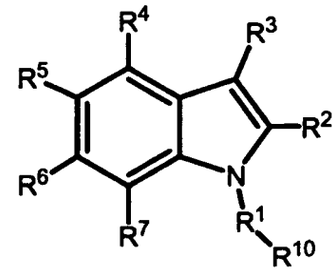
In another aspect the present invention provides a kit comprising an amount of at least one 2,3-Substituted Indole Derivative, or a pharmaceutically acceptable salt, solvate, ester or prodrug of said compound and an amount of at least one additional therapeutic agent listed above, wherein the amounts 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:



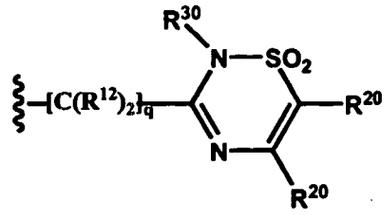
(I)

or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof,

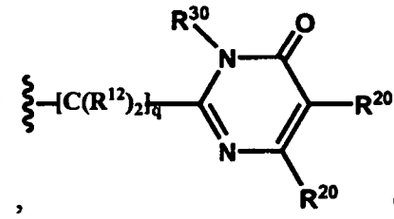
wherein:

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≡C-$[C(R^{12})_2]_q$-, or -$[C(R^{12})_2]_q$-SO_2-$[C(R^{12})_2]_q$-;

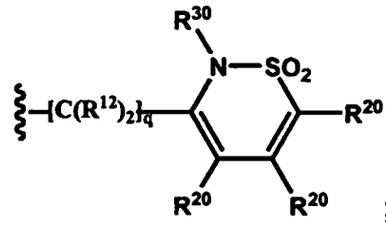
R^2 is -$[C(R^{12})_2]_q$-$C(O)N(R^9)SOR^{11}$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)SO_2R^{11}$, -$[C(R^{12})_2]_q$-$C(O)N(R^9)SO_2N(R^9)_2$,



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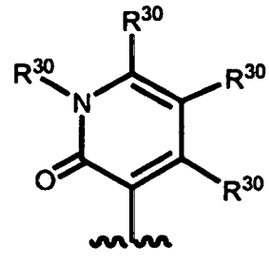


or

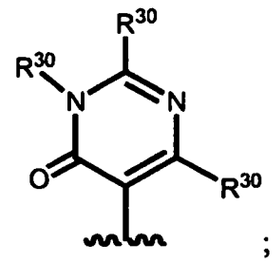


;

R^3 is:



or



;

R^4, R^5, 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)$_p R^{11}$, -[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})$_2$]$_q$-O-alkyl, -[C(R^{12})$_2$]$_q$-N(alkyl)$_2$, -[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})$_2$]$_q$-heterocycloalkenyl, -[C(R^{12})$_2$]$_q$-heteroaryl, haloalkyl or hydroxyalkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally and independently 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)$_p R^{11}$, -[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 and independently 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_2alkyl, -[C(R^{12})$_2$]$_q$-NHSO_2cycloalkyl, -[C(R^{12})$_2$]$_q$-NHSO_2aryl, -[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 and independently 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)NH-alkyl, $-C(O)N(alkyl)_2$, -O-alkyl, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -NHC(O)alkyl, $-NHSO_2$alkyl, $-SO_2$alkyl or $-SO_2$NH-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 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;

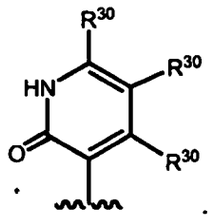
each occurrence of q is independently an integer ranging from 0 to 4; and

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

2. The compound of claim 1, wherein R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, -alkyl-$N(alkyl)_2$, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and

R^{11} is alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

3. The compound of claim 2, wherein R^3 is :



4. The compound of claim 2, wherein R^1 is -[C(R^{12})$_2$]$_r$-.

5. The compound of claim 4, wherein R^1 is –CH_2-, -CH_2CH_2-, -CH(CH_3)- or

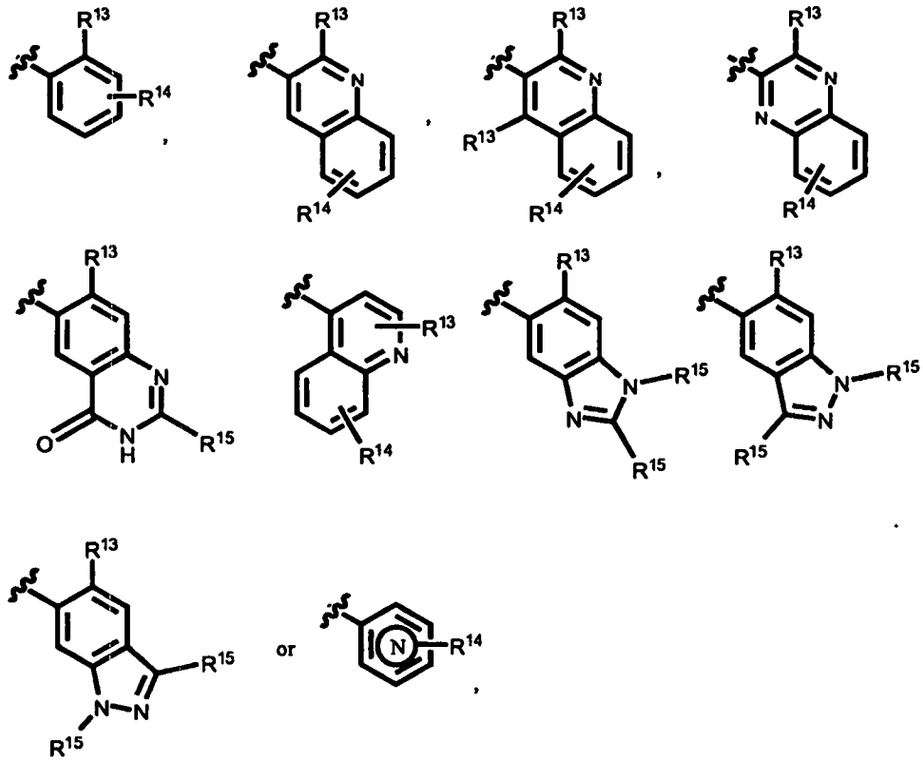


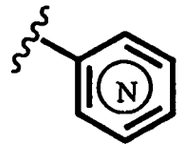
6. The compound of claim 5, wherein R^1 is –CH_2-.

7. The compound of claim 2, wherein R^4 and R^7 are each independently H, alkyl, halo or –OH; R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN; and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, -NH_2 or –CN.

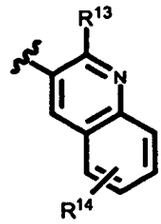
8. The compound of claim 2, wherein R^{10} is aryl or heteroaryl.

9. The compound of claim 8, wherein R^{10} is:

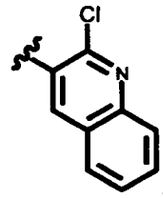


wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

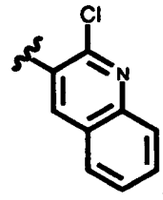
10. The compound of claim 9, wherein R^{10} is:



11. The compound of claim 10, wherein R^{10} is:



12. The compound of claim 6, wherein R^{10} is:



13. The compound of claim 9, wherein R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or

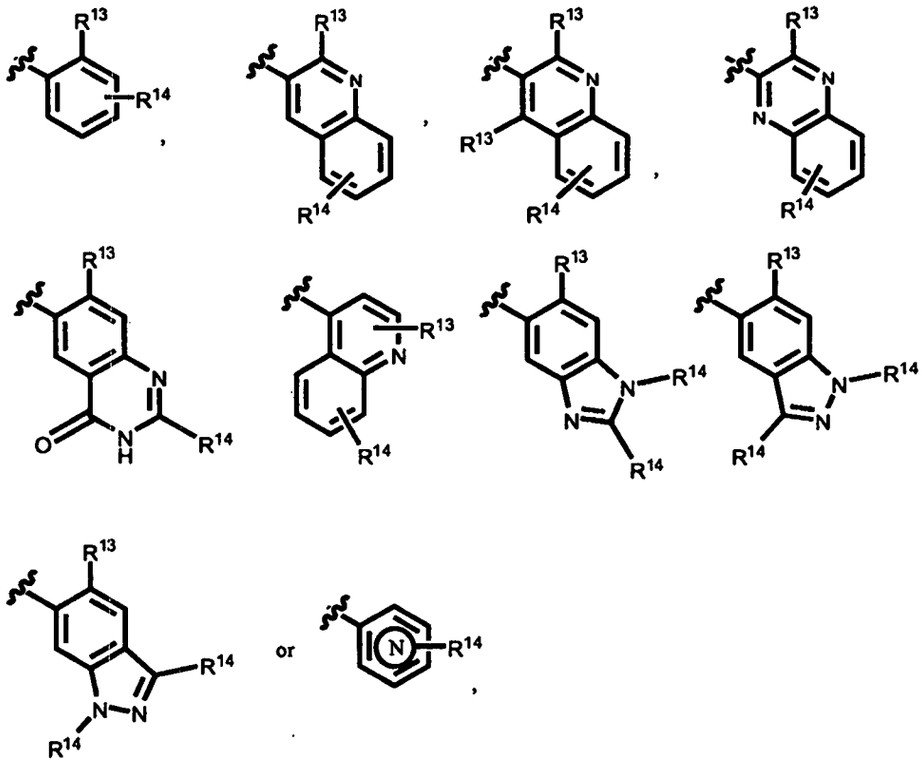


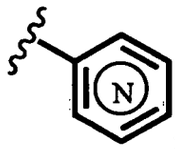
14. The compound of claim 13, wherein R^1 is $-CH_2-$.

15. The compound of claim 9, wherein R^4 and R^7 are each independently H, alkyl, halo or -OH, R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN, and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

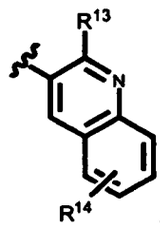
16. The compound of claim 15, wherein R^{10} is aryl or heteroaryl.

17. The compound of claim 16, wherein R^{10} is:

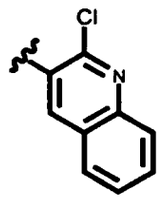


wherein R^{13} is H, F, Br or Cl; R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl; and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

18. The compound of claim 17, wherein R^{10} is:



19. The compound of claim 18, wherein R^{10} is:

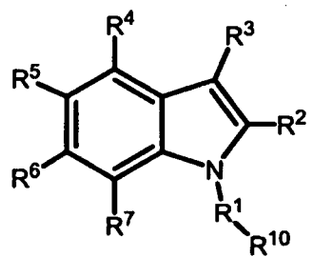


20. The compound of claim 3, wherein each occurrence of R^{30} is H.

21. The compound of claim 9, wherein each occurrence of R^{30} is H.

22. The compound of claim 17, wherein each occurrence of R^{30} is H.

23. The compound of claim 1 having the formula:



(Ia)

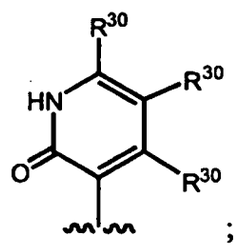
or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof,

wherein:

R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ;

R^2 is $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alkyl)SO_2R^{11}$ or $-C(O)N(alkyl)SO_2N(R^9)_2$;

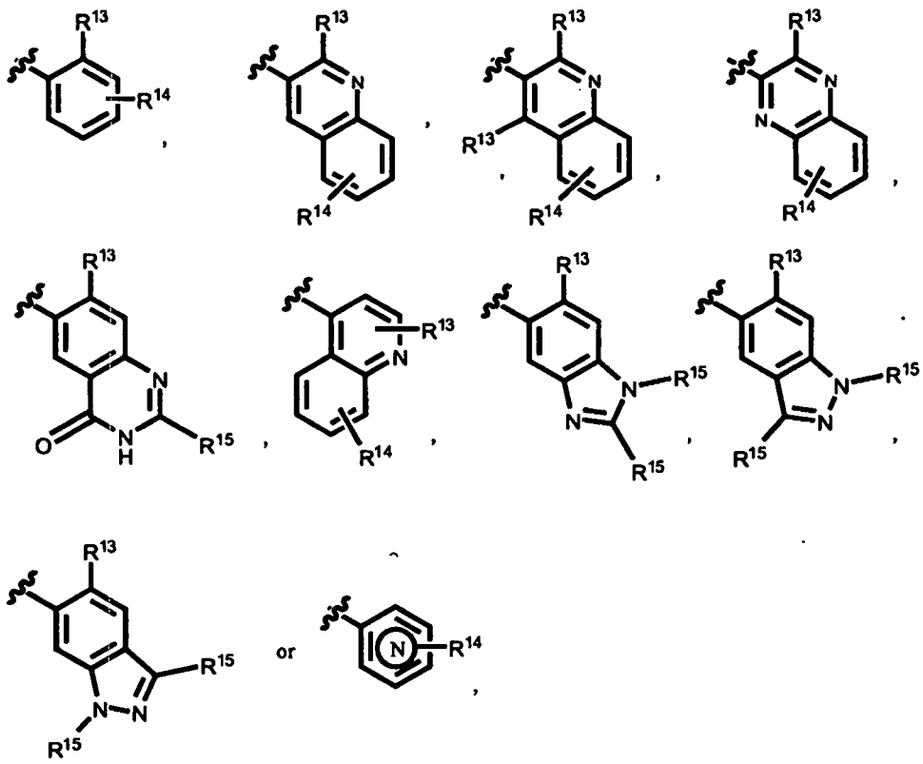
R^3 is:

 ;

R^4, R^5, R^6 and R^7 are each, independently, H, alkyl, $-[C(R^{12})_2]_q$-cycloalkyl, $-[C(R^{12})_2]_q$-heterocycloalkyl, haloalkyl, halo, -OH, $-OR^9$ or $-N(R^9)_2$;

each occurrence of R^9 is independently H, alkyl, -alkyl-N(alkyl)$_2$, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl;

R^{10} is:



such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, -alkyl-N(alkyl)$_2$, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl;

each occurrence of R^{12} is independently H, halo, -N(alkyl)$_2$, -OH, -O-alkyl, alkyl, cycloalkyl or heterocycloalkyl, 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;

R^{13} is H, F, Br or Cl;

R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -NHSO$_2$-alkyl, -NO$_2$, -C(O)NH$_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH$_2$, -SO$_2$alkyl, -SO$_2$NH-alkyl, -S-alkyl, -CH$_2$NH$_2$, -CH$_2$OH, -SO$_2$NH$_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl;

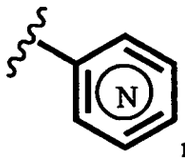
each occurrence of R^{15} is independently alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl,-NHSO$_2$-alkyl, -NO$_2$, -C(O)NH$_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH$_2$, -SO$_2$alkyl, -

SO_2NH-alkyl, -S-alkyl, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl or heteroaryl;

each occurrence of R^{30} is independently, H, halo, $-N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, 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 q is independently an integer ranging from 0 to 4;

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



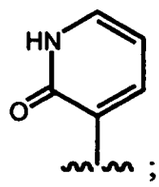
represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

24. The compound of claim 23 wherein

R^1 is $-CH_2-$;

R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$;

R^3 is:



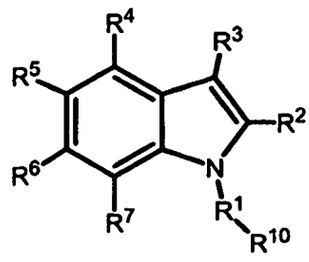
;

R^4, R^5, R^6 and R^7 are each independently H, alkyl, haloalkyl or halo;

each occurrence of R^9 is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl; and

each occurrence of R^{11} is independently alkyl, aryl or cycloalkyl.

25. A compound having the formula:



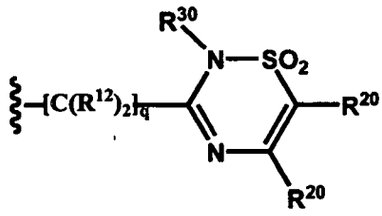
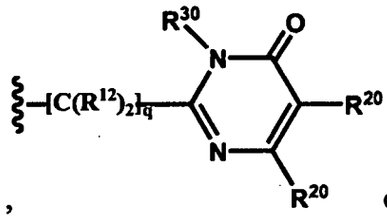
(II)

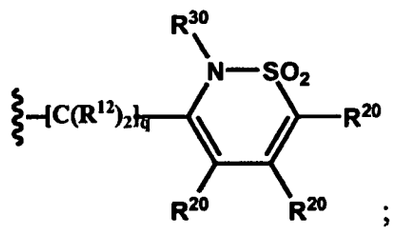
and pharmaceutically acceptable salts, solvates, esters and prodrugs thereof,

wherein:

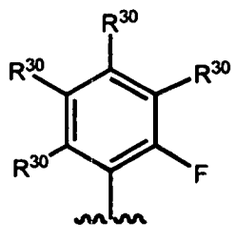
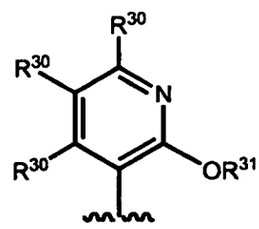
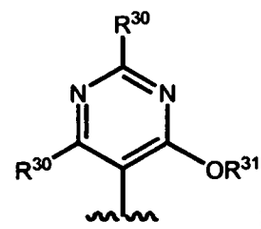
R^1 is a bond, -$[C(R^{12})_2]_r$-, -$[C(R^{12})_2]_r$-O-$[C(R^{12})_2]_q$-, -$[C(R^{12})_2]_r$-$N(R^9)$-$[C(R^{12})_2]_q$-, -$[C(R^{12})_2]_q$-CH=CH-$[C(R^{12})_2]_q$-, -$[C(R^{12})_2]_q$-C≡C-$[C(R^{12})_2]_q$-, or -$[C(R^{12})_2]_q$-SO_2-$[C(R^{12})_2]_q$-;

R^2 is -$[C(R^{12})_2]_q$-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)$N(R^9)SO_2N(R^9)_2$,



or


;

R^3 is


,

or

;

R^4, R^5, 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, -$[C(R^{12})_2]_q$-O-alkyl, -$[C(R^{12})_2]_q$-N(alkyl)$_2$, -$[C(R^{12})_2]_q$-aryl, -$[C(R^{12})_2]_q$-cycloalkyl, -$[C(R^{12})_2]_q$-cycloalkenyl, -$[C(R^{12})_2]_q$-heterocycloalkyl, -$[C(R^{12})_2]_q$-heterocycloalkenyl, -$[C(R^{12})_2]_q$-heteroaryl, haloalkyl or hydroxyalkyl;

R^{10} is H, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, wherein a cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl or heteroaryl group can be optionally and independently 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 and independently 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_2alkyl, -$[C(R^{12})_2]_q$-NHSO_2cycloalkyl, -$[C(R^{12})_2]_q$-NHSO_2aryl, -$[C(R^{12})_2]_q$-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 and independently 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)NH-alkyl, -C(O)N(alkyl)$_2$, -O-alkyl, -NH_2, -NH(alkyl), -N(alkyl)$_2$, -NHC(O)alkyl, -NHSO_2alkyl, -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 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 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 $-SO_2N(R^9)C(O)N(R^9)_2$, 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;

R^{31} is 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 or $-[C(R^{12})_2]_q$-hydroxyalkyl;

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

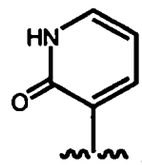
each occurrence of q is independently an integer ranging from 0 to 4; and

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

26. The compound of claim 25, wherein R^2 is $-C(O)NHSO_2R^{11}$ or $-C(O)NHSO_2N(R^9)_2$, wherein R^9 is H, alkyl, aryl, cycloalkyl, heteroaryl or heterocycloalkyl and R^{11} is alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl.

27. The compound of claim 26, wherein each occurrence of R^{30} is independently, H, halo, -$N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group.

28. The compound of claim 27, wherein R^3 is :



29. The compound of claim 28, wherein R^1 is $-[C(R^{12})_2]_r-$.

30. The compound of claim 29 wherein R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or

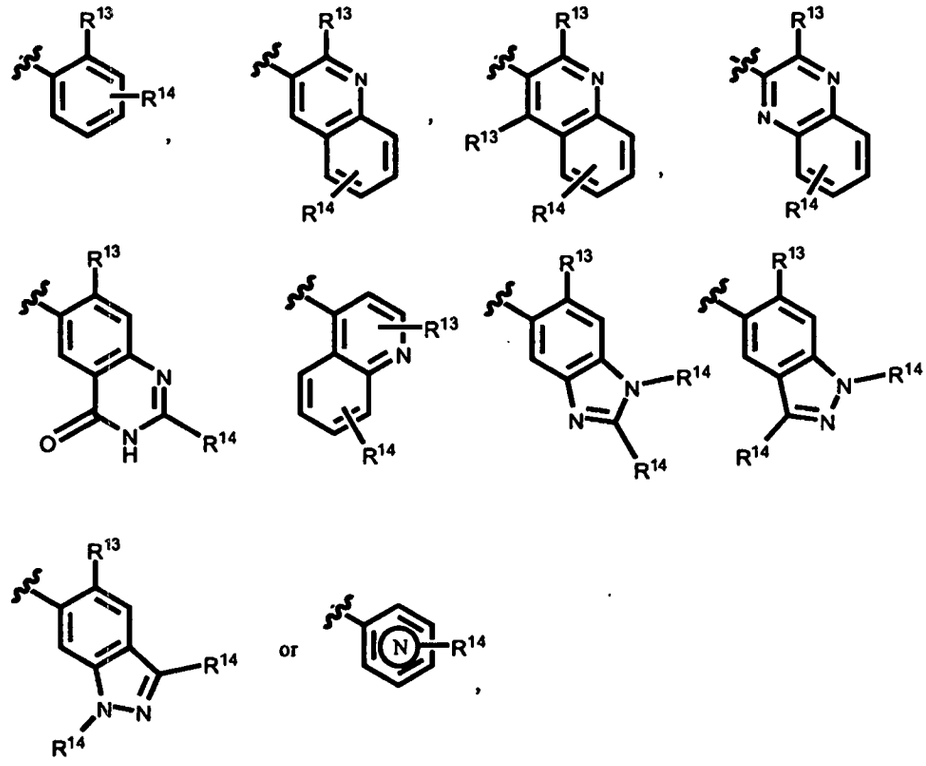


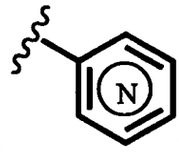
31. The compound of claim 30 wherein R^1 is $-CH_2-$.

32. The compound of claim 29, wherein R^4 and R^7 are each independently H, halo or -OH, R^5 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN, and R^6 is H, alkyl, -O-alkyl, -O-haloalkyl, cycloalkyl, halo, haloalkyl, -OH, hydroxyalkyl, $-NH_2$ or –CN.

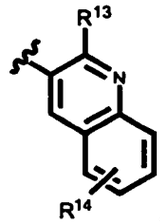
33. The compound of claim 32, wherein R^{10} is aryl or heteroaryl.

34. The compound of claim 33, wherein R^{10} is:

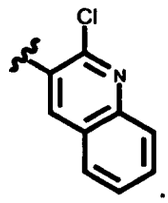


wherein R^{13} is H, F, Br or Cl, R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2-alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl, and  represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

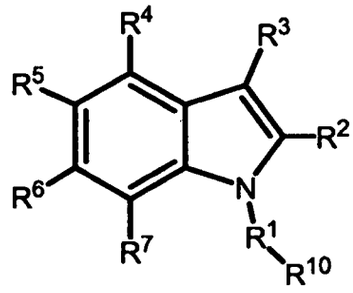
35. The compound of claim 34, wherein R^{10} is:



36. The compound of claim 35, wherein R^{10} is:



37. The compound of claim 25 having the formula:

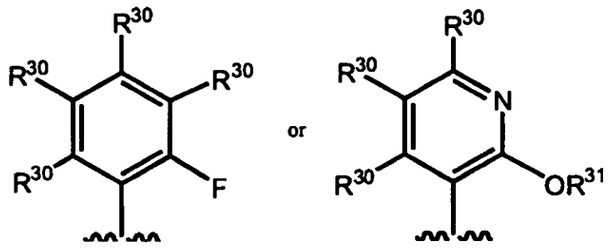


or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, wherein:

R^1 is $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ or  ;

R^2 is $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alkyl)SO_2R^{11}$ or $-C(O)N(alkyl)SO_2N(R^9)_2$;

R^3 is:

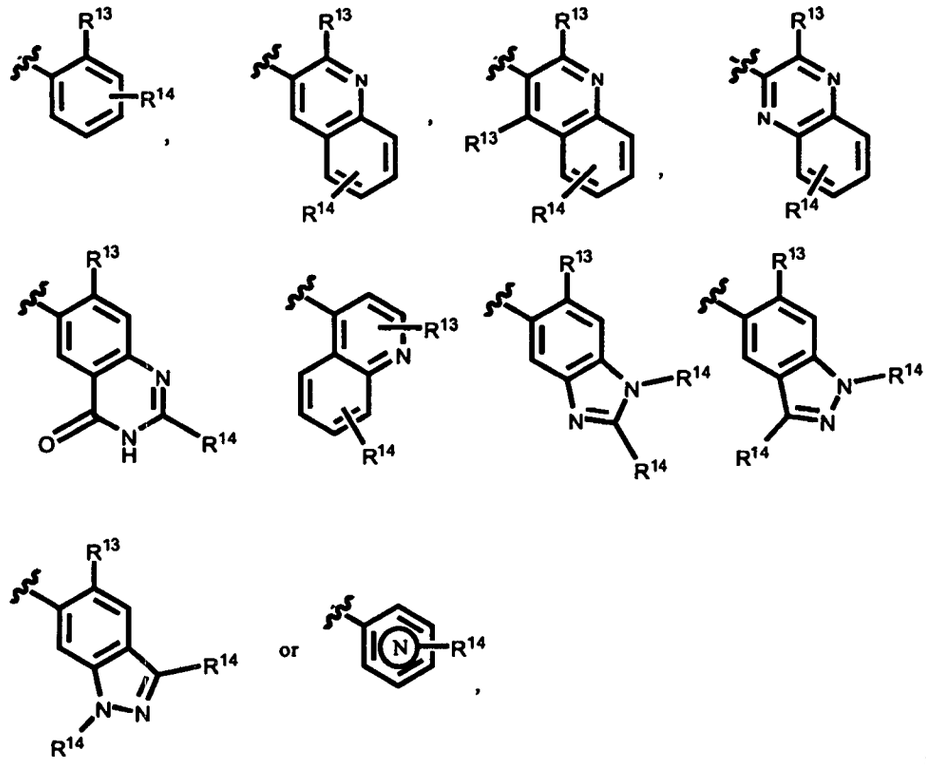


;

R^4, R^5, R^6 and R^7 are each, independently, H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl, halo, -OH, -OH, -O-alkyl, -O-haloalkyl, $-NH_2$, -NH-alkyl or $-N(alkyl)_2$;

each occurrence of R^9 is independently H, alkyl, cycloalkyl, heterocycloalkyl, haloalkyl or hydroxyalkyl;

R^{10} is:



such that when R^1 is a bond, R^{10} is not H;

each occurrence of R^{11} is independently alkyl, aryl, cycloalkyl, haloalkyl, heteroaryl, heterocycloalkyl or hydroxyalkyl;

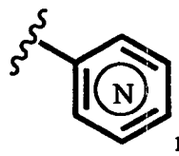
R^{13} is H, F, Br or Cl;

R^{14} represents up to 4 optional and additional substituents, each independently selected from alkyl, cycloalkyl, CF_3, -CN, halo, -O-alkyl, -O-haloalkyl, -$NHSO_2$-alkyl, -NO_2, -$C(O)NH_2$, -C(O)NH-alkyl, -C(O)OH, -OH, -NH_2, -SO_2alkyl, -SO_2NH-alkyl, -S-alkyl, -CH_2NH_2, -CH_2OH, -SO_2NH_2, -NHC(O)-alkyl, -C(O)O-alkyl, -C(O)-heterocycloalkyl and heteroaryl;

each occurrence of R^{30} is independently, H, halo, -$N(alkyl)_2$, -OH, -O-alkyl, -O-haloalkyl, alkyl, cycloalkyl or heterocycloalkyl, or two adjacent R^{30} groups, together with the carbon atoms to which they are attached, join to form an aryl, cycloalkyl, heteroaryl or heterocycloalkyl group;

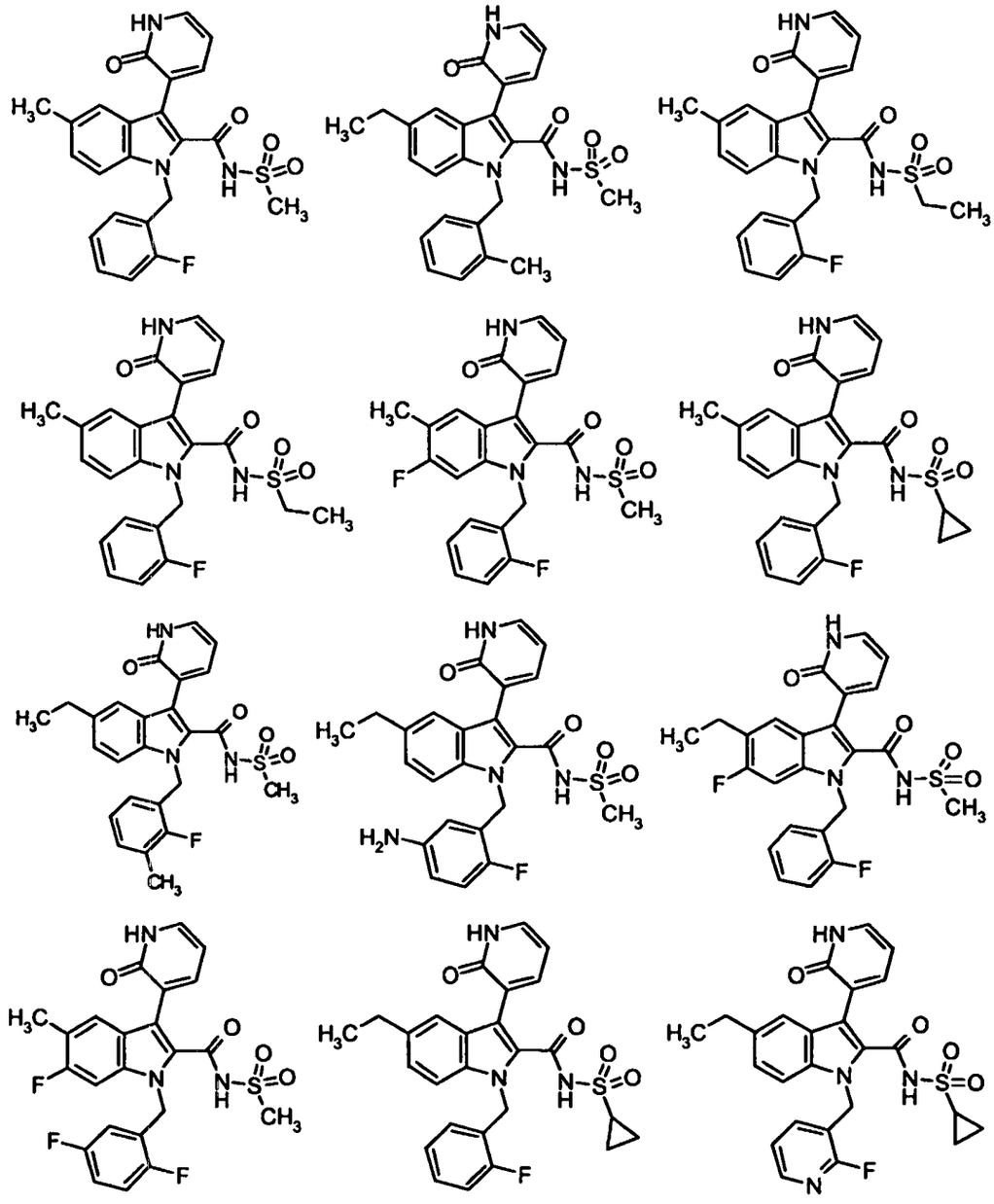
each occurrence of q is independently an integer ranging from 0 to 4;

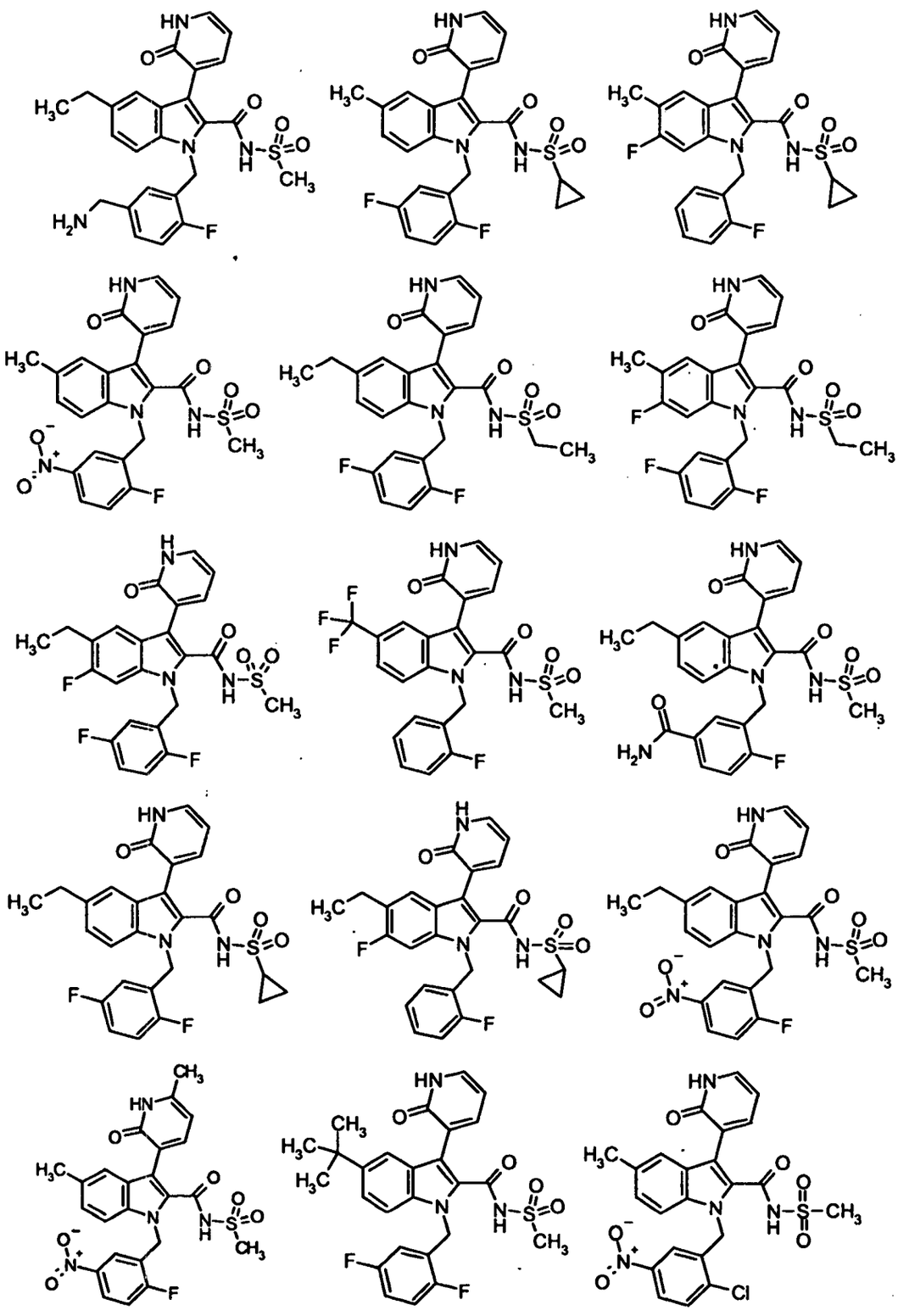
each occurrence of r is independently an integer ranging from 1 to 4; and



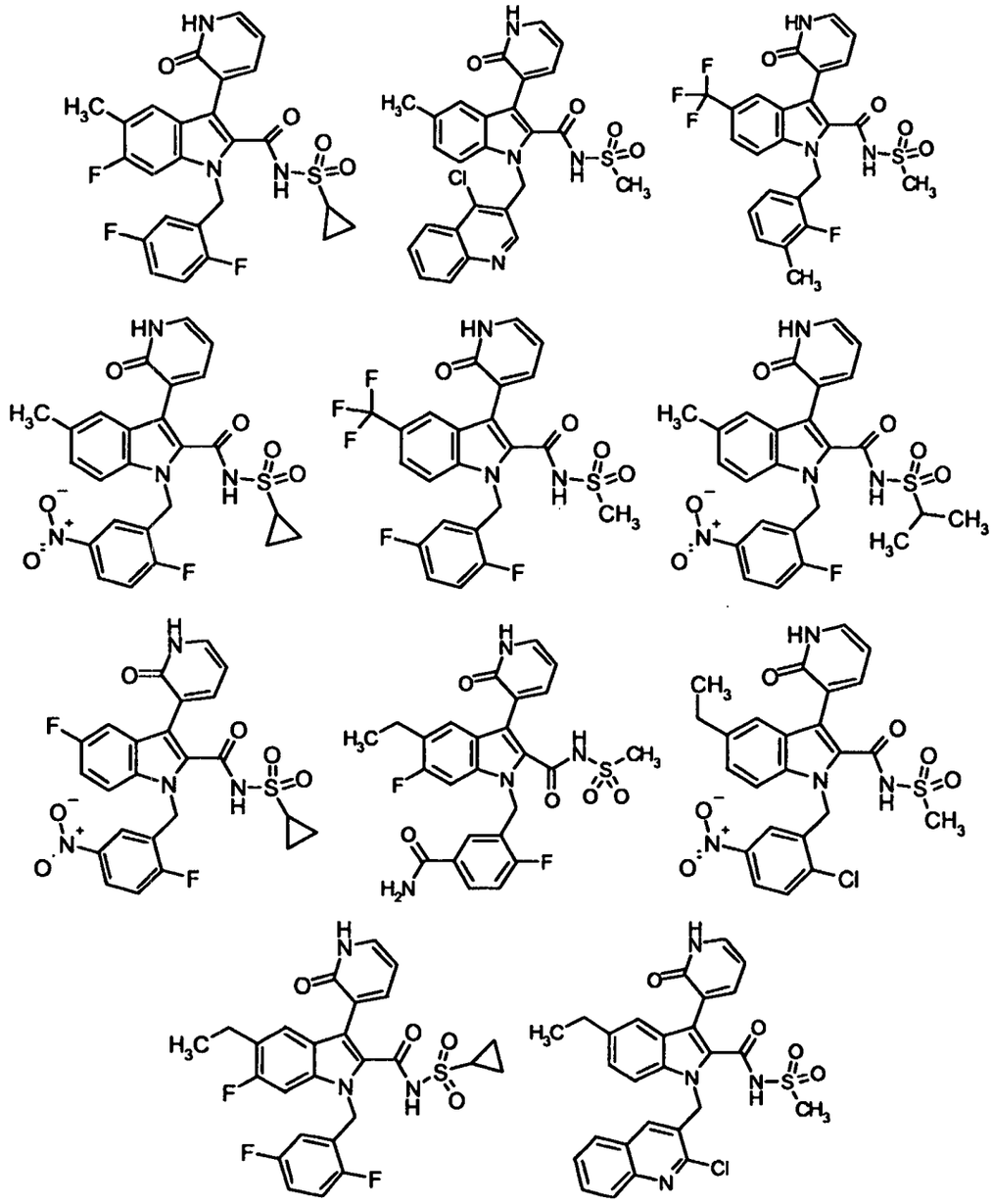
represents a pyridyl group, wherein the ring nitrogen atom can be at any of the five unsubstituted ring atom positions.

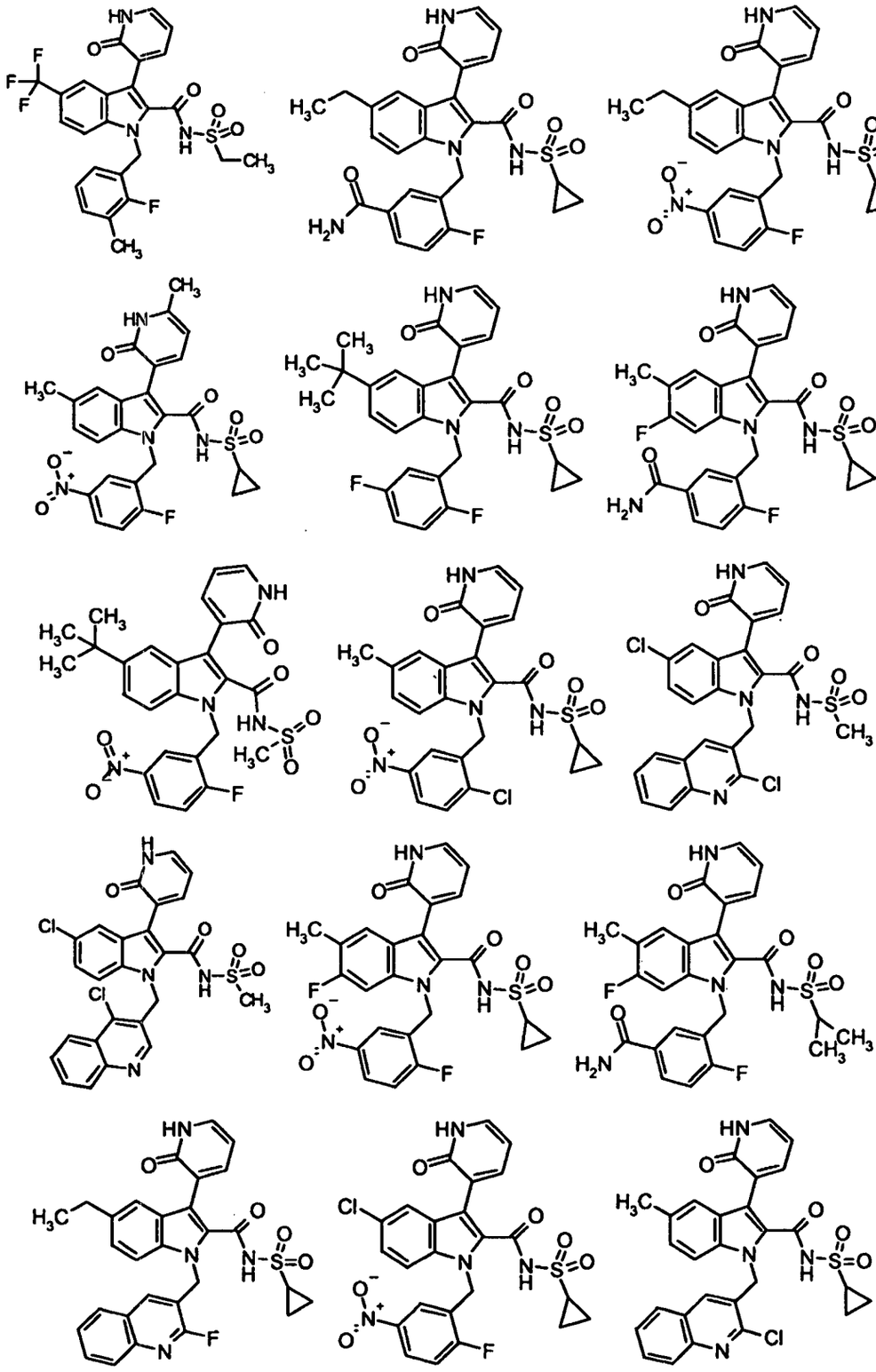
38. A compound having the structure:



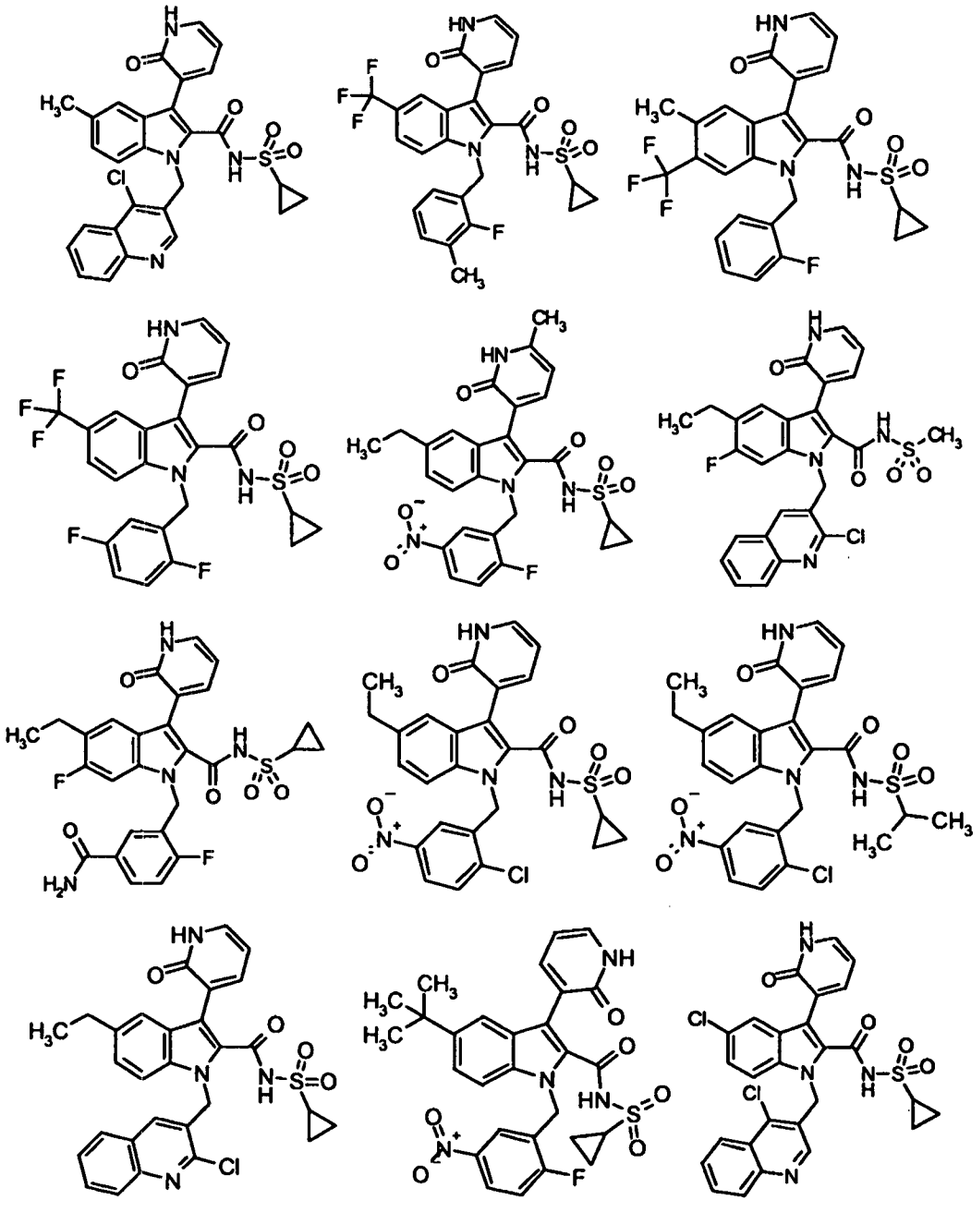


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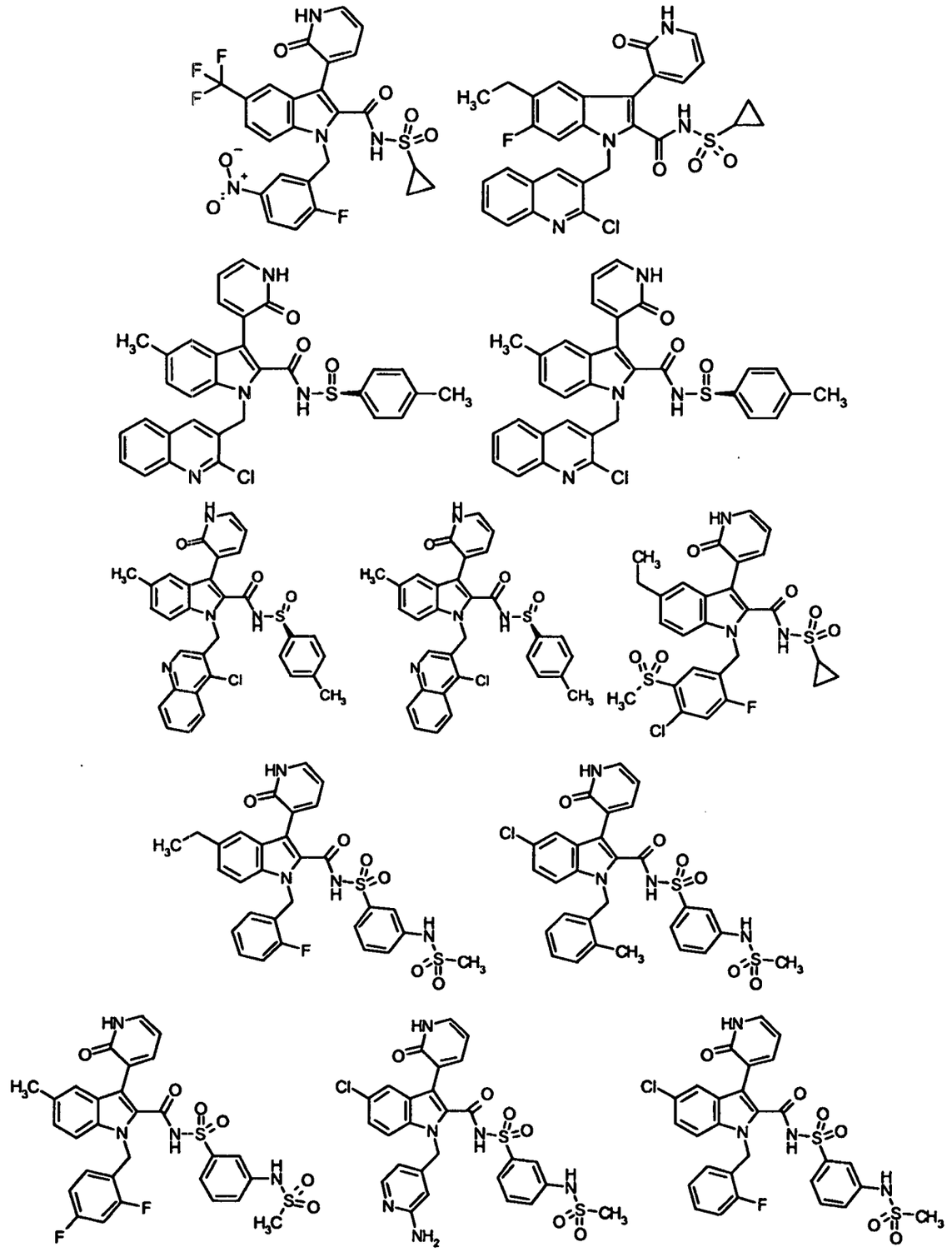




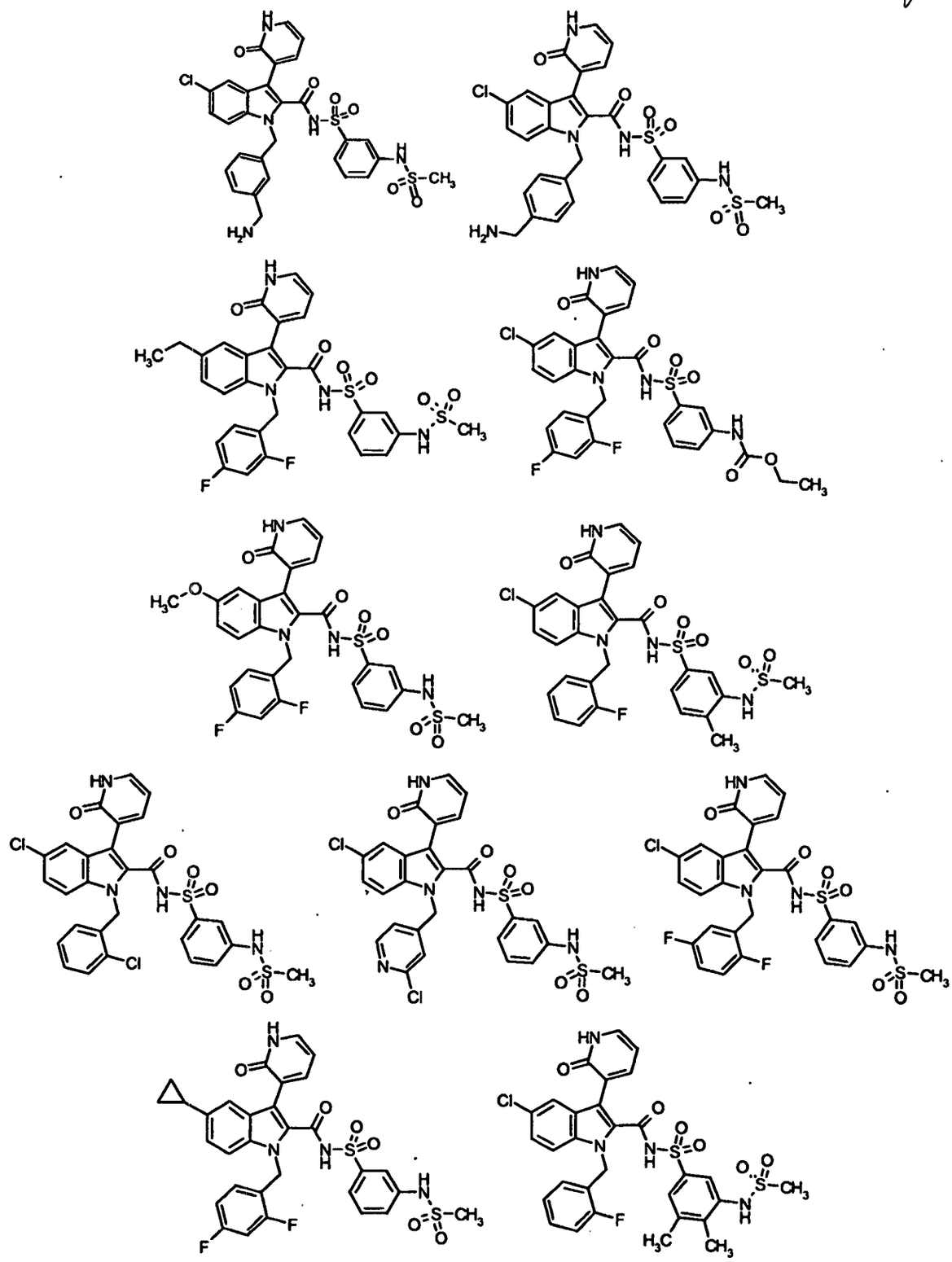
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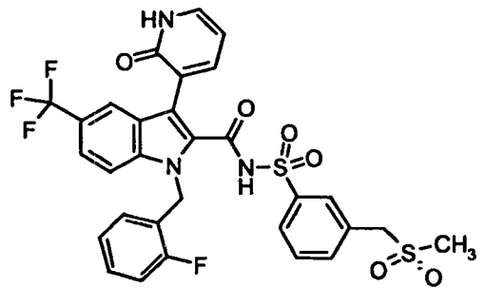
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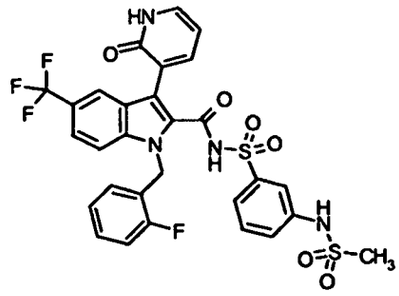


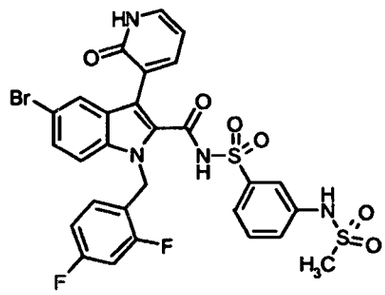
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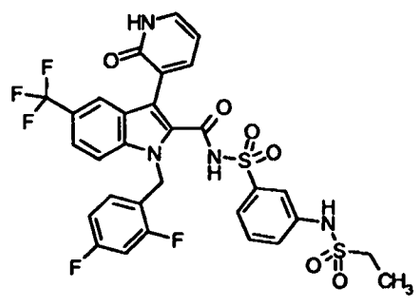


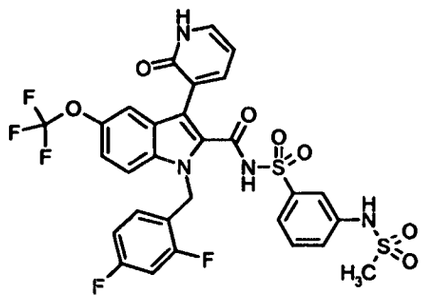
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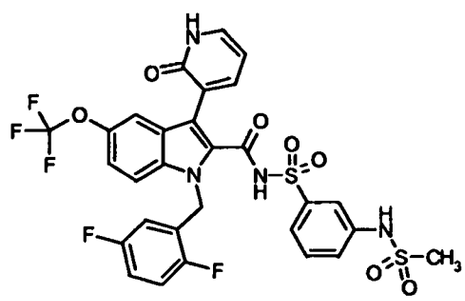


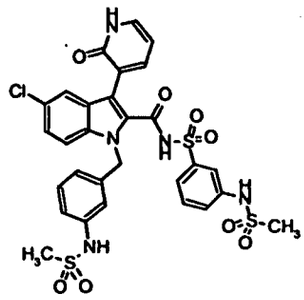


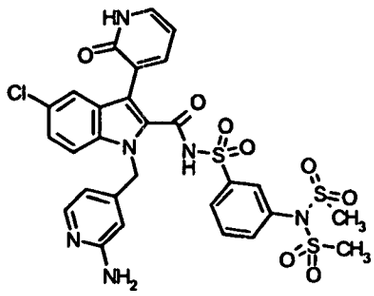


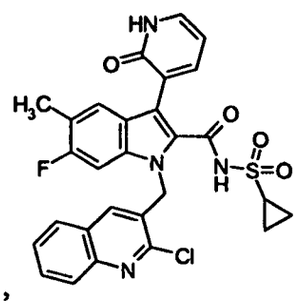


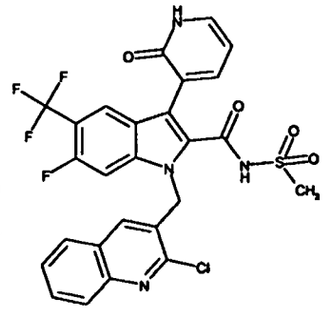




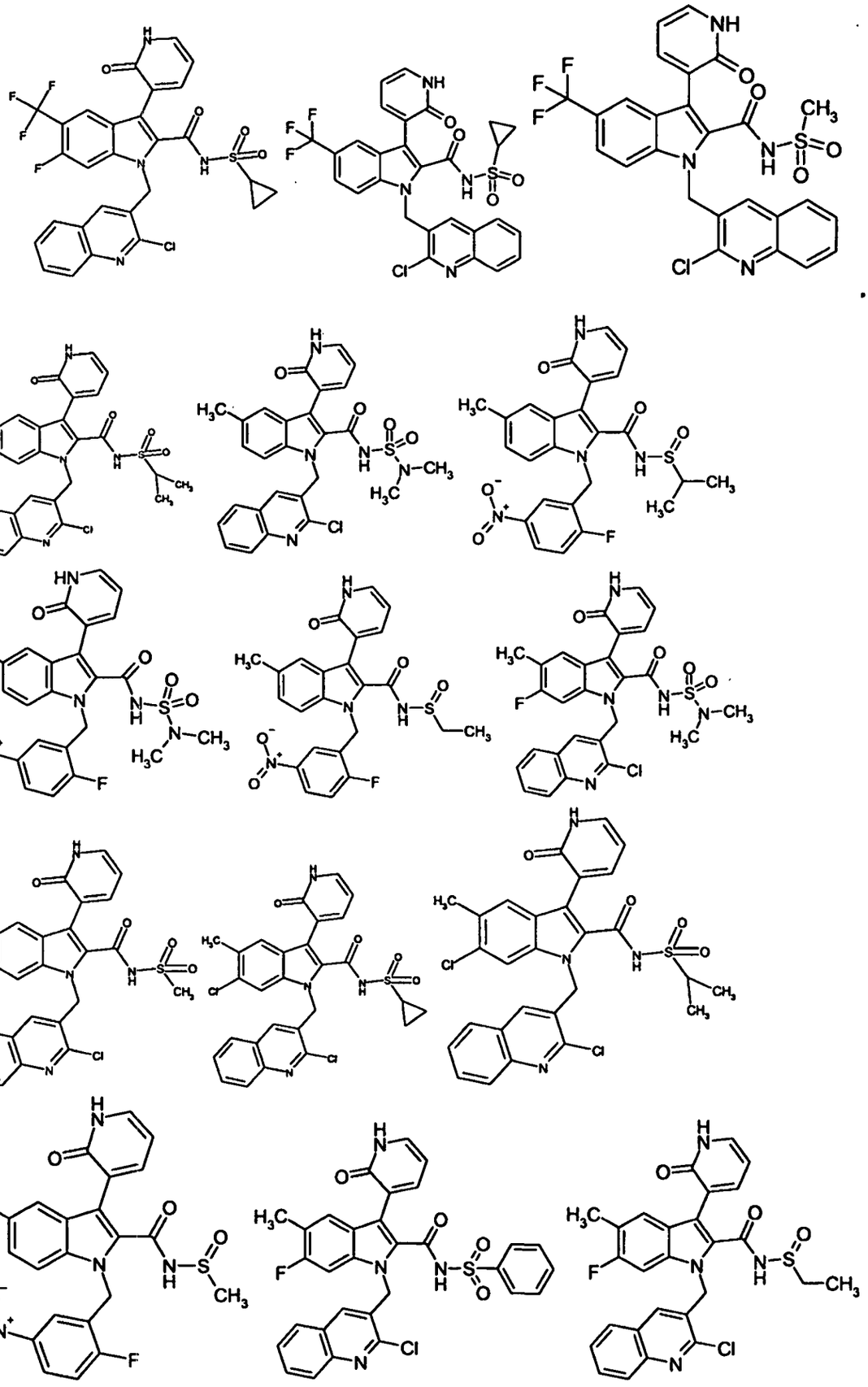


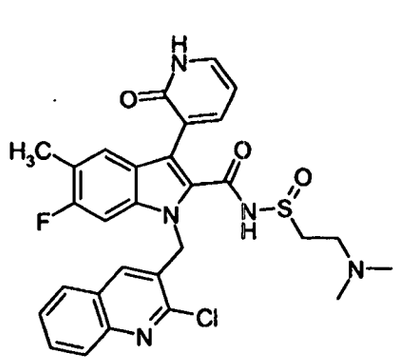


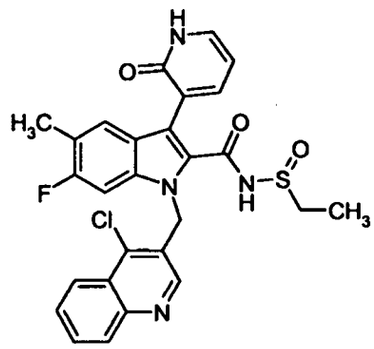


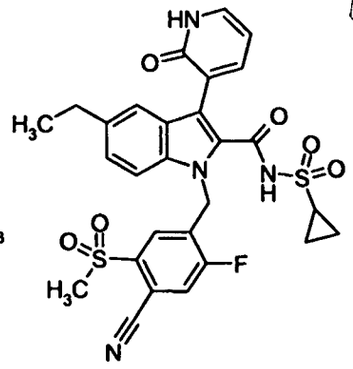


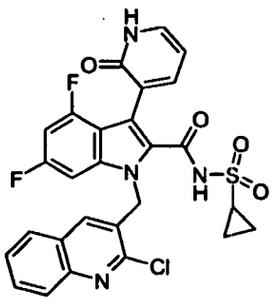
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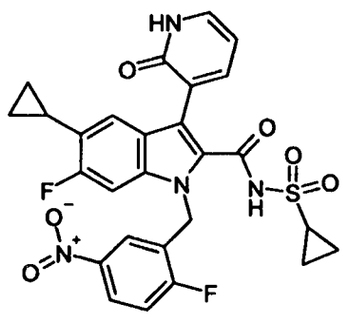


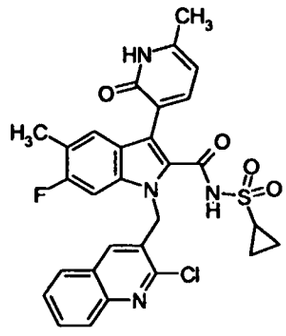




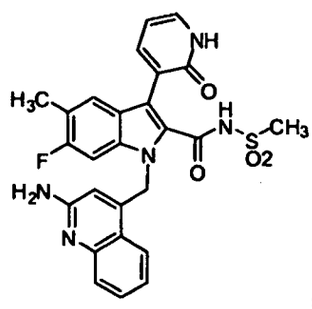




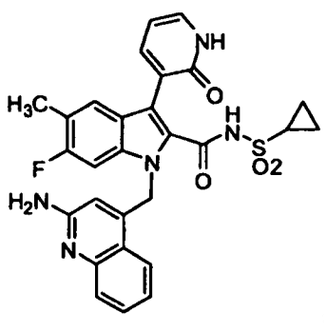




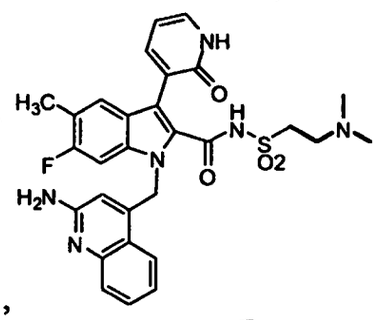
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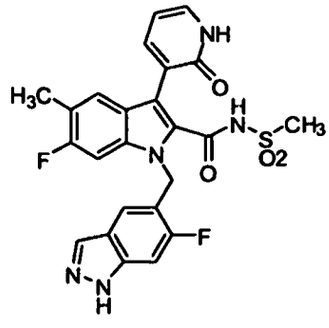


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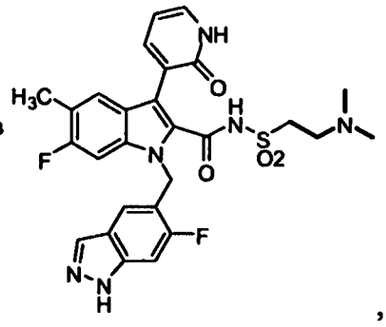


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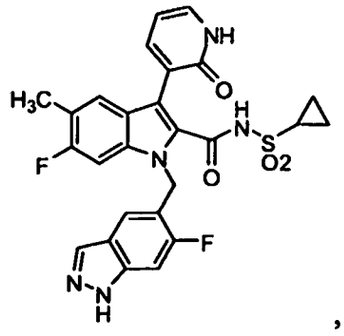




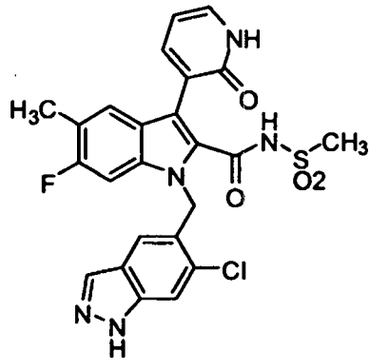
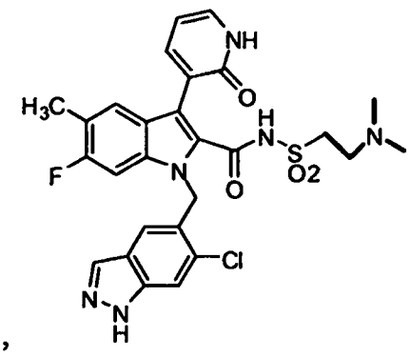
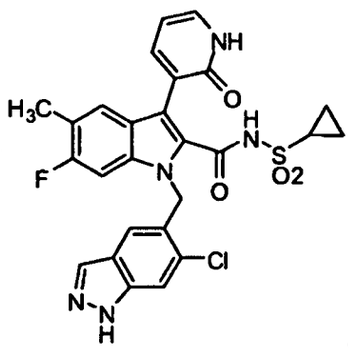
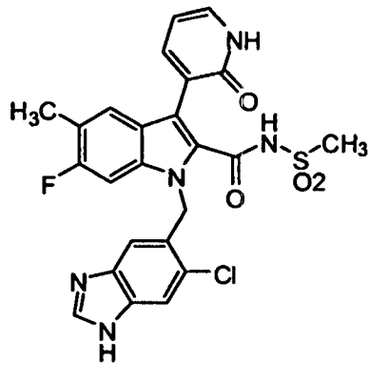
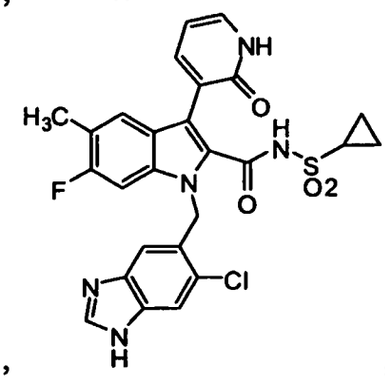
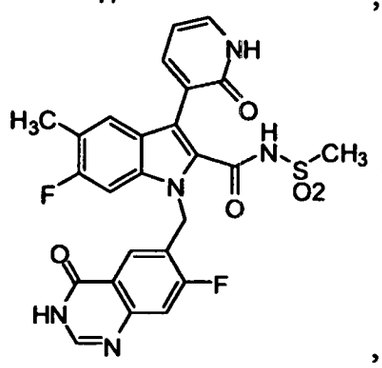
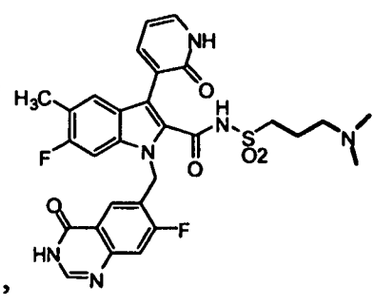
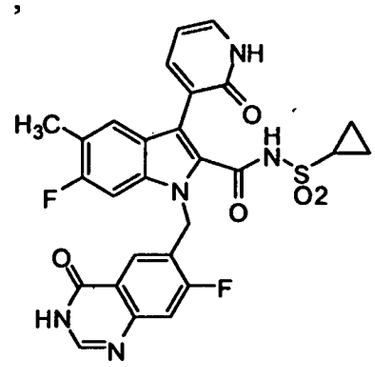
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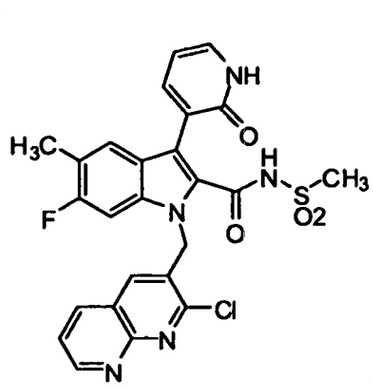
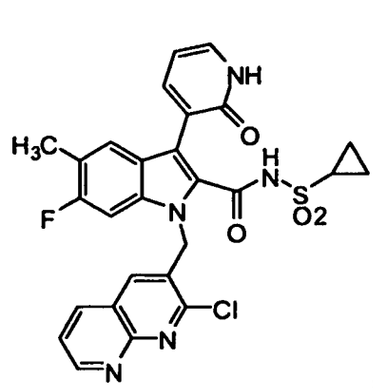
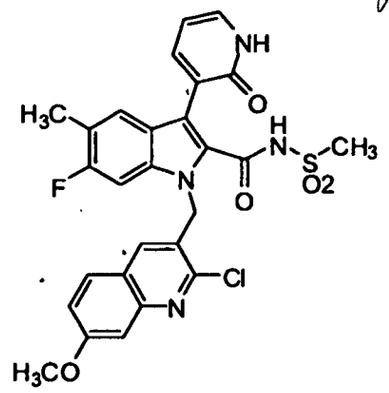
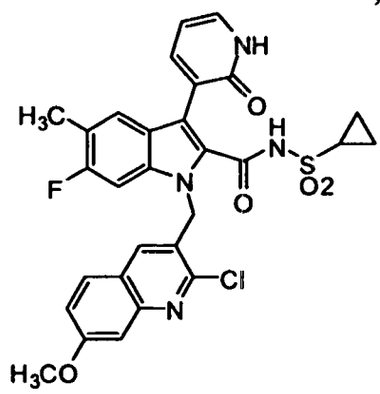


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or


or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

39. A composition comprising at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and at least one pharmaceutically acceptable carrier.

40. A composition comprising at least one compound of claim 25 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and at least one pharmaceutically acceptable carrier.

41. A composition comprising at least one compound of claim 38 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and at least one pharmaceutically acceptable carrier.

42. 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, solvate, ester or prodrug thereof.

43. 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 25 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

44. 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 38 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof.

45. The method of claim 42, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

46. The method of claim 43, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

47. The method of claim 44, further comprising administering to the patient at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

48. The method of claim 45, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

49. The method of claim 74, wherein the viral replication inhibitor is ribavirin.

50. The method of claim 49, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

51. The method of claim 50, wherein the viral replication inhibitor is ribavirin.

52. The method of claim 47, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

53. The composition of claim 39, further comprising at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

54. The composition of claim 40, further comprising at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

55. The composition of claim 41, further comprising at least one additional antiviral agent, wherein the additional agent is selected from an HCV polymerase inhibitor, an interferon, a viral replication inhibitor, a nucleoside, 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.

56. The composition of claim 53, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

57. The composition of claim 56, wherein the viral replication inhibitor is ribavirin.

58. The composition of claim 54, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

59. The composition of claim 58, wherein the viral replication inhibitor is ribavirin.

60. The composition of claim 55, wherein the additional agent(s) are selected from one or more of an HCV polymerase inhibitor, a viral protease inhibitor, a nucleoside, an interferon, a pegylated interferon or a viral replication inhibitor.

61. The composition of claim 60, wherein the viral replication inhibitor is ribavirin.

62. The method of claim 42, wherein the viral infection is hepatitis C infection.

63. The method of claim 43, wherein the viral infection is hepatitis C infection.

64. The method of claim 44, wherein the viral infection is hepatitis C infection.

DERIVADOS INDÓLICOS 2,3 SUSTITUIDOS Y MÉTODOS DE USO DE LOS MISMOS

CAMPO DE LA INVENCIÓN

La presente invención se refiere a derivados indólicos 2,3 sustituidos, composiciones que comprenden por lo menos un derivado indólico 2,3 sustituido, y métodos de uso de los derivados indólicos 2,3 sustituidos para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

FUNDAMENTO DE LA INVENCIÓN

El VHC es un virus de ARN de hebra simple (+)-sentido que se ha involucrado como el principal agente causante en la hepatitis no A, no B (NANBH). La NANBH se distingue de otros tipos de enfermedad hepática inducida por virus, tales como el virus de la hepatitis A (VHA), virus de la hepatitis B (VHB), virus de la hepatitis delta (VHD), como también de otras formas de enfermedad hepática tales como el alcoholismo y la cirrosis biliar primaria.

El virus de la hepatitis C es un miembro del género de hepacivirus en la familia Flaviviridae. Es el principal agente causante de hepatitis no A, no B y es la principal causa de hepatitis asociadas con transfusiones y justifica una proporción significativa de casos de hepatitis en todo el mundo. Aunque con frecuencia la infección por VHC es asintomática, casi el 80% de los casos desembocan en hepatitis crónica. Aproximadamente el 60% de los pacientes desarrollan enfermedad hepática con varias evoluciones clínicas que varían desde estado portador asintomático hasta hepatitis activa crónica y cirrosis hepática (que ocurre en aproximadamente el 20% de los pacientes), la cual está fuertemente asociada con el desarrollo de carcinoma hepatocelular (que ocurre 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 una estimación de 4 millones de pobladores de los Estados Unidos.

El VHC ha sido relacionado con la cirrosis del hígado y la inducción de carcinoma hepatocelular. El pronóstico para pacientes que sufren de infección por VHC sigue siendo pobre ya que la infección por VHC es más difícil de tratar que otras formas de hepatitis. Los datos actuales indican un índice de sobrevida a los cuatro años por debajo del 50% para pacientes que sufren cirrosis y sobrevida a los cinco años por debajo del 30% para pacientes con diagnóstico de carcinoma hepatocelular localizado extirpable. Los pacientes con diagnóstico de carcinoma hepatocelular localizado no extirpable están aun peor, con una sobrevida a los cinco años de menos del 1%.

El VHC es un virus de ADN con envoltura que contiene un genoma de ARN de sentido positivo de hebra simple de aproximadamente 9,5 kb de longitud. El genoma de ARN contiene una región no traducida 5' (5' NTR por sus siglas en inglés) de 341 nucleótidos, un marco abierto de lectura abierto (ORF) que codifica un polipéptido de 3,010 a 3,040 aminoácidos, y una región no traducida 3' (3'–NTR por sus siglas en inglés) de longitud variable de aproximadamente 230 nucleótidos. El VHC es similar en la secuencia de aminoácidos y organización en el genoma a los flavivirus y pestivirus, y por lo tanto el VHC se ha clasificado como un tercer género de la familia de los Flaviviridae.

El 5' NTR, una de las regiones más conservadas del genoma del virus, contiene un sitio de entrada al ribosoma interno (IRES por sus siglas en inglés) que cumple una función pivotante en el inicio de la traducción de la poli proteína viral. Un marco abierto de lectura codifica una poli proteína, que se procesa en forma conjunta o luego de la traducción en proteínas estructurales (núcleo, E1, E2 y p7) y no estructurales (NS2, NS3, NS4A, NS4B, NS5A, y NS5B) tanto por proteinasas virales o celulares. La 3' NTR consiste en tres regiones distintas: una región variable de aproximadamente 38 nucleótidos que siguen al codón de interrupción de la poli proteína, un tracto de poliuridina de longitud variable con

sustituciones intercaladas de citidinas, y 98 nucleótidos (nt) en el extremo 3' que son altamente conservados entre varios aislados de aislados de VHC. Por analogía a otros virus de ARN de hebra adicional, se considera que la 3'–NTR cumple una función importante en la síntesis de 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 las proteínas estructurales (C), la proteína de envoltura 1 y (E1, E2), y la región p7 está mediada por las peptidasas de señal huésped. En contraste, la maduración de la región no estructural (NS) se logra por dos enzimas virales. La poli proteína del VHC se disocia (cliva) primero por una peptidasa de 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, entonces se disocia en la unión NS2/NS3. El complejo de proteinasa NS3/4A (donde NS3 es una proteasa de serina y NS4A actúa como co-factor de la proteasa NS3), es responsable entonces del procesamiento de todas las uniones de disociación restantes. Las actividades de helicasa de ARN y NTPasa también se han identificado en la proteína NS3. Un tercio de las uniones de la proteína NS3 funciona como proteasa, y los dos tercios restantes de la molécula actúan como la helicasa/ATPasa que se considera involucrada en la replicación del VHC. La NS5A puede estar fosforilada y actúa como co-factor putativo de NS5B. La cuarta enzima viral, NS5B, es una polimerasa de ARN dependiente del ARN asociado a la membrana (RdRp) y un componente clave responsable de la replicación del genoma de ARN viral. La NS5B contiene el motivo de la secuencia "GDD", que es altamente conservado entre todos los RdRps caracterizados hasta la fecha.

Se considera que la replicación del VHC ocurre en complejos de replicación asociados a la membrana. Dentro de estos, el ARN de hebra más

genómico se transcribe en ARN de hebra menos, el cual a su vez puede usarse como patrón para la síntesis de hebras más genómicas de la progenie. Por lo menos dos enzimas virales aparecen involucradas en esta reacción: la helicasa NS3 /NTPasa, y la polimerasa de ARN dependiente del ARN NS5B. Mientras que la función de NS3 en la replicación del ARN es menos clara, NS5B es la enzima principal responsable de la síntesis de las hebras de ARN de la progenie. El uso de baculovirus recombinantes para expresar NS5B en células de insectos y un ARN no viral sintético como sustrato, dos actividades enzimátcas se han identificado como asociadas con estos: una actividad de RdRp dependiente del cebador y transferasa terminal (TNTasa). Posteriormente se confirmó y luego se caracterizó a través del uso del genoma de ARN del VHC como sustrato. Otros estudios han demostrado que NS5B con una truncación de 21 aminoácidos C–terminal expresada en Escherichia coli también es activa para la síntesis de ARN *in vitro*. En ciertos patrones de ARN, NS5B ha demostrado que cataliza la síntesis de ARN a través de un mecanismo de iniciación *de novo*, que se ha postulado como el modo de replicación viral *in vivo*. Se ha encontrado que los patrones con términos 3' de hebra simple, especialmente aquellos que contienen un resto citidilato 3'–terminal, dirigen la síntesis *de novo* en forma eficiente. Además ha habido 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 se relaciona 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 métodos de tratamiento actuales para la infección por VHC sufren una escasa eficiencia y efectos colaterales no favorables y actualmente hay un gran esfuerzo orientado al descubrimiento de los inhibidores de replicación del VHC que son útiles para el tratamiento y la prevención de trastornos relacionados con el VHC. Se

encuentran actualmente en investigación nuevas metodologías que incluyen el desarrollo de vacunas profilácticas y terapéuticas, la identificación de interferones con características de farmacocinética mejoradas, y el descubrimiento de agentes diseñados para inhibir la función de tres proteínas virales mayores: proteasa, helicasa y polimerasa. Además, el mismo genoma de ARN del VHC, particularmente el elemento IRES, se explota activamente como blanco antiviral que usa ribozimas catalíticos y moléculas antisentido.

Los tratamientos particulares para la infección por VHC incluyen monoterapia con interferón α y tratamiento combinado que comprende interferón α y ribavirina. Estos tratamientos han demostrado ser efectivos en algunos pacientes con infección crónica por VHC. El uso de oligonucleótidos antisentido para el tratamiento de la infección por VHC también se ha propuesto como el uso de ácidos biliares libres, tales como ácido ursodesoxicólico y quenodesoxicólico, y ácidos biliares conjugados, tales como ácido tauroursodesoxicólico. Los ésteres de ácido fosfonofórmicos también se han propuesto como potencialmente para el tratamiento de varias infecciones incluyendo el VHC. El desarrollo de la vacuna, sin embargo, se ha opacado con el alto grado de heterogenicidad de la cepa viral y la evasión inmune y la falta de protección contra la re-infección, incluso con el mismo inóculo.

El desarrollo de inhibidores de moléculas pequeñas dirigidos contra los blancos virales específicos se ha convertido en un foco mayor de investigación anti–VHC. La determinación de estructuras cristalinas para la proteasa NS3, helicasa de ARN NS3, y polmerasa NS5B ha demostrado aspectos estructurales importantes que deberían asistir en el diseño racional de los inhibidores específicos.

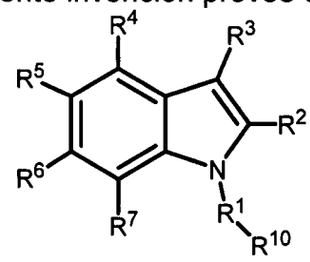
NS5B, la polimerasa de ARN dependiente del ARN, es un blanco atractivo e importante para inhibidores de moléculas pequeñas. Estudios realizados con

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 con mucha probabilidad inhibe la enzima NS5B ya que las cepas resistentes se mutan en este gen. También se ha observado la inhibición de la actividad de RdRp por (–)β–L–2',3'–didesoxi–3'–tiacitidina 5'–trifosfato (3TC; trifosfato de lamivudina) y ácido fosfonoacético.

A pesar del intensivo esfuerzo orientado al tratamiento y la prevención del VHC y las infecciones virales relacionadas, existe la necesidad en el arte de compuestos no peptídicos de moléculas pequeñas que tienen propiedades fisicoquímicas deseables o mejoradas que son útiles para inhibir virus y tratar infecciones virales y trastornos relacionados con virus.

BREVE DESCRIPCIÓN DE LA INVENCIÓN

En un aspecto, la presente invención provee compuestos de fórmula (I):



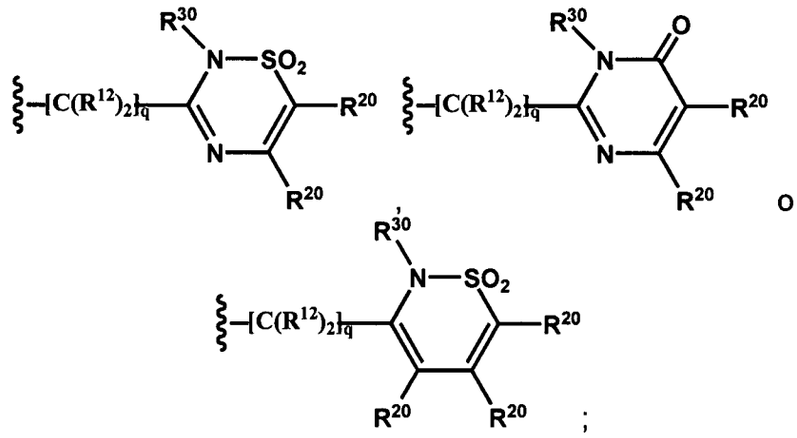
(I)

y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico,

en los cuales:

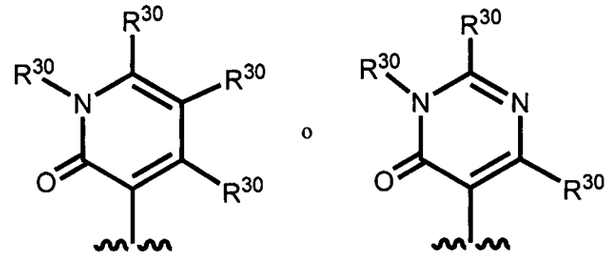
R^1 es un enlace, $–[C(R^{12})_2]_r–$, $–[C(R^{12})_2]_r–O–[C(R^{12})_2]_q–$, $–[C(R^{12})_2]_r–N(R^9)–[C(R^{12})_2]_q–$, $–[C(R^{12})_2]_q–CH=CH–[C(R^{12})_2]_q–$, $–[C(R^{12})_2]_q–C\equiv C–[C(R^{12})_2]_q–$, o $–[C(R^{12})_2]_q–SO_2–[C(R^{12})_2]_q–$;

R^2 es $-[C(R^{12})_2]_q–C(O)N(R^9)SOR^{11}$, $–[C(R^{12})_2]_q–C(O)N(R^9)SO_2R^{11}$, $–[C(R^{12})_2]_q–C(O)N(R^9)SO_2N(R^9)_2$,



;

R^3 es:



;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, 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 vez que ocurre R^8 es en forma independiente 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 vez que ocurre R^9 es en forma independiente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q-O-$alquilo, $-[C(R^{12})_2]_q-N(alquil)_2$, $-[C(R^{12})_2]_q-$arilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$cicloalquenilo, $-[C(R^{12})_2]_q-$heterocicloalquilo,

$-[C(R^{12})_2]_q-$heterocicloalquenilo, $-[C(R^{12})_2]_q-$heteroarilo, haloalquilo o hidroxialquilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 vez que ocurre R^{12} es en forma independiente H, halo, $-N(R^9)_2$, $-OR^9$, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan en forma independiente de alquilo, halo, haloalquilo, hidroxialquilo, –OH, –CN, –C(O)alquilo, –C(O)Oalquilo, –C(O)NH–alquilo, $-C(O)N(alquil)_2$, –O–alquilo, $-NH_2$, –NH(alquilo), $-N(alquil)_2$, $-NHC(O)alquilo$, $-NHSO_2alquilo$, $-SO_2alquilo$ o $-SO_2NH-alquilo$, o dos grupos R^{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

cada vez que ocurre R^{20} es en forma independiente alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los cuales 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, que se seleccionan 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 vez que ocurre R^{30} es en forma independiente 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, $-[C(R^{12})_2]_q-C(O)R^8$, $-[C(R^{12})_2]_q-C(O)OR^9$, $-[C(R^{12})_2]_q-C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-$

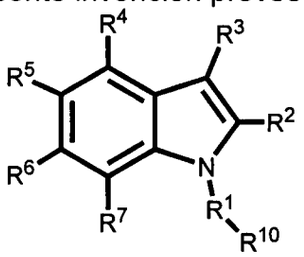
OR^9, $-[C(R^{12})_2]_q-N(R^9)_2$, $-[C(R^{12})_2]_q-NHC(O)R^8$, $-[C(R^{12})_2]_q-NR^8C(O)N(R^9)_2$, $-[C(R^{12})_2]_q-NHSO_2R^{11}$, $-[C(R^{12})_2]_q-S(O)_pR^{11}$, $-[C(R^{12})_2]_q-SO_2N(R^9)_2$ o $-SO_2N(R^9)C(O)N(R^9)_2$, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

cada vez que ocurre p es en forma independiente 0, 1 o 2;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4; y

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4.

En otro aspecto, la presente invención provee compuestos de fórmula (II):



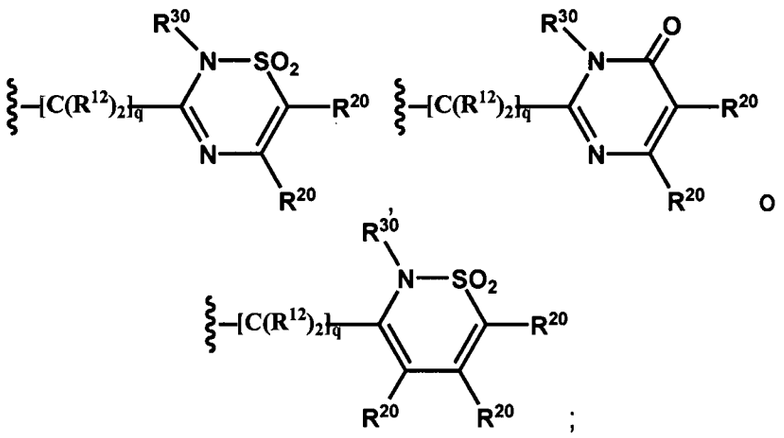
(II)

y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico,

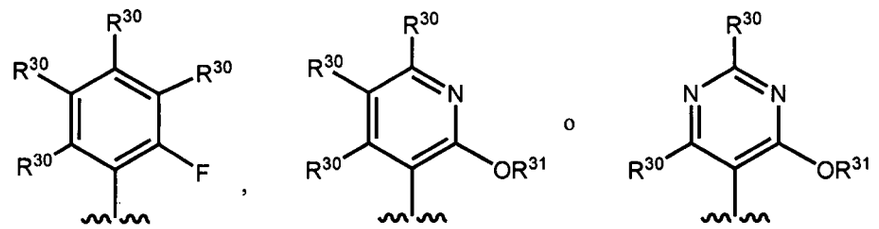
en los cuales:

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 $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$,



R^3 es



R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, 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 vez que ocurre R^8 es en forma independiente 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 vez que ocurre R^9 es en forma independiente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q-O-$alquilo, $-[C(R^{12})_2]_q-N(alquil)_2$, $-[C(R^{12})_2]_q-$arilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$cicloalquenilo, $-[C(R^{12})_2]_q-$heterocicloalquilo,

$-[C(R^{12})_2]_q-$heterocicloalquenilo, $-[C(R^{12})_2]_q-$heteroarilo, haloalquilo o hidroxialquilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 vez que ocurre R^{12} es en forma independiente H, halo, $-N(R^9)_2$, $-OR^9$, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan en forma independiente de alquilo, halo, haloalquilo, hidroxialquilo, –OH, –CN, –C(O)alquilo, –C(O)Oalquilo, –C(O)NH–alquilo, $-C(O)N(alquil)_2$, –O–alquilo, $-NH_2$, –NH(alquilo), $-N(alquil)_2$, $-NHC(O)alquilo$, $-NHSO_2alquilo$, $-SO_2alquilo$ ° $-SO_2NH-alquilo$, o dos grupos R_{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

cada vez que ocurre R^{20} es en forma independiente alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los cuales 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, que se seleccionan 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 vez que ocurre R^{30} 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 $-SO_2N(R^9)C(O)N(R^9)_2$, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

R^{31} es 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 o $-[C(R^{12})_2]_q-$hidroxialquilo;

cada vez que ocurre p es en forma independiente 0, 1 o 2;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4; y

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4.

Los compuestos de fórmulas (I) y (II) (referidos aquí en forma colectiva como los "derivados indólicos 2,3 sustituidos") y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico pueden ser útiles para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

La invención provee, además, métodos para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente, que comprenden administrar al paciente una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido.

La presente invención provee, además, composiciones farmacéuticas que comprenden una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido o una de sus sales, solvatos aceptables desde el punto de vista

farmacéutico, y un vehículo aceptable desde el punto de vista farmacéutico. Las composiciones pueden ser útiles para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

Los detalles de la invención se indican en la descripción detallada adjunta que sigue.

Aunque puede usarse cualquier método y material similar a los descritos aquí en la práctica o evaluación de la presente invención, métodos ilustrativos y materiales se describirán a continuación. Otras características, objetivos, y ventajas de la invención resultarán obvios a partir de la descripción y las reivindicaciones. Todas las patentes y publicaciones citadas en esta memoria descriptiva se incorporan aquí a modo de referencia.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

En una realización, la presente invención provee derivados indólicos 2,3 sustituidos, composiciones farmacéuticas que comprenden por lo menos un derivado indólico 2,3 sustituido, y métodos de uso de los derivados indólicos 2,3 sustituidos para tratar o prevenir una infección viral en un paciente.

Definiciones y Abreviaturas

Los términos usados aquí tienen su significado usual y el significado de dichos términos es independiente en cada una de sus apariciones. Que no obstante y excepto donde se indique de otro modo, las siguientes definiciones se aplican en la totalidad de la memoria descriptiva y reivindicaciones. Los nombres químicos, nombres comunes y estructuras químicas pueden usarse en forma indistinta para describir la misma estructura. Si se hace referencia a un compuesto químico usando tanto una estructura química como un nombre químico y existe una ambigüedad entre la estructura y el nombre, predomina la estructura. Estas definiciones se aplican sin tener en cuenta si el término se usa solo o combinado con otros términos, salvo que se indique de otro modo. Por

consiguiente, la definición de "alquilo" se aplica a "alquilo" como también a las porciones "alquilo" de "hidroxialquilo," "haloalquilo," "alcoxi," etc...

Como se usa aquí, y en toda esta memoria descriptiva, los siguientes términos, salvo que se indique de otro modo, tendrán los siguientes significados:

Un "paciente" es un mamífero humano o no humano. En una realización, un paciente es un humano. En otra realización, un paciente es un mamífero no humano, incluyendo, sin carácter limitativo, un mono, perro, babuino, macaco, ratón, rata, caballo, gato o conejo. En otra realización, un paciente es un animal de compañía, incluyendo sin carácter limitativo un perro, gato, conejo o hurón. En una realización, un paciente es un perro. En otra realización, un paciente es un gato.

El término "alquilo" como se usa aquí, se refiere a un grupo hidrocarbonado alifático, en el cual uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquilo puede ser recto o ramificado y puede contener desde aproximadamente 1 hasta aproximadamente 20 átomos de carbono. En una realización, un grupo alquilo contiene desde aproximadamente 1 hasta aproximadamente 12 átomos de carbono. En otra realización, un grupo alquilo contiene desde aproximadamente 1 hasta aproximadamente 6 átomos de carbono. Ejemplos no limitativos de grupos alquilo incluyen metilo, etilo, n–propilo, isopropilo, n–butilo, sec–butilo, isobutilo, ter-butilo, n–pentilo, neopentilo, isopentilo, n–hexilo, isohexilo y neohexilo. Un grupo alquilo puede no estar sustituido o estar sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente se selecciona en forma independiente del grupo que consiste en halo, alquenilo, alquinilo, –O–arilo, arilo, heteroarilo, cicloalquilo, cicloalquenilo, ciano, –OH, –O–alquilo, –O–haloalquilo, –alquileno–O–alquilo, alquiltio, $–NH_2$, –NH(alquilo), $–N(alquil)_2$, –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 no está sustituido. En otra realización, un grupo alquilo es un grupo alquilo de cadena recta. En otra realización, un grupo alquilo es un grupo alquilo de cadena ramificada.

El término "alquenilo" como se usa aquí, se refiere a un grupo hidrocarbonado alifático que tiene por lo menos un doble enlace carbono-carbono, en el cual uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquenilo puede ser recto o ramificado y puede contener desde aproximadamente 2 hasta aproximadamente 15 átomos de carbono. En una realización, un grupo alquenilo contiene desde aproximadamente 2 hasta aproximadamente 10 átomos de carbono. En otra realización, un grupo alquenilo contiene desde aproximadamente 2 hasta aproximadamente 6 átomos de carbono. Ejemplos no limitativos de grupos alquenilo ilustrativos incluyen etenilo, propenilo, n–butenilo, 3–metilbut–2–enilo, n–pentenilo, octenilo y decenilo. Un grupo alquenilo puede no estar sustituido o estar sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente se selecciona en forma independiente del grupo que consiste en halo, alquilo, alquinilo, –O–arilo, arilo, cicloalquilo, cicloalquenilo, ciano, –OH, –O–alquilo, –O–haloalquilo, –alquileno–O–alquilo, alquiltio, $–NH_2$, –NH(alquilo), $–N(alquil)_2$, –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 no está sustituido. En otra

realización, un grupo alquenilo es un grupo alquenilo de cadena recta. En otra realización, un grupo alquenilo es un grupo alquenilo ramificado.

El término "alquinilo" como se usa aquí, se refiere a un grupo hidrocarbonado alifático que tiene por lo menos un triple enlace carbono carbono, en el cual uno de los átomos de hidrógeno del grupo hidrocarbonado alifático se reemplaza con un enlace simple. Un grupo alquinilo puede ser recto o ramificado y puede contener desde aproximadamente 2 hasta aproximadamente 15 átomos de carbono. En una realización, un grupo alquinilo contiene desde aproximadamente 2 hasta aproximadamente 10 átomos de carbono. En otra realización, un grupo alquinilo contiene desde aproximadamente 2 hasta aproximadamente 6 átomos de carbono. Ejemplos no limitativos de grupos alquinilo ilustrativos incluyen etinilo, propinilo, 2–butinilo y 3–metilbutinilo. Un grupo alquinilo puede no estar sustituido o estar sustituido en forma opcional por uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente se selecciona en forma independiente del grupo que consiste en halo, alquilo, alquenilo, –O–arilo, arilo, cicloalquilo, cicloalquenilo, ciano, –OH, –O–alquilo, –alquileno–O–alquilo, –O–haloalquilo, –alquiltio, $–NH_2$, –NH(alquilo), $–N(alquil)_2$, –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 no está sustituido. En otra realización, un grupo alquinilo es un grupo alquinilo de cadena recta. En otra realización, un grupo alquinilo un grupo alquinilo ramificado.

El término “alquileno” como se usa aquí, se refiere a un grupo alquilo, como se definió con anterioridad, en el cual uno de los átomos de hidrógeno del grupo alquilo está reemplazado con un enlace. Ejemplos ilustrativos de alquileno

incluyen, sin carácter limitativo, $-CH_2-$, $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH_2CH_2CH_2CH_2-$, $-CH(CH_3)CH_2CH_2-$, $-CH_2CH(CH_3)CH_2-$ y $-CH_2CH_2CH(CH_3)-$. En una realización, un grupo alquileno es un grupo alquileno de cadena recta. En otra realización, un grupo alquileno un grupo alquileno ramificado.

"Arilo" significa un sistema anular aromático monocíclico o multicíclico que tiene desde aproximadamente 6 hasta aproximadamente 14 átomos de carbono en el anillo. En una realización, un grupo arilo tiene desde aproximadamente 6 hasta aproximadamente 10 átomos de carbono en el anillo. Un grupo arilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se define aquí más adelante. Ejemplos no limitativos de grupos arilo ilustrativos incluyen fenilo y naftilo. En una realización, un grupo arilo no está sustituido. En otra realización, un grupo arilo es un grupo fenilo.

El término "cicloalquilo" como se usa aquí, se refiere a un sistema anular no aromático mono- o multicíclico que tiene desde aproximadamente 3 hasta aproximadamente 10 átomos de carbono en el anillo. En una realización, un cicloalquilo tiene desde aproximadamente 5 hasta aproximadamente 10 átomos de carbono en el anillo. En otra realización, un cicloalquilo tiene desde aproximadamente 5 hasta aproximadamente 7 átomos de carbono en el anillo. Ejemplos no limitativos de cicloalquilos monocíclicos ilustrativos incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos ilustrativos incluyen 1–decalinilo, norbornilo, adamantilo y similares. Un grupo cicloalquilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se define aquí más adelante. En una realización, un grupo cicloalquilo no está sustituido.

El término "cicloalquenilo" como se usa aquí, se refiere a un sistema anular no aromático mono- o multicíclico que comprende desde aproximadamente 3 hasta aproximadamente 10 átomos de carbono en el anillo y contiene por lo menos un enlace doble endocíclico. En una realización, a cicloalquenilo contiene desde aproximadamente 5 hasta aproximadamente 10 átomos de carbono en el anillo. En otra realización, un cicloalquenilo contiene 5 o 6 átomos de carbono en el anillo. Ejemplos no limitativos de cicloalquenilos monocíclicos ilustrativos incluyen ciclopentenilo, ciclohexenilo, ciclohepta–1,3–dienilo, y similares. Un grupo cicloalquenilo puede estar sustituido en forma opcional con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se define aquí más adelante. En una realización, un grupo cicloalquenilo no está sustituido.

El término "halo" como se usa aquí, significa –F, –Cl, –Br o –I. En una realización, halo se refiere a –Cl o –F.

El término "haloalquilo" como se usa aquí, se refiere a un grupo alquilo como se definió con anterioridad, 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 desde 1 hasta 6 átomos de carbono. En otra realización, un grupo haloalquilo está sustituido con desde 1 hasta 3 F átomos. Ejemplos no limitativos de grupos haloalquilo ilustrativos incluyen $–CH_2F$, $–CHF_2$, $–CF_3$, $–CH_2Cl$ y $–CCl_3$.

El término "hidroxialquilo" como se usa aquí, se refiere a un grupo alquilo como se definió con anterioridad, 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 desde 1 hasta 6 átomos de carbono. Ejemplos no limitativos de grupos hidroxialquilo ilustrativos incluyen hidroximetilo, 2–hidroxietilo, 3–hidroxipropilo, 4–hidroxibutilo y $–CH(OH)CH_2CH_3$.

El término "heteroarilo" como se usa aquí, se refiere a un sistema anular aromático monocíclico o multicíclico que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, en los cuales desde 1 hasta 4 de los átomos en el anillo es en forma independiente O, N o S y los átomos restantes en el anillo son átomos de carbono. En una realización, un grupo heteroarilo tiene 5 a 10 átomos en el anillo. En otra realización, un grupo heteroarilo es monocíclico y tiene 5 o 6 átomos en el anillo. En otra realización, un grupo heteroarilo es monocíclico y tiene 5 o 6 átomos en el anillo y por lo menos un átomo de nitrógeno en el anillo. Un grupo heteroarilo puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se define aquí más adelante. Un grupo heteroarilo está unido a través de un átomo de carbono en el anillo y cualquier átomo de nitrógeno de un heteroarilo puede oxidarse en forma opcional al correspondiente N-óxido. El término "heteroarilo" abarca, además, un grupo heteroarilo, como se definió con anterioridad, que se ha fusionado a un anillo benceno. Ejemplos no limitativos 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, bencimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4–triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere, además, a restos 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.

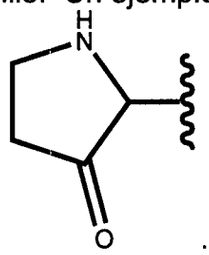
Salvo que se indique de otro modo, el grupo:



representa un grupo heteroarilo de 6 miembros que contiene 1 o 2 átomos de nitrógeno en el anillo y ningún otro heteroátomos anular. Ejemplos de dicho grupo incluyen, sin carácter limitativo piridilo, pirimidinilo, piridazinilo y pirazinilo. En una realización, este grupo tiene 1 átomo de nitrógeno en el anillo. En otra realización, este grupo tiene 2 átomos de nitrógeno en el anillo. Este grupo puede estar en forma opcional y

El término "heterocicloalquilo" como se usa aquí, se refiere a un sistema anular no aromático saturado monocíclico o multicíclico que comprende 3 hasta aproximadamente 10 átomos en el anillo, en los cuales desde 1 hasta 4 de los átomos en el anillo son en forma independiente O, S o N y el resto de los átomos en el anillo son átomos de carbono. En una realización, un grupo heterocicloalquilo tiene desde aproximadamente 5 hasta aproximadamente 10 átomos en el anillo. En otra realización, un grupo heterocicloalquilo tiene 5 o 6 átomos en el anillo. No hay átomos de oxígeno y/o azufre adyacentes presentes en el sistema anular. Cualquier grupo –NH en un anillo heterocicloalquilo puede existir protegido, tal como, por ejemplo, un grupo –N(Boc), –N(CBz), –N(Tos) y similares; dichos grupos heterocicloalquilo protegidos se consideran parte de esta invención. Un grupo heterocicloalquilo puede estar sustituido en forma opcional por uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes, y son como se define aquí más adelante. El átomo de nitrógeno o azufre del heterociclilo puede oxidarse en forma opcional al correspondiente N-óxido, S–óxido o S,S–dióxido. Ejemplos no limitativos de anillos heterocicloalquilo monocíclicos incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4–dioxanilo, tetrahidrofuranilo,

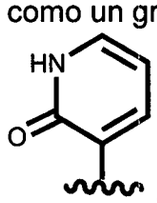
tetrahidrotiofenilo, lactama, lactona, y similares. Un átomo de carbono en el anillo de un grupo heterocicloalquilo puede estar funcionalizado como un grupo carbonilo. Un ejemplo ilustrativo de dicho grupo heterocicloalquilo es pirrolidonilo:



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.

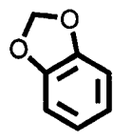
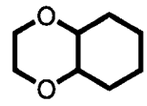
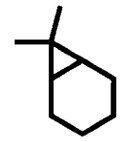
El término "heterocicloalquenilo" como se usa aquí, se refiere a un grupo heterocicloalquilo, como se definió con anterioridad, donde el grupo heterocicloalquilo contiene desde 3 hasta 10 átomos en el anillo, y por lo menos un doble enlace endocíclico carbono–carbono o carbono–nitrógeno. En una realización, un grupo heterocicloalquenilo tiene desde 5 hasta 10 átomos en el anillo. En otra realización, un grupo heterocicloalquenilo es monocíclico y tiene 5 o 6 átomos en el anillo. Un grupo heterocicloalquenilo puede estar sustituido en forma opcional por uno o más sustituyentes del sistema anular, donde "sustituyente del sistema anular" es como se definió con anterioridad. El átomo de nitrógeno o azufre del heterocicloalquenilo puede oxidarse en forma opcional al correspondiente N-óxido, S-óxido o S,S–dióxido. Ejemplos no limitativos 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, dihidroimidazolilo, dihidrooxazolilo, dihidrooxadiazolilo, dihidrotiazolilo, 3,4–dihidro–2H–piranilo, dihidrofuranilo, fluorodihidrofuranilo, 7–oxabiciclo[2,2,1]heptenilo, dihidrotiofenilo, dihidrotiopiranilo, y similares. Un átomo

de carbono en el anillo de un grupo heterociclenilo puede estar funcionalizado como un grupo carbonilo. Un ejemplo ilustrativo de dicho 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 "sustituyente del sistema anular" como se usa aquí, se refiere a un grupo sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Los sustituyentes del sistema anular pueden ser iguales o diferentes, donde cada uno, en forma independiente, se selecciona del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, –OH, hidroxialquilo, –O–alquilo, –alquileno–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–alquileno–, $Y_1Y_2NC(O)$–, $Y_1Y_2NSO_2$– y –$SO_2NY_1Y_2$, donde Y_1 y Y_2 pueden ser iguales o diferentes y se seleccionan en forma independiente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema anular" también puede significar un resto simple que reemplaza en forma simultánea dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema anular. Ejemplos de dicho resto son metilen dioxi, etilendioxi, –$C(CH_3)_2$– y similares que forman restos tales como, por ejemplo:



y


El término "sustituido," como se usa aquí, significa que uno o más hidrógenos en el átomo designado está reemplazado con una selección del grupo indicado, siempre que la valencia normal del átomo designado en las circunstancias existentes no se exceda, y que la sustitución genere un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles sólo si dichas combinaciones producen compuestos estables. Por "compuesto estable' o "estructura estable" se entiende un compuesto que es lo suficientemente robusto para sobrevivir el aislamiento hasta un grado útil de pureza a partir de la mezcla de una mezcla de reacción, y la formulación en un agente terapéutico eficaz.

El término "sustituido en forma opcional" como se usa aquí, significa la sustitución opcional con los grupos, radicales o restos específicos.

Los términos "purificado", "en forma purificada " o "en forma purificada y aislada" como se usa aquí, para un compuesto, se refiere al estado físico de dicho compuesto luego de aislarse a partir de un proceso de síntesis (por ej., de una mezcla de reacción), o una de sus combinaciones o fuentes naturales. 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 luego de obtenerse a partir de un proceso de purificación o los procesos descritos aquí o conocidos por los expertos en el arte (por ej., cromatografía, recristalización y similares) , en pureza suficiente para poder caracterizarse por técnicas de análisis estándar descritas aquí o conocidas para los expertos en el arte.

Debe observarse que se supone que cualquier carbono, como también heteroátomo, con valencias no satisfechas en el texto, los esquemas, ejemplos y

Tablas de esta invención tienen el número suficiente de átomo(s) de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo se encuentra en forma modificada para evitar reacciones colaterales no deseadas en el sitio protegido cuando el compuesto se somete a reacción. Los grupos protectores apropiados serán reconocidos por aquellos con experiencia usual en el arte como también por referencia a libros de texto estándares tales como, por ejemplo, T. W. Greene *et al*, *Protective Grupos in organic Synthesis* (1991), Wiley, New York.

Cuando cualquier variable (por ej., arilo, heterociclo, R^{11}, etc.) ocurre más de una vez en cualquier constituyente o en la Fórmula (I) o (II), su definición cada vez que ocurre es independiente de su definición en cualquier otro caso, salvo que se indique de otro modo.

Las prodrogas y los solvatos de los compuestos de la invención también se contemplan aquí. Una discusión sobre prodrogas se provee en T. Higuchi and 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 Association and Pergamon Press. El término "prodroga" como se usa aquí, se refiere a un compuesto (por ej. un precursor farmacológico) que se transforma *in vivo* para proveer un derivado indólico 2,3 sustituido o una sal, un hidrato o un solvato aceptables desde el punto de vista farmacéutico del compuesto. La transformación puede ocurrir por varios mecanismos (por ej., por procesos metabólicos o procesos químicos), tales como, por ejemplo, a través de hidrólisis en sangre. Una discusión sobre el uso de prodrogas se provee en T. Higuchi and W. Stella, "Pro–drugs as Novel Delivery Systems," Vol. 14 of the 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 derivado indólico 2,3 sustituido o una sal, un hidrato o un solvato aceptables desde el punto de vista farmacéutico del compuesto contiene un grupo funcional ácido carboxílico, una prodroga 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 desde 4 hasta 9 átomos de carbono, 1–metil–1–(alcanoiloxi)–etilo que tiene desde 5 hasta 10 átomos de carbono, alcoxicarboniloximetilo que tiene desde 3 hasta 6 átomos de carbono, 1–(alcoxicarboniloxi)etilo que tiene desde 4 hasta 7 átomos de carbono, 1–metil–1–(alcoxicarboniloxi)etilo que tiene desde 5 hasta 8 átomos de carbono, N–(alcoxicarbonil)aminometilo que tiene desde 3 hasta 9 átomos de carbono, 1–(N–(alcoxicarbonil)amino)etilo que tiene desde 4 hasta 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) (tales como β–dimetilaminoetil), carbamoil-alquilo (C_1–C_2), N,N–di alquilcarbamoil (C_1–C_2) alquilo (C_1–C_2) y piperidino–, pirrolidino– o morfolino alquilo (C_2–C_3), y similares.

En forma similar, si un derivado indólico 2,3 sustituido contiene un grupo funcional alcohol, una prodroga puede formarse por el reemplazo del átomo de hidrógeno del grupo alcohólico con un grupo tal como, por ejemplo, alcanoiloximetilo (C_1–C_6), 1–(alcanoiloxi (C_1–C_6))etilo, 1–metil–1–(alcanoiloxi (C_1–C_6))etilo, alcoxicarboniloximetilo (C_1–C_6), N–(C_1–C_6)alcoxicarbonilaminometilo, succinoilo, alcanoilo (C_1–C_6), α–amino(C_1–C_4)alcanilo, arilacilo y α–aminoacilo, o α– aminoacil-α–aminoacilo, donde cada grupo α–aminoacilo se selecciona en forma independiente de los L–aminoácidos naturales, $P(O)(OH)_2$, $–P(O)(O(C_1–C_6)alquil)_2$ o glicosilo (el radical que se obtiene

como resultado de la eliminación de un grupo hidroxilo de la forma semi-acetal de un carbohidrato), y similares.

Si un derivado indólico 2,3 sustituido incorpora un grupo funcional amina, una prodroga puede formarse 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 R y R' son cada uno en forma independiente alquilo (C_1–C_{10}), cicloalquilo (C_3–C_7), bencilo, o R–carbonilo es un α–aminoacilo natural o α–aminoacilo natural, –C(OH)C(O)OY^1 en el cual Y^1 es H, alquilo (C_1–C_6) o bencilo, –$C(OY^2)Y^3$ en el cual Y^2 es alquilo (C_1–C_4) y Y^3 es alquilo (C_1–C_6), carboxi alquilo (C_1–C_6), amino alquilo (C_1–C_4) o mono–N–o di–N,N-alquilaminoalquilo (C_1–C_6), –$C(Y^4)Y^5$ en el cual Y^4 es H o metilo y Y^5 es mono–N– o di–N,N– alquilamino (C_1–C_6) morfolino, piperidin–1–ilo o pirrolidin–1–ilo, y similares.

Uno o más compuestos de la invención pueden existir en forma no solvatada como también en formas solvatadas con solventes aceptables desde el punto de vista farmacéutico tales como agua, etanol, y similares, y se busca que la invención abarque tanto las formas solvatadas como no solvatadas. "Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física incluye grados variables de unión iónica y covalente, incluyendo unión por hidrógeno. En ciertos casos, el solvato será capaz de aislarse, por ejemplo cuando una o más moléculas de solvente se incorporan en el retículo de cristales del sólido cristalino. "Solvato" abarca ambos solvatos de fase en solución y susceptibles de aislamiento. Ejemplos no limitativos de solvatos ilustrativos incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula de solvente es H_2O.

Uno o más compuestos de la invención pueden convertirse en forma adicional en un solvato. La preparación de solvato resulta generalmente conocida. De este modo, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*,

93(3), 601–611 (2004) describen la preparación de los solvatos del anti fúngico fluconazol en acetato de etilo como también a partir de agua. Preparaciones similares de solvatos, hemisolvato, hidratos y similares se describen en el texto escrito por 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 limitativo, incluye la disolución del compuesto de la invención en las cantidades deseadas del solvente deseado (orgánico o agua o mezclas de los anteriores) a una temperatura superior a la temperatura ambiente, y enfriamiento de la solución a una velocidad suficiente para formar cristales que luego se aíslan por métodos estándar. Las técnicas de análisis tales como, por ejemplo espectroscopía por I. R., muestran la presencia del solvente (o agua) en los cristales como solvato (o hidrato).

El término "cantidad efectiva" o "cantidad efectiva para fines terapéuticos" pretende describir una cantidad de compuesto o composición de la presente invención que es efectiva para tratar o prevenir una infección viral o un trastorno relacionado con un virus.

Los conjugados metabólicos, tales como glucuronidas y sulfatos que pueden sufrir conversión reversible de los derivados indólicos 2,3 sustituidos se contemplan en la presente invención.

Los derivados indólicos 2,3 sustituidos pueden formar sales, y todas esas sales se contemplan dentro del alcance de esta invención. La referencia a un derivado indólico 2,3 sustituido aquí pretende incluir referencia a sus sales, salvo que se indique de otro modo. El término "sal(es)", como se emplea aquí, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, como también sales alcalinas formadas con bases inorgánicas y/u orgánicas. Además, cuando un derivado indólico 2,3 sustituido contiene tanto un resto alcalino, tales como, sin carácter limitativo una piridina o imidazol, como un esto ácido, tales como, sin

carácter limitativo un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y se incluyen se incluyen dentro del término "sal(es)" como se usa aquí. Las sales aceptables desde el punto de vista farmacéutico (es decir, no tóxicas, fisiológicamente aceptables) son las preferidas, aunque pueden también ser útiles otras sales. Las sales de los compuestos de la Fórmula I pueden formarse, por ejemplo, haciendo reaccionar un derivado indólico 2,3 sustituido con una cantidad de ácido o base, tales como una cantidad equivalente, en un medio tal como aquel en el cual la sal se precipita o en un medio acuoso seguido de liofilización.

Las sales de adición con ácido ejemplificativas 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, tartaratos, tiocianatos, toluensulfonatos (también conocidos como tosilatos) y similares. En forma adicional, los ácidos que generalmente se consideran aptos para la formación de sales útiles desde el punto de vista farmacéutico a partir de compuestos farmacéuticos alcalinos se discuten, por ejemplo, en 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; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio en internet). Estas descripciones se incorporan aquí a modo de referencia.

Las sales alcalinas ejemplificativas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalino térreos tales como sales de calcio y magnesio, sales con bases orgánicas

(por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t–butil aminas, colina, y sales con aminoácidos tales como arginina, lisina y similares. Los grupos alcalinos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ej. cloruros, bromuros y yoduros de metilo, etilo, y butilo), dialquil sulfatos (por ej. dimetil, dietil, y dibutil sulfatos), 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 dichas sales ácidas y sales alcalinas pretenden ser sales aceptables desde el punto de vista farmacéutico dentro del alcance de la invención y todas las sales ácidas y alcalinas se consideran equivalentes a las formas libres de los correspondientes compuestos para los fines de la invención.

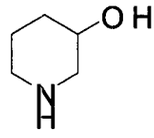
Los ésteres aceptables desde el punto de vista farmacéutico de los presentes compuestos incluyen los siguientes grupos: (1) ésteres de ácido carboxílico obtenidos por esterificación de los grupos hidroxi, en los cuales el resto no carbonilo de la porción ácido carboxílico de la agrupación éster se selecciona de alquilo de cadena recta 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 sustituido en forma opcional con, por ejemplo, halógeno, alquilo $C_{1–4}$, o alcoxi $C_{1–4}$ o amino); (2) ésteres de sulfonato, tales como alquil– o aralquilsulfonilo (por ejemplo, metansulfonilo); (3) ésteres de aminoácidos (por ejemplo, L–valilo o L–isoleucilo); (4) ésteres de fosfato y (5) ésteres de mono–, di– o trifosfato. Los ésteres de fosfato pueden esterificarse en forma adicional por, por ejemplo, un alcohol $C_{1–20}$ o su derivado reactivo, o por un 2,3–di ($C_{6–24}$)acil glicerol.

Los derivados indólicos 2,3 sustituidos pueden contener centros asimétricos o quirales, y, por lo tanto, existir en diferentes formas estereoisoméricas. Se pretende que todas las formas estereoisoméricas de los

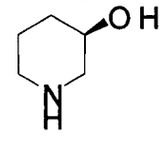
derivados indólicos 2,3 sustituidos como también mezclas de los anteriores, incluyendo mezclas racémicas, formen parte de la presente invención. Además, la presente invención abarca todos los isómeros geométricos y de posición. Por ejemplo, si un derivado indólico 2,3 sustituido incorpora un doble enlace o un anillo fusionado, tanto las formas cis– y trans–, como también mezclas, están abarcadas dentro del alcance de la invención.

Las mezclas diasteroméricas pueden separarse en sus diastereoisómeros individuales en base a sus diferencias físicas por métodos conocidos por aquellos expertos en el arte, tales como, por ejemplo, por cromatografía y/o cristalización fraccional. Los enantiómeros pueden separarse por conversión de la mezcla enantiomérica en una mezcla diasteromérica por reacción con un compuesto ópticamente activo apropiado (por ej., auxiliar quiral tal como un alcohol quiral o cloruro ácido de Mosher), separación de los diasterómeros y conversión (por ej., hidrólisis) de los diasterómeros individuales en los correspondientes enantiómeros puros. Además, algunos de los derivados indólicos 2,3 sustituidos pueden ser atropisómeros (por ej., biarilos sustituidos) y se consideran parte de esta invención. Los enantiómeros también pueden separarse por el uso de columna de HPLC quiral.

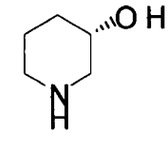
La línea recta ——— como enlace generalmente indica una mezcla de, o cualquiera de, los posibles isómeros, ejemplos no limitativos incluyen, que contienen estereoquímica (R)– y (S)–. Por ejemplo,



significa que contiene ambos

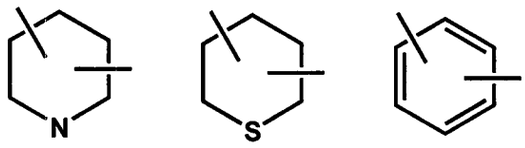


y



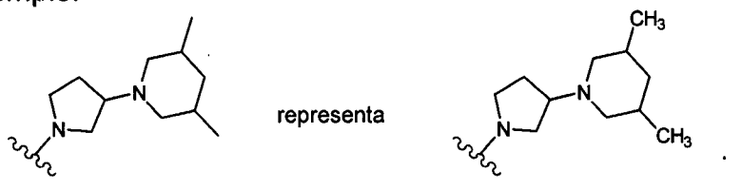
Una línea punteada (———) representa un enlace opcional.

Las líneas dibujadas hacia el interior de los sistemas anulares, tales como, por ejemplo:



indican que la línea indicada (enlace) puede estar unida a cualquiera de los átomos en el anillo susceptibles de sustitución, ejemplos no limitativos incluyen átomos de carbono, nitrógeno y azufre en el anillo.

Como se conoce en el arte, un enlace dibujado desde un átomo particular en el cual no se muestra resto en el extremo terminal del enlace indica un grupo metilo unido a través de ese enlace al átomo, salvo que se indique de otro modo. Por ejemplo:



Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos, hidratos, ésteres y prodrogas de los compuestos como también las sales, los solvatos y los ésteres de las prodrogas), tales como aquellos que pueden existir debido a los carbonos asimétricos en varios sustituyentes, incluyendo formas enantioméricas (que pueden existir en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros, y formas diasteroméricas, se contemplan dentro del alcance de esta invención, como son los isómeros de posición (tales como, por ejemplo, 4–piridilo y 3–piridilo). Por ejemplo, si un derivado indólico 2,3 sustituido incorpora un doble enlace o un anillo fusionado, tanto las formas cis– y trans–, como también sus mezclas, están abarcadas dentro del alcance de la invención.

Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, ser sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los otros estereoisómeros, u

otros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R como se define en las Recomendaciones de la *IUPAC* de 1974. El uso de los términos "sal", "solvato", "éster", "prodroga" y similares, pretende aplicarse igualmente a la sal, el solvato y la prodroga de los enantiómeros, estereoisómeros, rotámeros, isómeros de posición, racematos o prodrogas de los compuestos de la invención.

La presente invención también abarca compuestos isotópicamente marcados de la presente invención que son idénticos a aquellos mencionados aquí, aunque por el hecho de que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o número de masa diferente de la masa atómica o número de masa que usualmente se encuentra en la naturaleza. Dichos compuestos son útiles como reactivos terapéuticos, de diagnóstico o de investigación. Ejemplos de isótopos que pueden incorporarse 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 derivados indólicos 2,3 sustituidos rotulados en forma isótopica (por ej., aquellos marcados con ^{3}H y ^{14}C) son útiles en los ensayos de distribución en tejido de compuesto y/o sustrato. Los isótopos titulados (es decir, ^{3}H) y carbono–14 (es decir, ^{14}C) se prefieren particularmente por su facilidad de preparación y capacidad de detección. Además, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H) puede producir ciertas ventajas terapéuticas como resultado de una mayor estabilidad metabólica (por ej., aumento de la vida media o reducción de los requerimientos de dosificación) y por consiguiente pueden preferirse en algunas circunstancias. Los derivados indólicos 2,3 sustituidos isotópicamente marcados pueden prepararse en general siguiendo procedimientos análogos a aquellos descritos en los Esquemas y/o en

los Ejemplos que siguen a continuación, sustituyendo un reactivo isotópicamente marcado apropiado en lugar de un reactivo no isotópicamente marcado.

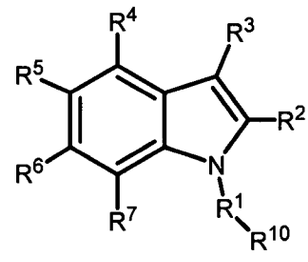
Las formas polimórficas de los derivados indólicos 2,3 sustituidos, y de las sales, solvatos, hidratos, ésteres y prodrogas de los derivados indólicos 2,3 sustituidos, pretenden incluirse en la presente invención.

La siguientes abreviaturas se usan a continuación y tienen los siguientes significados:

Bn es bencilo; Bu es butilo; CDI es N,N'–carbonildiimidazol; DABCO es 1,4–Diazabiciclo[2,2,2]octano; dba es dibencilideneacetona; DBU es 1,8–Diazabiciclo[5,4,0]undec–7–eno; DCM es diclorometano; DIEA es dietilamina; DIPEA es diisopropiletilamina; DME es dimetoxietano; DMF es dimetilformamida; DMSO es dimetilsulfóxido; dppf es 1,1'–bis(difenilfosfin)ferroceno; EDCI es 1–(3–dimetilaminopropil)–3–etilcarbodiimida; Et es etil; Et_3N es trietilamina; EtOAc es acetato de etilo; HATU es N–(dietilamino)–1H–1,2,3–triazolo[4,5–b]piridina–1–il-metilen]–N–metilmetanaminio hexafluorofosfato N-óxido; HPLC es cromatografía líquida de alta resolución; Me es metilo; MeOH es metanol; MS es espectrometría de masa; NBS es N–bromosuccinimida; NIS es N–yodosuccinimida; PPA es ácido polifosfórico; TBAF es fluoruro de tetra–n–butilamonio; THF es tetrahidrofurano; TLC es cromatografía de fase delgada y TMS es trimetilsililo.

Derivados indólicos 2,3 sustituidos de Fórmula (I)

La presente invención provee derivados indólicos 2,3 sustituidos que tienen la fórmula:



(I)

y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico, en los cuales R^1, R^2, R^3, R^4, R^5, R^6, R^7 y R^{10} se definió con anterioridad para los compuestos de fórmula (I).

En una realización, R^1 es un enlace.

En otra realización, R^1 es $-[C(R^{12})_2]_r-$.

En otra realización, R^1 es $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$.

Incluso en otra realización, R^1 es $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$.

Además en otra realización, R^1 es $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$.

En otra realización, R^1 es $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$.

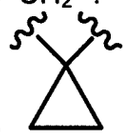
En una realización adicional, R^1 es $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$.

En una realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o



.

En otra realización, R^1 es $-CH_2-$.

En otra realización, R^1 es  .

En una realización, R^{10} es arilo o heteroarilo.

En otra realización, R^{10} es arilo.

En otra realización, R^{10} es H.

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

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

Incluso en otra realización, R^{10} es heterocicloalquenilo.

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

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

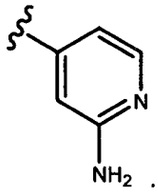
En otra realización, R^{10} es fenilo.

En otra realización, R^{10} es fenilo, que está sustituido con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2-$alquilo,

haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2.

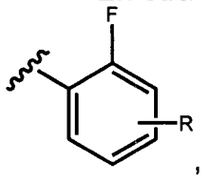
Además en otra realización, R^{10} es piridilo.

En una realización adicional, R^{10} es



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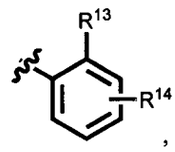
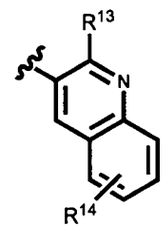
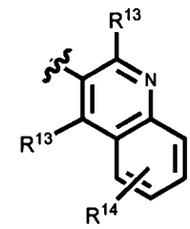
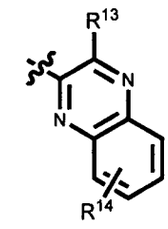
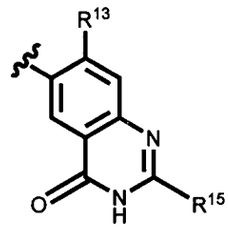
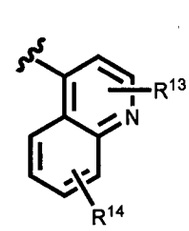
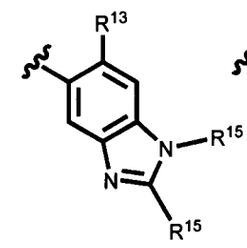
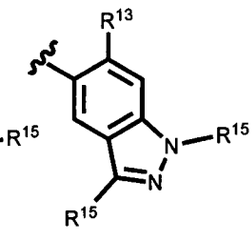
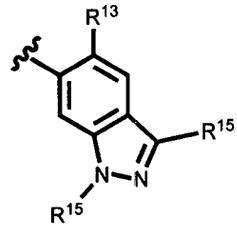
En otra realización, –R^{10} es:



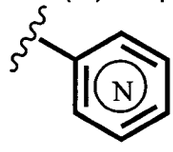
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donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, $-CF_3$, –CN, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)OH, $-NH_2$, $-SO_2$–alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

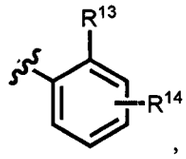
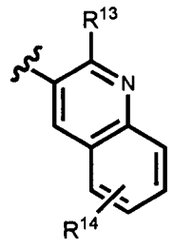
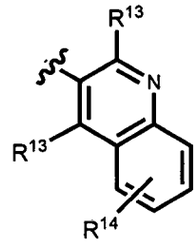
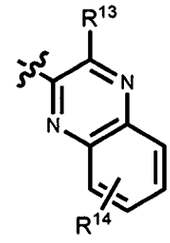
En una realización, R^{10} es:


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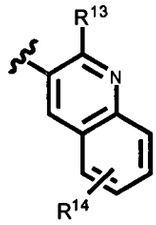
en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

En otra realización, R^{10} es


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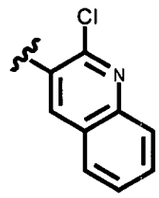
en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

Además en otra realización, R^{10} es:

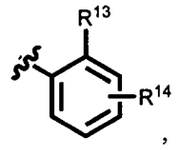
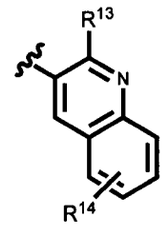
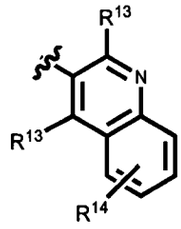
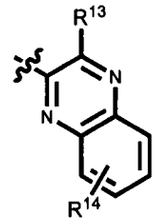
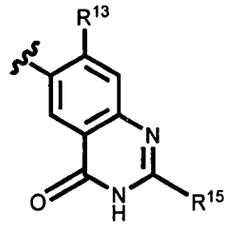
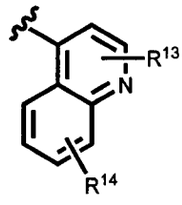
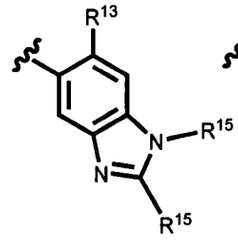
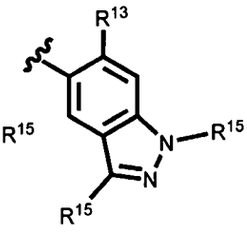
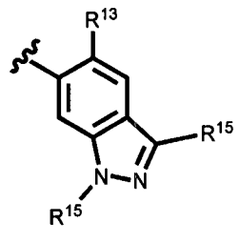
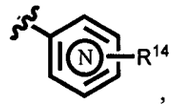


en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En una realización adicional, R^{10} es :

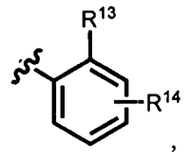

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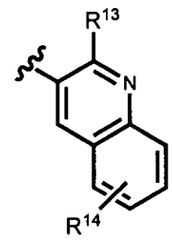
En otra realización, R^1 es $-CH_2-$ o  y R^{10} es

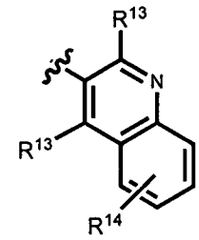

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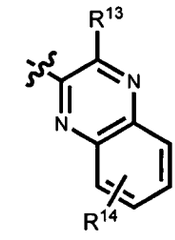
en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2-$alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH-$alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2-$alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH-$alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

Incluso en otra realización, R^1 es $-CH_2-$ o  y R^{10} es



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o


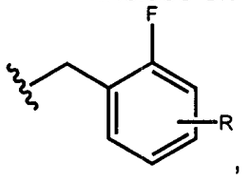
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en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En una realización, $–R^1–R^{10}$ es bencilo.

En otra realización, $–R^1–R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con desde 1–4 grupos seleccionados en forma independiente de: halo, $–NH_2$, $–NHSO_2–$alquilo, haloalquilo, metoxi, –O–haloalquilo, $–[C(R^{12})_2]_q–NHC(O)NH–$alquilo, alquilo, –OH, –CN, $–C(O)NH_2$ o $–[C(R^{12})_2]_q–NH_2$.

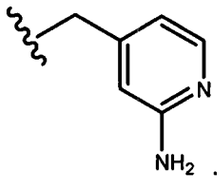
Incluso en otra realización, $–R^1–R^{10}$ es



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donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, $–CF_3$, –CN, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)OH, $–NH_2$, $–SO_2–$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En otra realización, $–R^1–R^{10}$ es



Incluso en otra realización, $-R^1-R^{10}$ es alquilo.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con 1 o 2 átomos de flúor.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con 1 o 2 grupos metilo.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con un átomo de flúor y un grupo metilo.

En otra realización, $-R^1-R^{10}$ es haloalquilo.

En una realización adicional, $-R^1-R^{10}$ es $-CH_2-$cicloalquilo.

En una realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$.

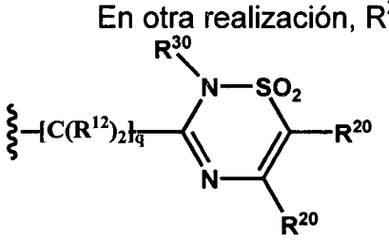
En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

En otra realización, R^2 es $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$.

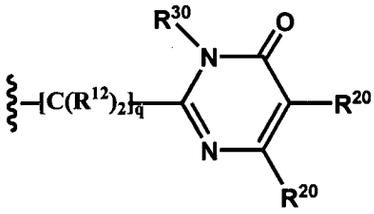
En otra realización, R^2 es $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$.

Incluso en otra realización, R^2 es $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^{11})_2$.

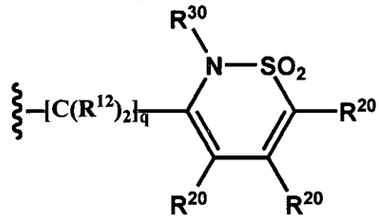
En otra realización, R^2 es



En otra realización, R^2 es



Además en otra realización, R^2 es



En otra realización, R^2 es $-C(O)N(R^9)SO_2R^{11}$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$alquilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$arilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$cicloalquilo.

En una realización adicional, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$heteroarilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$haloalquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$hidroxialquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es alquilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es arilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es cicloalquilo.

En una realización adicional, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es heteroarilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es haloalquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es hidroxialquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$fenilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es bencilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es naftilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-NH_2$ o $-N(CH_3)_2$.

En otra realización, R^2 es $-C(O)NHSO_2CH_3$.

En otra realización, R^2 es $-C(O)NHSO_2CH_2CH_3$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$, y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

En una realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es alquilo, cicloalquilo o arilo.

En una realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es $-[C(R^{12})_2]_q-O-$alquilo o $-[C(R^{12})_2]_q-N(alquil)_2$.

Incluso en otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es $-(CH_2)_2-N(CH_3)_2$ o $-(CH_2)_3-N(CH_3)_2$.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, alquilo o cicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es metilo, etilo, isopropilo, ciclopropilo o fenilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, metilo, etilo o ciclopropilo.

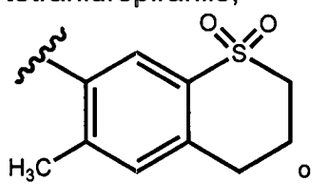
Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es ciclopropilo.

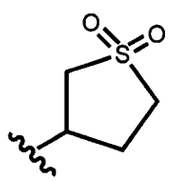
En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H o metilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, $-COOH$, $-[C(R^{12})_2]_q-C(O)O-$alquilo, $-OH$, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, $-CN$, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-NHSO_2-$alquilo, $-[C(R^{12})_2]-O-$alquilo, o $-[C(R^{12})_2]-$alquilo.

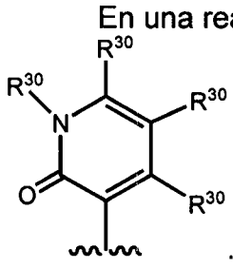
Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es imidazolilo, piridilo, tienilo, furanilo, benzofuranilo, benzo[1,3]dioxolilo, tetrahidropiranilo,



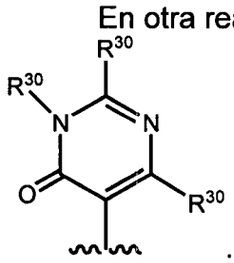


Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

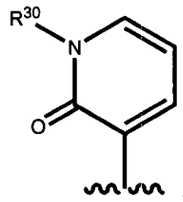
En una realización, R^3 es



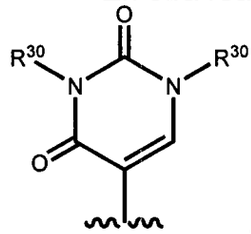
En otra realización, R^3 es



En otra realización, R^3 es



En otra realización, R^3 es



En una realización, R^4 es H.

En otra realización, R^4 es H o F.

En otra realización, R^4 es F.

En otra realización, R^5 es H.

En otra realización, R^6 es H.

En otra realización, R^6 es H o F.

En otra realización, R^6 es F.

Incluso en otra realización, R^7 es H.

En otra realización, R^4 y R^7 son cada uno H.

Además en otra realización, R^4, R^6 y R^7 son cada uno H.

En otra realización, R^4, R^5, R^6 y R^7 son cada uno H.

En una realización adicional, R^4, R^6 y R^7 son cada uno H y R^5 es distinto de H.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es alquilo.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es halo.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es metilo.

En una realización adicional, R^4, R^6 y R^7 son cada uno H y R^5 es Cl.

En otra realización, R^4 y R^7 son cada uno H y R^5 y R^6 son distintos de H.

En otra realización, R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN.

En otra realización, R^5 es distinto de H.

Incluso en otra realización, R^5 es alquilo.

Además en otra realización, R^5 es halo.

Incluso en otra realización, R^5 es metilo.

En otra realización, R^5 es etilo.

En otra realización, R^6 es H.

En otra realización, R^6 es distinto de H.

En una realización adicional, R^6 es alquilo.

Además en otra realización, R^6 es halo.

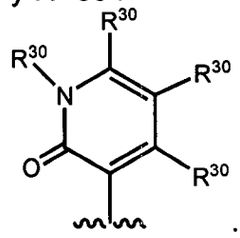
Incluso en otra realización, R^6 es metilo.

En otra realización, R^6 es F.

En una realización, R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En una realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$,

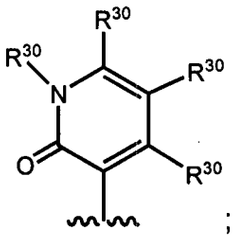
y R^3 es :



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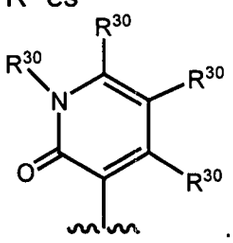
En una realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$;

R^3 es :



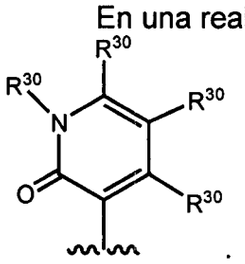
; y dos grupos R^{30} adyacentes y los átomos de carbono a los cuales están unidos, se unen para formar un anillo de benceno.

En una realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; y R^3 es



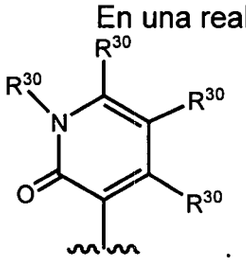
.

En una realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^3 es



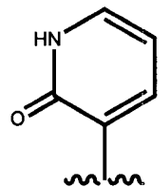
.

En una realización, R^2 es $-C(O)NHSO_2CH_3$, y R^3 es

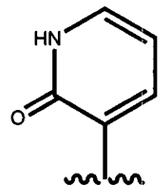


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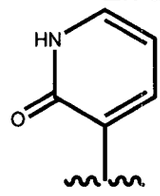
En una realización, R^2 es $-C(O)NHSO_2R^{11}$; R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, $-COOH$, $-[C(R^{12})_2]_q-C(O)O-$alquilo, $-OH$, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, $-CN$, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$; y R^3 es



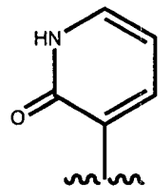
En una realización, R^2 es $-C(O)NHSO_2R^1$ y R^3 es



En una realización, R^2 es $-C(O)NHSO_2CH_3$, y R^3 es

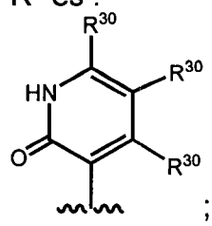


En una realización, R^2 es $-C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, $-COOH$, $-[C(R^{12})_2]_q-C(O)O-$alquilo, $-OH$, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, $-CN$, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$; y R^3 es



En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

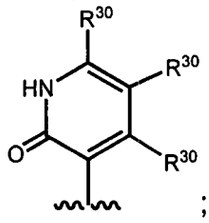
R^3 es :



; y R^4 y R^7 son cada uno en forma independiente H, halo o hidroxi.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

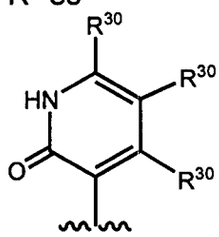
R^3 es :



; y R^5 es H, alquilo, –O–alquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

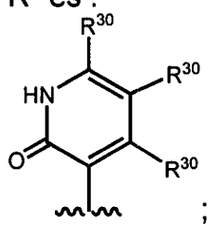
R^3 es



; y R^5 es alquilo, cicloalquilo, halo o hidroxi.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

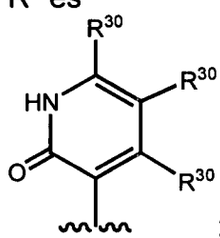
R^3 es :



; y R^6 es H, alquilo, –O–alquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN.

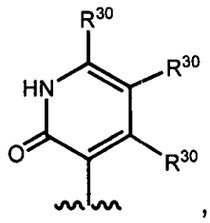
En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

R^3 es



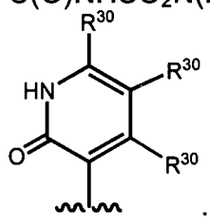
; y R^6 es alquilo, cicloalquilo, halo o hidroxi.

Incluso en otra realización, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :

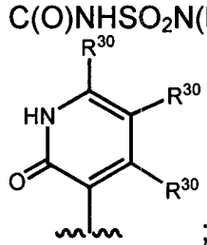


, y R^{10} es arilo o heteroarilo;

En una realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —C(O)$NHSO_2R^{11}$ o —C(O)$NHSO_2N(R^9)_2$; y R^3 es :

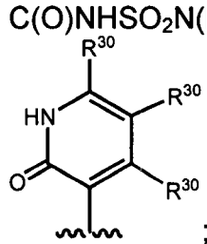


En otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —C(O)$NHSO_2R^{11}$ o —C(O)$NHSO_2N(R^9)_2$; R^3 es :

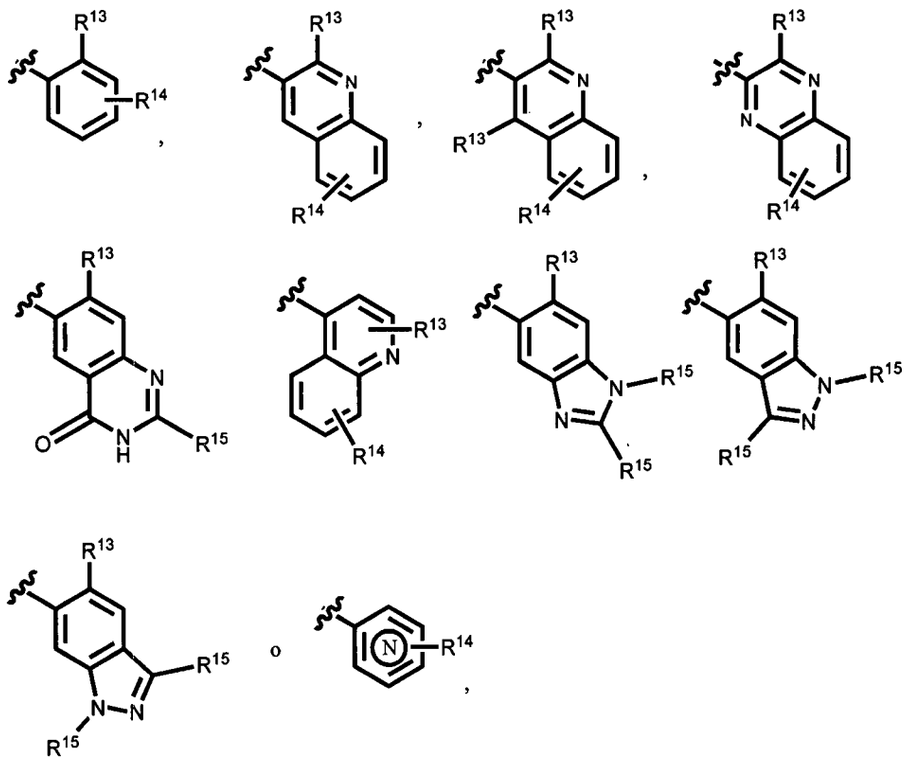


; y R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la reivindicación 1;

En una realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —C(O)$NHSO_2R^{11}$ o —C(O)$NHSO_2N(R^9)_2$; R^3 es :

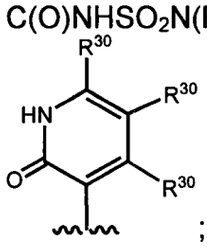


; y R^{10} es:

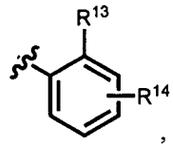
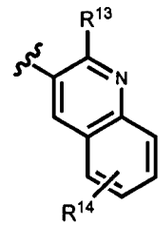
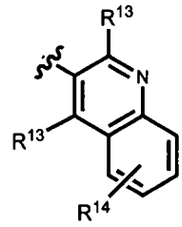
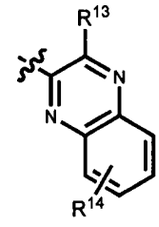


en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

Además en otra realización, R^1 es -[$C(R^{12})_2$]–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es :

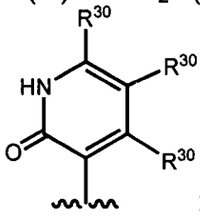


; y R^{10} es:

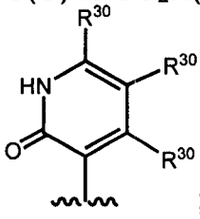

,

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o

,

en los cuales R^{13} es H, F, Br o Cl, y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

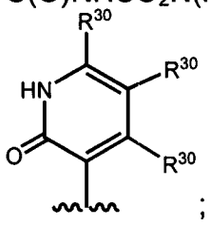
En otra realización, R^1 es -$[C(R^{12})_2]_r$–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es :


; R^5 es H, alquilo, –O–alquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; R^6 es H, alquilo, –O–alquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la reivindicación 1.

En una realización adicional, R^1 es -$[C(R^{12})_2]_r$–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es :


; R^5 es H, metilo, etilo o ciclopropilo; R^6 es H, F o –OH; y R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la reivindicación 1.

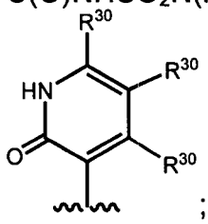
En otra realización, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :



; R^9 es H, metilo o etilo; R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la reivindicación 1;

y R^{11} es metilo, etilo, ciclopropilo o fenilo.

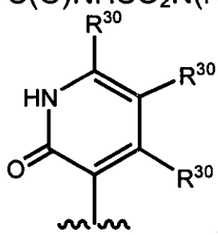
En una realización, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :

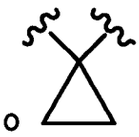


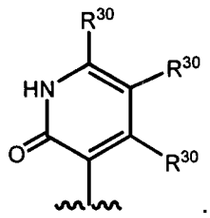
; R^9 es H, metilo o etilo; R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la reivindicación 1;

y R^{11} es metilo, ciclopropilo o fenilo.

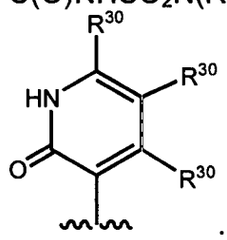
En otra realización, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; y R^3 es



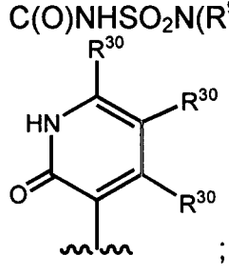
En otra realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  ; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; y R^3 es :



En otra realización, R^1 es -CH_2– o  ; R^2 es –C(O)$NHSO_2R^{11}$ o –C(O)$NHSO_2N(R^9)_2$; y R^3 es



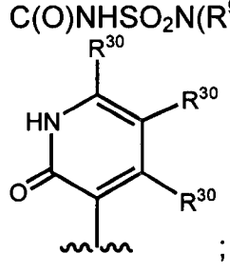
En una realización, R^1 es -CH_2– o  ; R^2 es –C(O)$NHSO_2R^{11}$ o –C(O)$NHSO_2N(R^9)_2$; R^3 es



; y

R^{10} es arilo o heteroarilo.

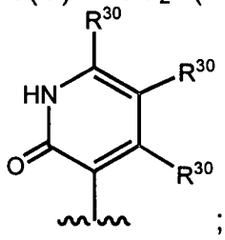
En una realización, R^1 es -CH_2– o  ; R^2 es –C(O)$NHSO_2R^{11}$ o –C(O)$NHSO_2N(R^9)_2$; R^3 es



; y

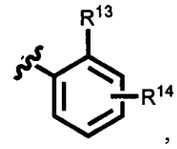
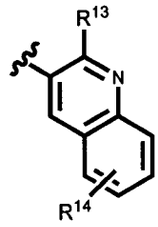
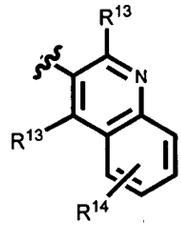
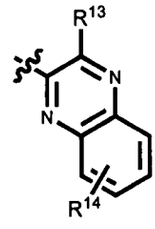
R^{10} es fenilo, naftilo, piridilo, quinolinilo o quinoxalinilo, cada uno de los cuales puede estar sustituido en forma opcional como se indica en la fórmula (I).

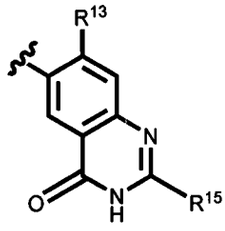
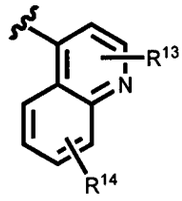
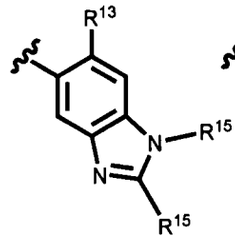
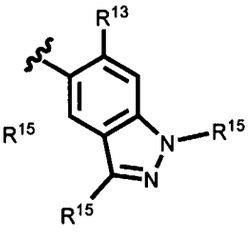
En una realización, R^1 es $-CH_2-$ o  ; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es

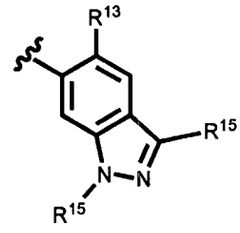
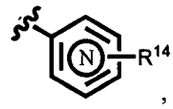


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R^{10} es


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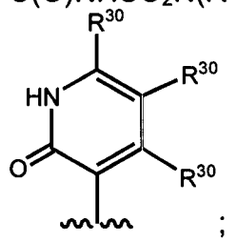






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en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –

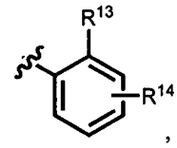
C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

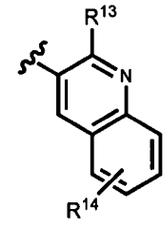
En otra realización, R^1 es $-CH_2-$ o  ; R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$; R^3 es

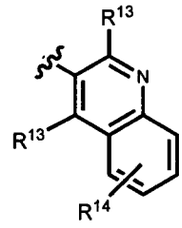


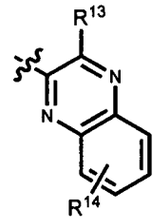
; y

R^{10} es



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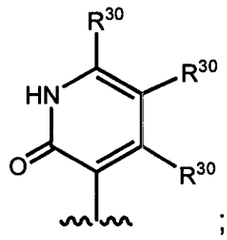
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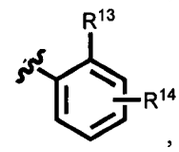
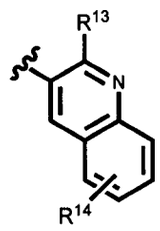
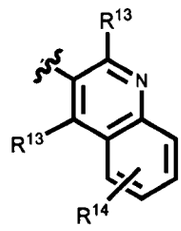
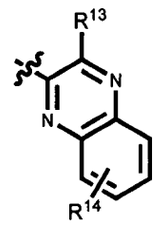
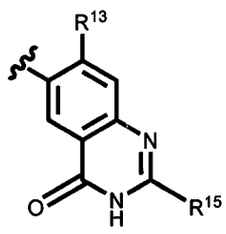
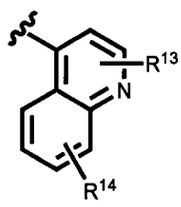
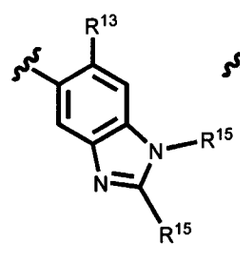
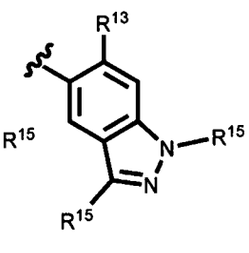
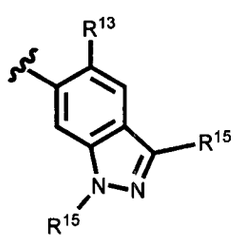
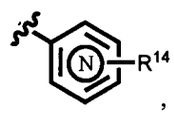
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en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En otra realización, R^1 es $-CH_2-$ o  ; R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$; R^3 es

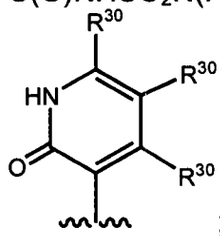


; R^5 es alquilo, cicloalquilo, halo o –OH; R^6 es alquilo, cicloalquilo, halo o –OH; y R^{10} es

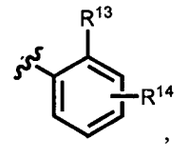
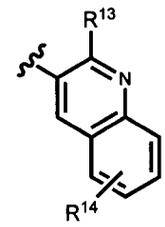
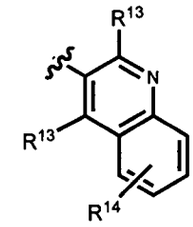
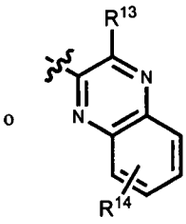

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en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es -CH_2– o  ; R^2 es –C(O)$NHSO_2R^{11}$ o –C(O)$NHSO_2N(R^9)_2$; R^3 es

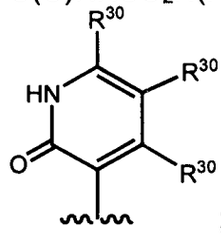


; R^5 es alquilo, cicloalquilo, halo o –OH; R^6 es alquilo, cicloalquilo, halo o –OH; y R^{10} es

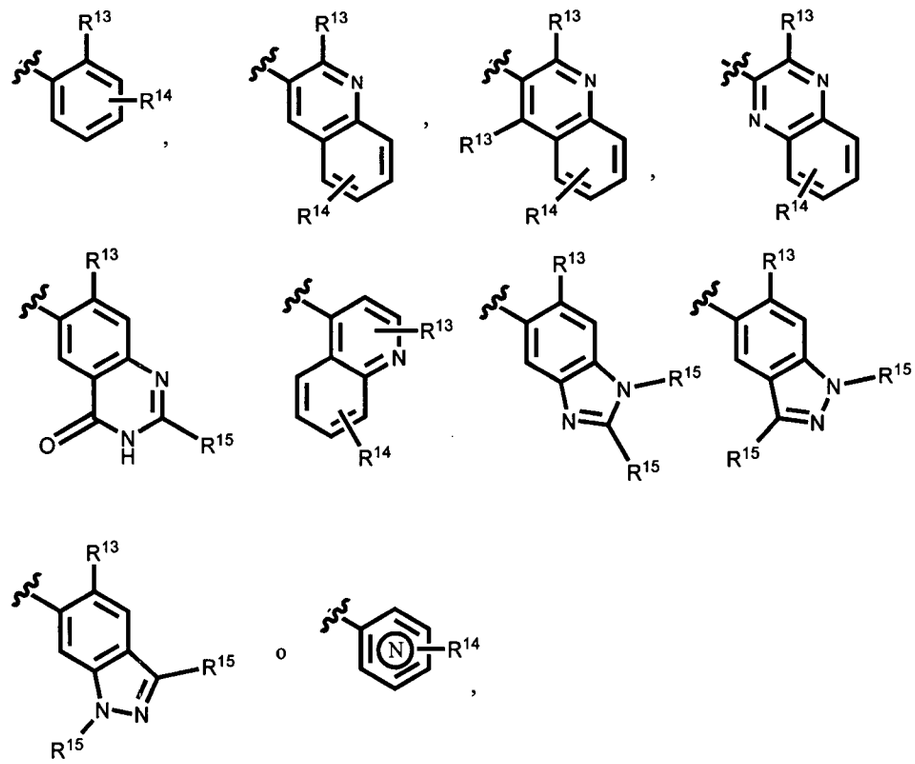
 ,  ,  o  ,

en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En una realización, R^1 es -CH_2– o  ; R^2 es –C(O)$NHSO_2R^{11}$ o –C(O)$NHSO_2N(R^9)_2$; R^3 es

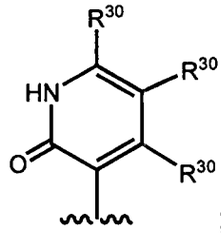


; R^5 es metilo, etilo o ciclopropilo; R^6 es H, F o –OH; y R^{10} es

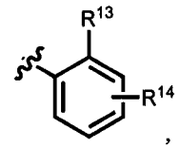
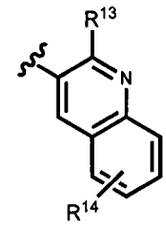
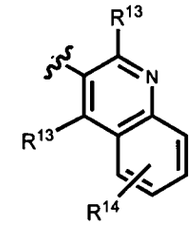
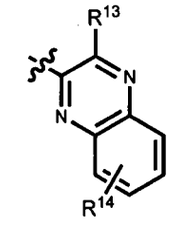


en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es $-CH_2-$ o  ; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es

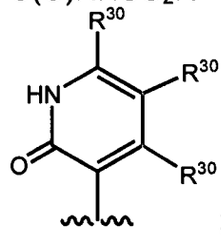


; R^5 es metilo, etilo o ciclopropilo; R^6 es H, F o –OH; y R^{10} es

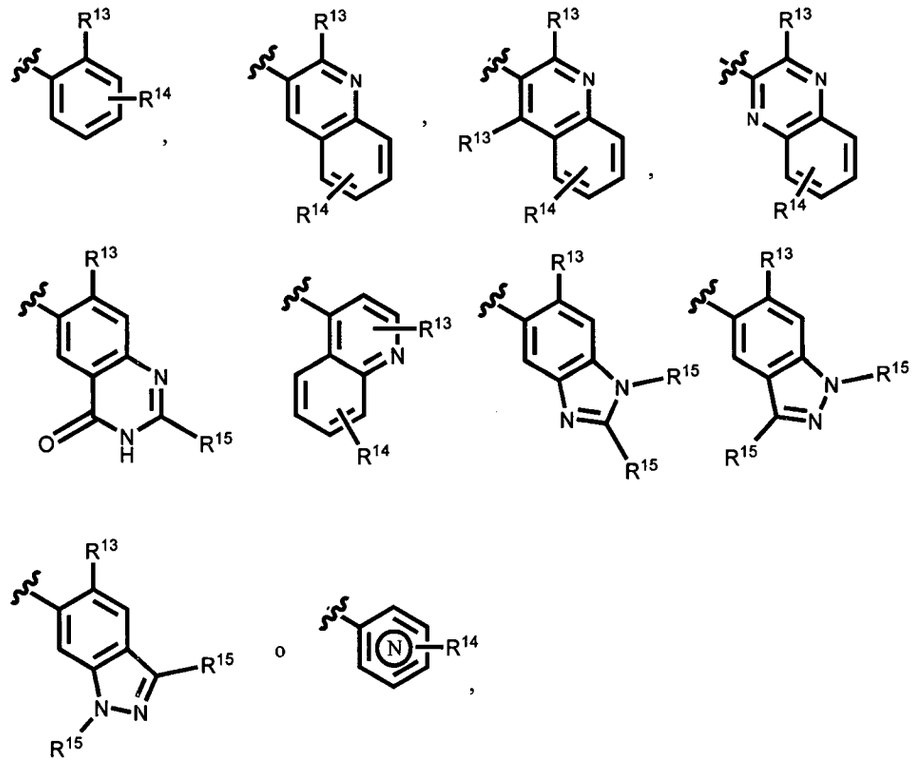

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en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

Incluso en otra realización, R^1 es -CH_2– o  ; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es

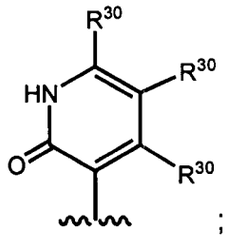

;

R^9 es H, metilo o etilo; R^{10} es



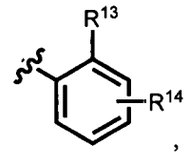
en los cuales R^{11} es metilo, etilo, ciclopropilo o fenilo; R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En una realización adicional, R^1 es -CH_2– o  ; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es

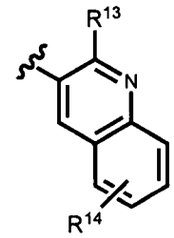


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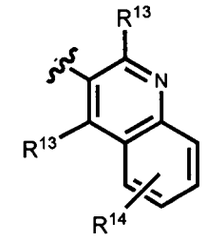
R^9 es H, metilo o etilo; R^{10} es



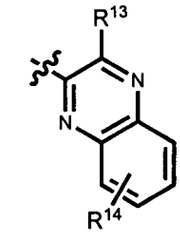
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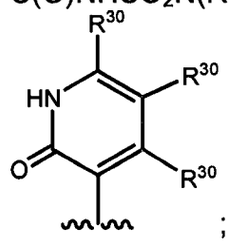
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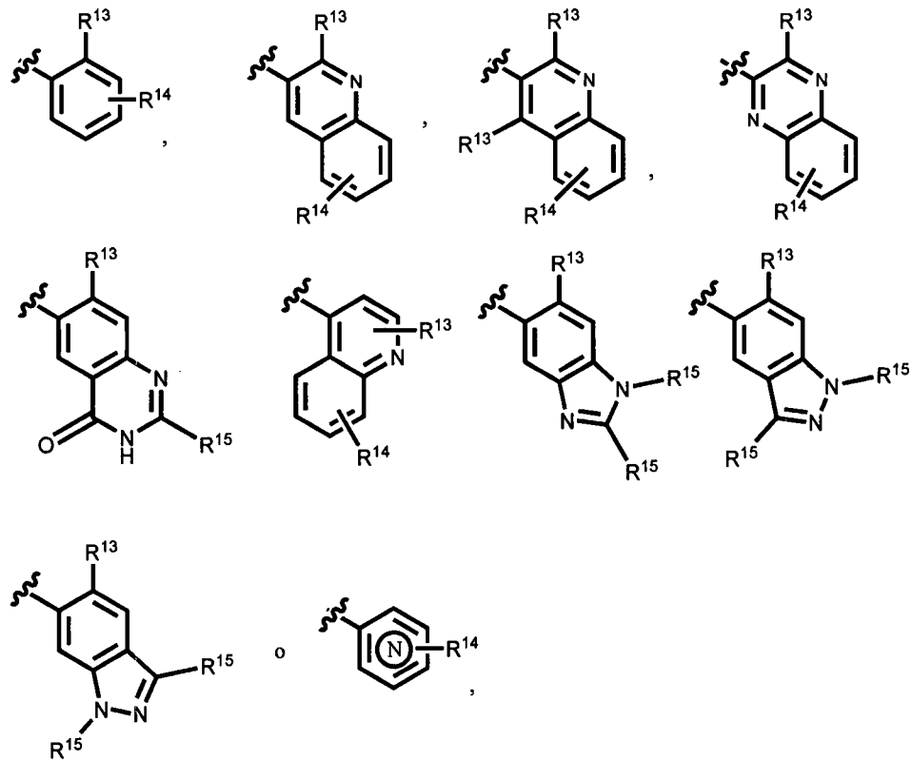
en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y R^{11} es metilo, etilo, ciclopropilo o fenilo.

En otra realización, R^1 es -CH_2– o  ; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es



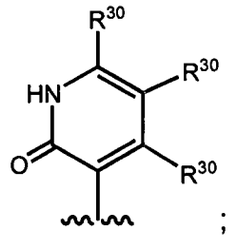
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R^9 es H, metilo o etilo; R^{10} es



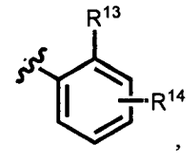
en los cuales R^{11} es metilo, etilo o fenilo; R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es -CH_2– o  ; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es

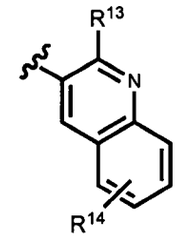


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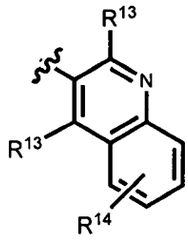
R^9 es H, metilo o etilo; R^{10} es



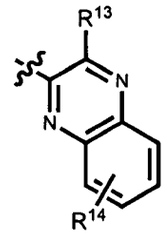
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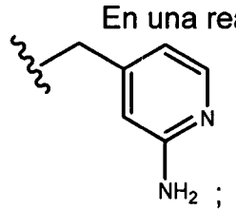
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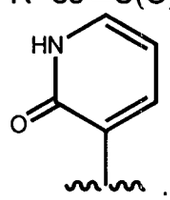
en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y R^{11} es metilo, etilo o fenilo.

En una realización, R^1–R^{10} es



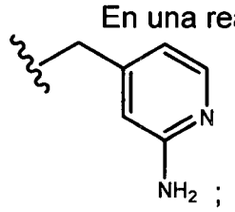
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R^2 es –$C(O)NHSO_2R^{11}$; y R^3 es



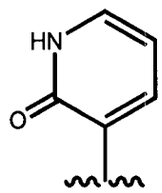
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En una realización, R^1–R^{10} es

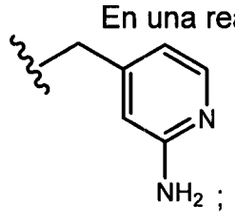


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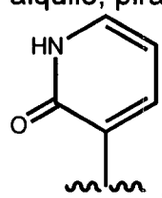
R^2 es –$C(O)NHSO_2CH_3$; y R^3 es



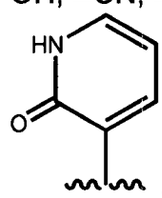
En una realización, R^1–R^{10} es



R^2 es –C(O)NHSO$_2$R^{11}, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –[C(R^{12})$_2$]$_q$–C(O)O–alquilo, –OH, –NHSO$_2$–alquilo, –[C(R^{12})$_2$]$_q$–SO$_2$–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –NHSO$_2$–fenilo, –NHSO$_2$–ciclopropilo, –NHSO$_2$–alquilo, –[C(R^{12})$_2$]$_q$–NHC(O)–alquilo, pirazolilo o –OCH$_2$C(O)NH_2; y R^3 es

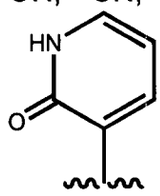


En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –NHSO$_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –[C(R^{12})$_2$]$_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –C(O)NH_2 o –[C(R^{12})$_2$]$_q$–NH_2; R^2 es –C(O)NHSO$_2$R^{11}; y R^3 es

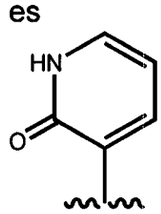


En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –NHSO$_2$–alquilo,

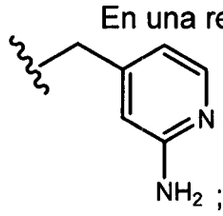
haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2CH_3$; y R^3 es



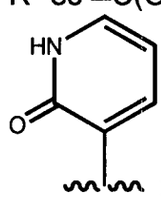
En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$; y R^3 es



En una realización, R^1–R^{10} es

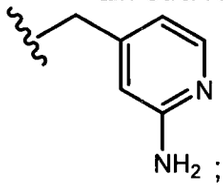


R^2 es –$C(O)NHSO_2R^{11}$; R^3 es

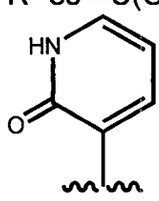


R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es

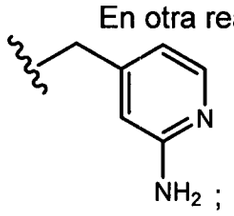


R^2 es –C(O)NHSO$_2$CH$_3$; R^3 es

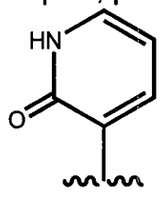


R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es



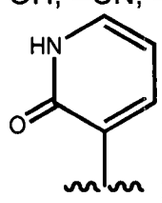
R^2 es –C(O)NHSO$_2$R^{11}, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH$_2$, –NO$_2$, metoxi, –SO$_2$NH$_2$, –COOH, –[C(R^{12})$_2$]$_q$–C(O)O–alquilo, –OH, –NHSO$_2$–alquilo, –[C(R^{12})$_2$]$_q$–SO$_2$–alquilo, –CF$_3$, –CN, tiazolilo, –C(O)NH–alquilo, –NHSO$_2$–fenilo, –NHSO$_2$–ciclopropilo, –NHSO$_2$–alquilo, –[C(R^{12})$_2$]$_q$–NHC(O)–alquilo, pirazolilo o –OCH$_2$C(O)NH$_2$; R^3 es



R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH$_2$, –NHSO$_2$–alquilo,

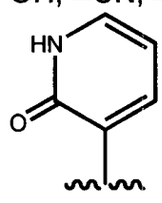
haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$; R^3 es



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R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

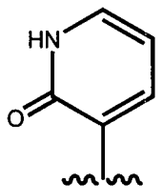
En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2CH_3$; R^3 es



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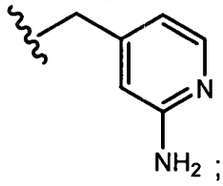
R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$; R^3 es

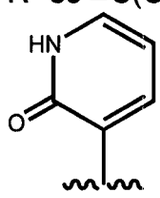


R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En una realización, R^1–R^{10} es

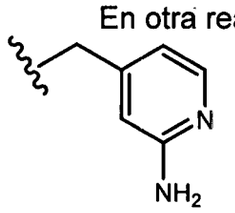


R^2 es –C(O)NHSO$_2$R^{11}; R^3 es

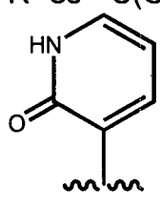


R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es

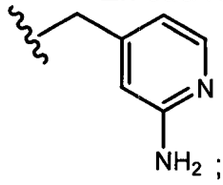


R^2 es –C(O)NHSO$_2$CH$_3$; R^3 es

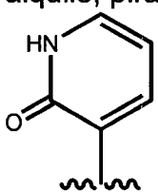


R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es



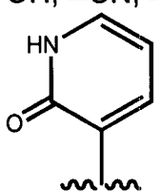
R^2 es $-C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, $-COOH$, $-[C(R^{12})_2]_q-C(O)O-$alquilo, $-OH$, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, $-CN$, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$; R^3 es



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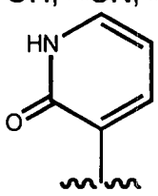
R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En una realización, R^1-R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2-$alquilo, haloalquilo, metoxi, $-O-$haloalquilo, $-[C(R^{12})_2]_q-NHC(O)NH-$alquilo, alquilo, $-OH$, $-CN$, $-C(O)NH_2$ o $-[C(R^{12})_2]_q-NH_2$; R^2 es $-C(O)NHSO_2R^{11}$; R^3 es



R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

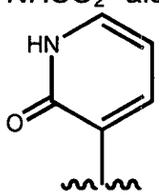
En otra realización, R^1-R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2-$alquilo, haloalquilo, metoxi, $-O-$haloalquilo, $-[C(R^{12})_2]_q-NHC(O)NH-$alquilo, alquilo, $-OH$, $-CN$, $-C(O)NH_2$ o $-[C(R^{12})_2]_q-NH_2$; R^2 es $-C(O)NHSO_2CH_3$; R^3 es



;

R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

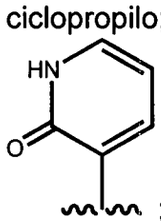
En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$; R^3 es



;

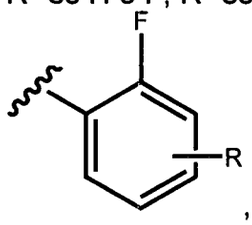
R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En una realización, R^1 es -CH_2–; R^2 es -$C(O)NHSO_2CH_3$ o –$C(O)NHSO_2$–ciclopropilo; R^3 es



;

R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; R^7 es H; y –R^{10} es:



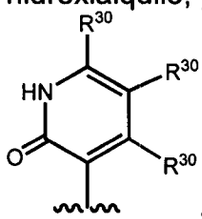
,

donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, –CF_3, –CN, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)OH, –NH_2, –SO_2–alquilo, –

SO_2NH–alquilo, –S–alquilo, $–CH_2NH_2$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

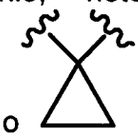
En una realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

En otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^3 es :



.

En otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^1 es $-[C(R^{12})_2]_r–$.

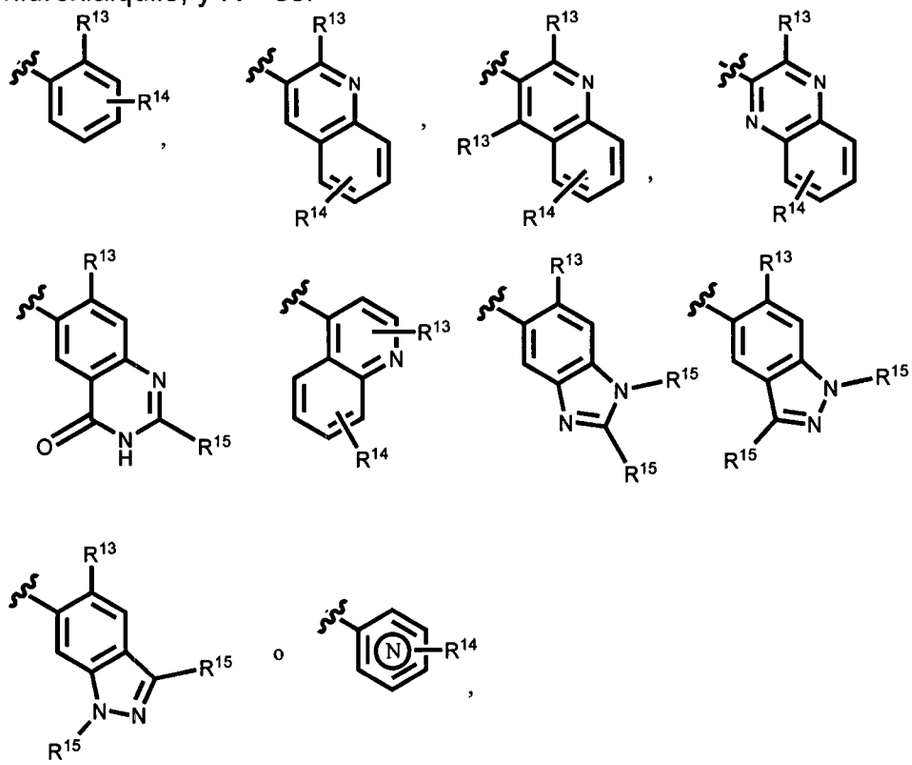
Incluso en otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^1 es $-CH_2–$, $–CH_2CH_2–$, $–CH(CH_3)–$ o  .

En otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y en los cuales R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH, R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo,

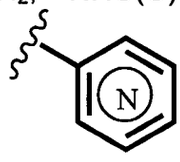
halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN, y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN.

Además en otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^{10} es arilo o heteroarilo.

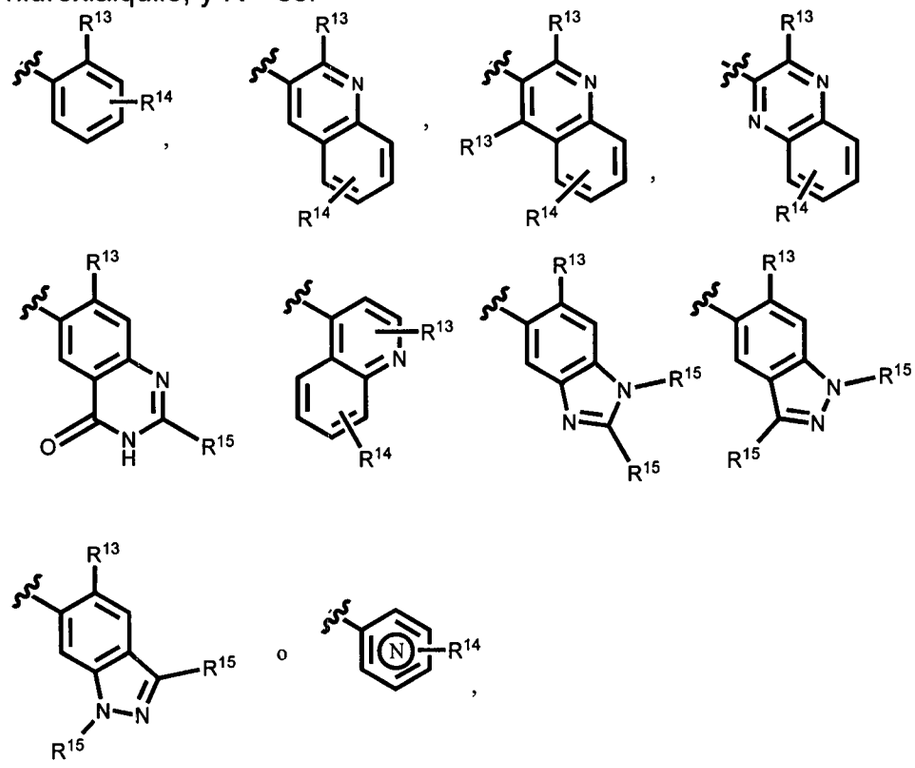
Además en otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^{10} es:



en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –

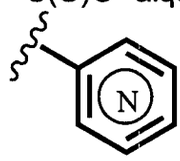
C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

En otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^{10} es:



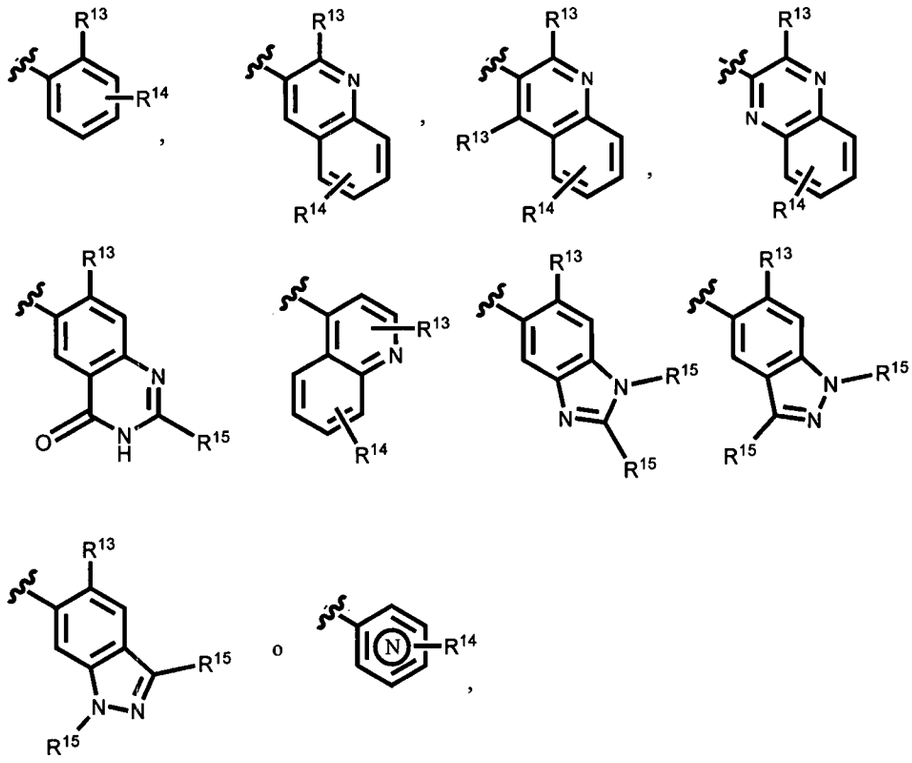
en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo,

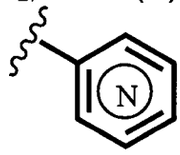
cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y



representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

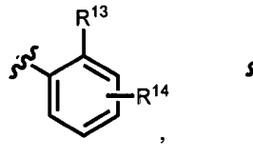
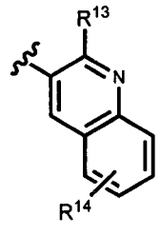
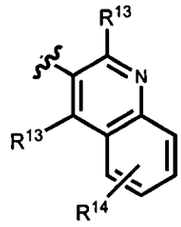
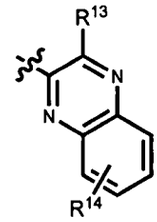
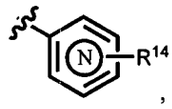
En otra realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^{10} es:

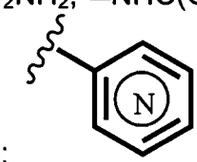


en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo;  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos; y R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–

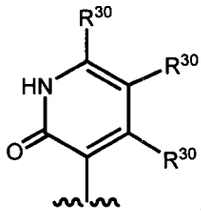
alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN.

Además en otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^{10} es:


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o

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en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,$–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo;  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos; y R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN.

En una realización, R^1 es -[$C(R^{12})_2$]–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^3 es :

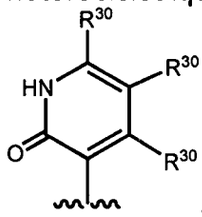


.

En otra realización, R^1 es -CH_2–, –CH_2CH_2–, –$CH(CH_3)$– o

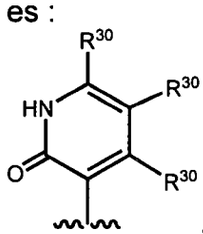


; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^3 es :



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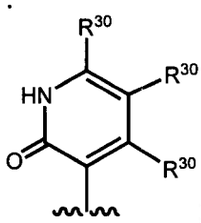
En otra realización, R^1 es -CH_2–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^3 es :



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Incluso en otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —$C(O)NHSO_2R^{11}$ o —$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, —alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, —alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es

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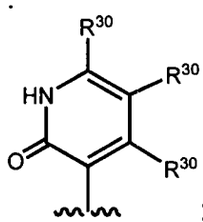


;

R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, $—NH_2$ o –CN; y R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, $—NH_2$ o –CN.

En otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —$C(O)NHSO_2R^{11}$ o —$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, —alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, —alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es

:



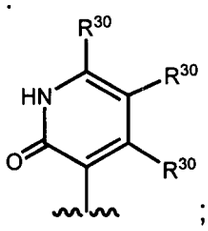
;

R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, $—NH_2$ o –CN; R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, $—NH_2$ o –CN; y R^{10} es arilo o heteroarilo.

Además en otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —$C(O)NHSO_2R^{11}$ o —$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, —alquil-$N(alquil)_2$, arilo,

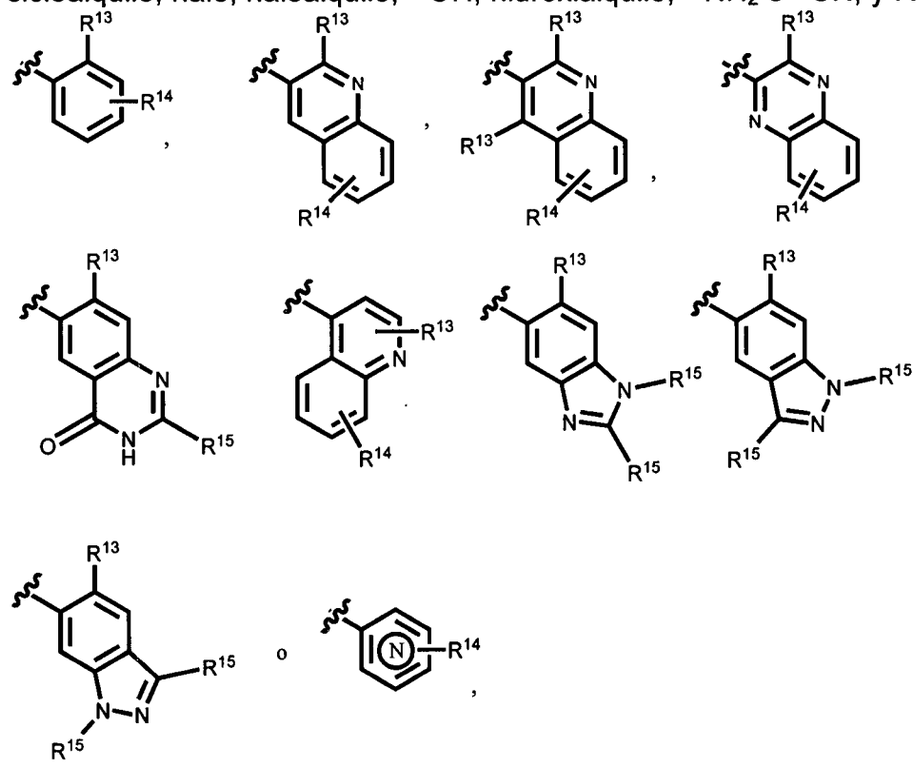
cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-N(alquil)$_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es

:

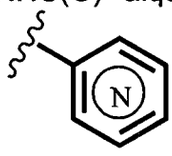


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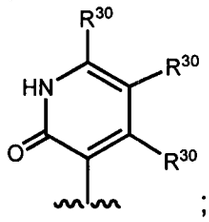
R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^{10} es:



en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –C(O)NH_2, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–

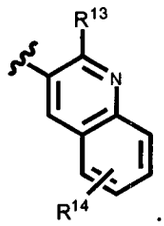
alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

En otra realización, R^1 es -$[C(R^{12})_2]_r$–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es :



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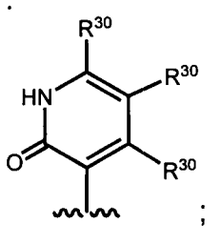
R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^{10} es:



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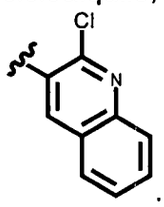
En una realización adicional, R^1 es -$[C(R^{12})_2]_r$–; R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo,

cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-N(alquil)$_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es :



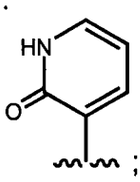
;

R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^{10} es:



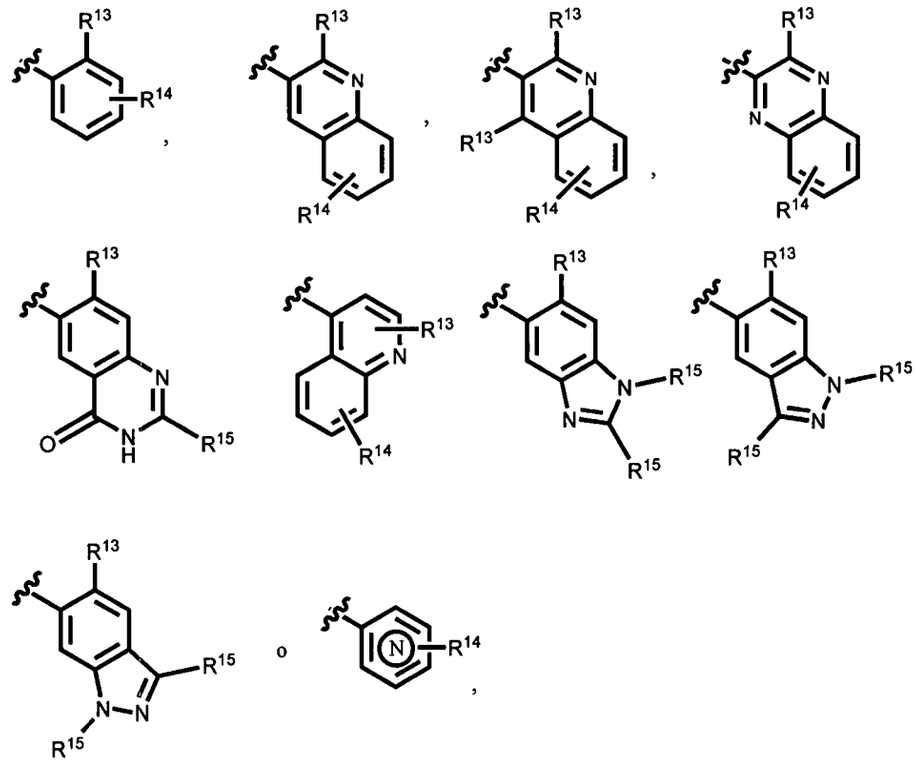
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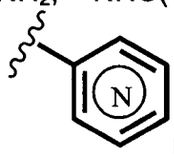
En otra realización, R^1 es -[C(R^{12})$_2$]$_r$–; R^2 es –C(O)NHSO$_2$$R^{11}$ o –C(O)NHSO$_2$N(R^9)$_2$, en los cuales R^9 es H, alquilo, –alquil-N(alquil)$_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-N(alquil)$_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^3 es :



;

R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^{10} es:

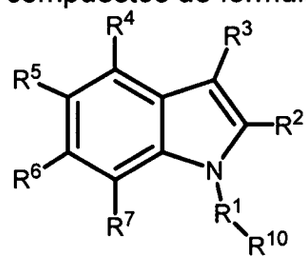


en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

En una realización, para los compuestos de fórmula (I), las variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 y R^{10} se seleccionan en forma independiente entre sí.

En otra realización, los compuestos de fórmula (I) están en forma purificada.

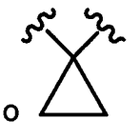
En una realización, los compuestos de fórmula (I) tienen la fórmula (Ia):



(Ia)

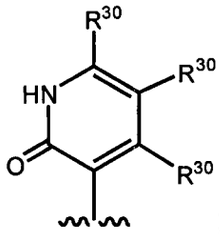
o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico,

en los cuales:

R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  ;

R^2 es $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alquil)SO_2R^{11}$ o $-C(O)N(alquil)SO_2N(R^9)_2$;

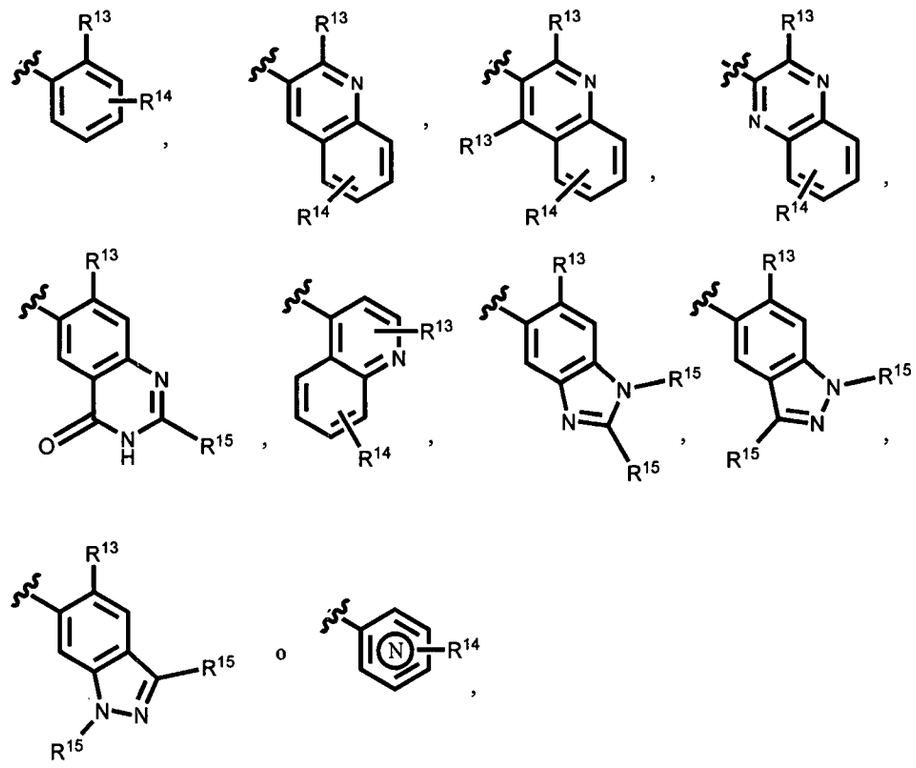
R^3 es:

 ;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, H, alquilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$heterocicloalquilo, haloalquilo, halo, $-OH$, $-OR^9$ o $-N(R^9)_2$;

cada vez que ocurre R^9 es en forma independiente H, alquilo, –alquil-$N(alquil)_2$, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo;

R^{10} es:



de manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, –alquil-N(alquil)$_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo;

cada vez que ocurre R^{12} es en forma independiente H, halo, –N(alquil)$_2$, –OH, –O–alquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R_{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

R^{13} es H, F, Br o Cl;

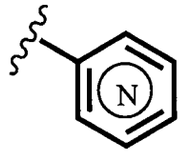
R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo;

cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo;

cada vez que ocurre R^{30} es en forma independiente, H, halo, –$N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4;

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4; y



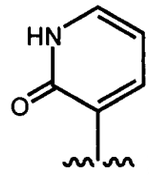
representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

En una realización, para los compuestos de fórmula (Ia),

R^1 es -CH_2–;

R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$;

R^3 es:



;

R^4, R^5, R^6 y R^7 son cada uno en forma independiente H, alquilo, haloalquilo o halo;

cada vez que ocurre R^9 es en forma independiente H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo; y

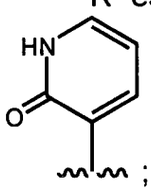
cada vez que ocurre R^{11} es en forma independiente alquilo, arilo o cicloalquilo.

En otra realización, para los compuestos de fórmula (Ia),

R^1 es $-CH_2-$;

R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$;

R^3 es:

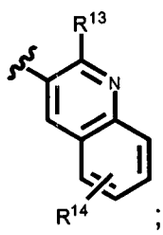


;

R^4, R^5, R^6 y R^7 son cada uno en forma independiente H, alquilo, o halo;

cada vez que ocurre R^9 es en forma independiente H, alquilo o cicloalquilo;

R^{10} es:



; y

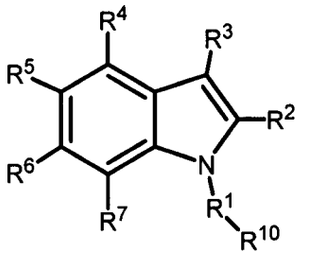
cada vez que ocurre R^{11} es en forma independiente alquilo, arilo o cicloalquilo.

En una realización, para los compuestos de fórmula (Ia), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 y R^{10} se seleccionan en forma independiente entre sí.

En otra realización, los compuestos de fórmula (Ia) están en forma purificada.

Los derivados indólicos 2,3 sustituidos de Fórmula (II)

La presente invención provee, además, derivados indólicos 2,3 sustituidos que tienen la fórmula:



(II)

y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico, en los cuales R^1, R^2, R^4, R^5, R^6, R^7 y R^{10} se definió con anterioridad para los compuestos de fórmula (II).

En una realización, R^1 es un enlace.

En otra realización, R^1 es $-[C(R^{12})_2]_r-$.

En otra realización, R^1 es $-[C(R^{12})_2]_r-O-[C(R^{12})_2]_q-$.

Incluso en otra realización, R^1 es $-[C(R^{12})_2]_r-N(R^9)-[C(R^{12})_2]_q-$.

Además en otra realización, R^1 es $-[C(R^{12})_2]_q-CH=CH-[C(R^{12})_2]_q-$.

En otra realización, R^1 es $-[C(R^{12})_2]_q-C\equiv C-[C(R^{12})_2]_q-$.

En una realización adicional, R^1 es $-[C(R^{12})_2]_q-SO_2-[C(R^{12})_2]_q-$.

En una realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  .

En otra realización, R^1 es $-CH_2-$.

En otra realización, R^1 es  .

En una realización, R^{10} es arilo.

En otra realización, R^{10} es -H.

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

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

Incluso en otra realización, R^{10} es heterocicloalquenilo.

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

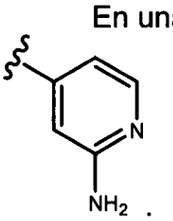
En otra realización, R^{10} es heterocicloalquilo.

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

En otra realización, R^{10} es fenilo, que está sustituido con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2.

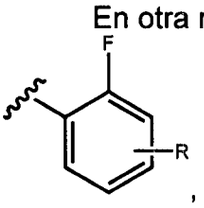
Además en otra realización, R^{10} es piridilo.

En una realización adicional, R^{10} es



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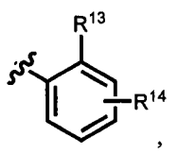
En otra realización, –R^{10} es:



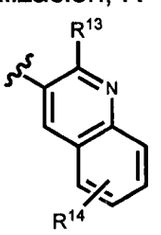
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donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, –CF_3, –CN, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)OH, –NH_2, –SO_2–alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

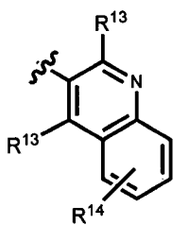
En otra realización, R^{10} es



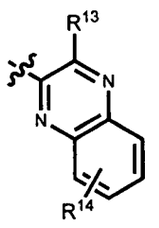
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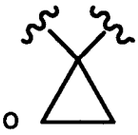
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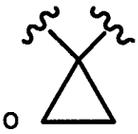


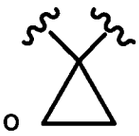
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en los cuales R^{13} es F o Cl y R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–

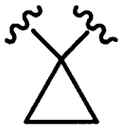
alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, -NHC(O)-alquilo, -C(O)O-alquilo, -C(O)-heterocicloalquilo y heteroarilo.

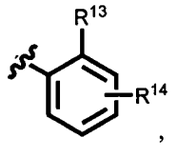
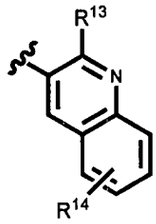
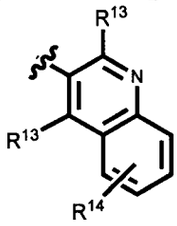
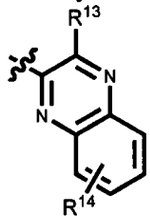
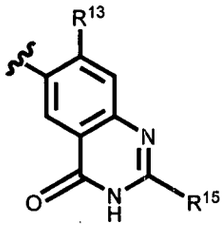
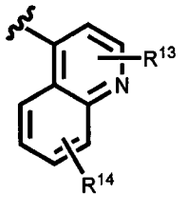
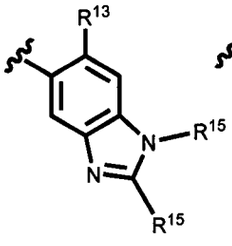
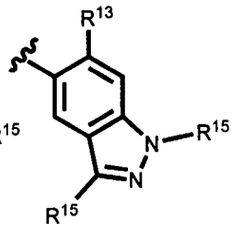
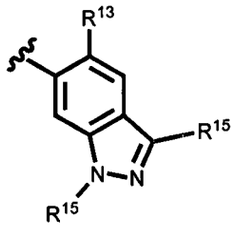
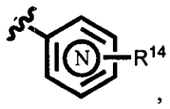
En otra realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  , y R^{10} es arilo o heteroarilo.

En otra realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  , y R^{10} es fenilo.

En otra realización, R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  , y R^{10} es alquilo o cicloalquilo.

En otra realización, R^1 es $-CH_2-$ y R^{10} es arilo o heteroarilo.

Incluso en otra realización, R^1 es $-CH_2-$ o  y R^{10} es

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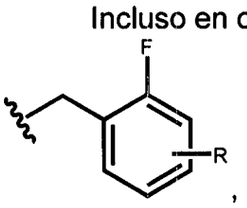
o
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en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En una realización, $–R^1–R^{10}$ es bencilo.

En otra realización, $–R^1–R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con desde 1–4 grupos seleccionados en forma independiente de: halo, $–NH_2$, $–NHSO_2–$alquilo, haloalquilo, metoxi, –O–haloalquilo, $–[C(R^{12})_2]_q–$NHC(O)NH–alquilo, alquilo, –OH, –CN, $–C(O)NH_2$ o $–[C(R^{12})_2]_q–NH_2$.

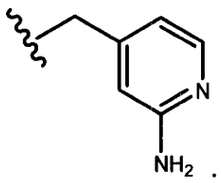
Incluso en otra realización, $–R^1–R^{10}$ es



,

donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, $–CF_3$, –CN, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)OH, $–NH_2$, $–SO_2–$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En otra realización, $–R^1–R^{10}$ es



Incluso en otra realización, $-R^1-R^{10}$ es alquilo.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con 1 o 2 átomos de flúor.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con 1 o 2 grupos metilo.

Además en otra realización, $-R^1-R^{10}$ es $-R^1-R^{10}$ es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido con un átomo de flúor y un grupo metilo.

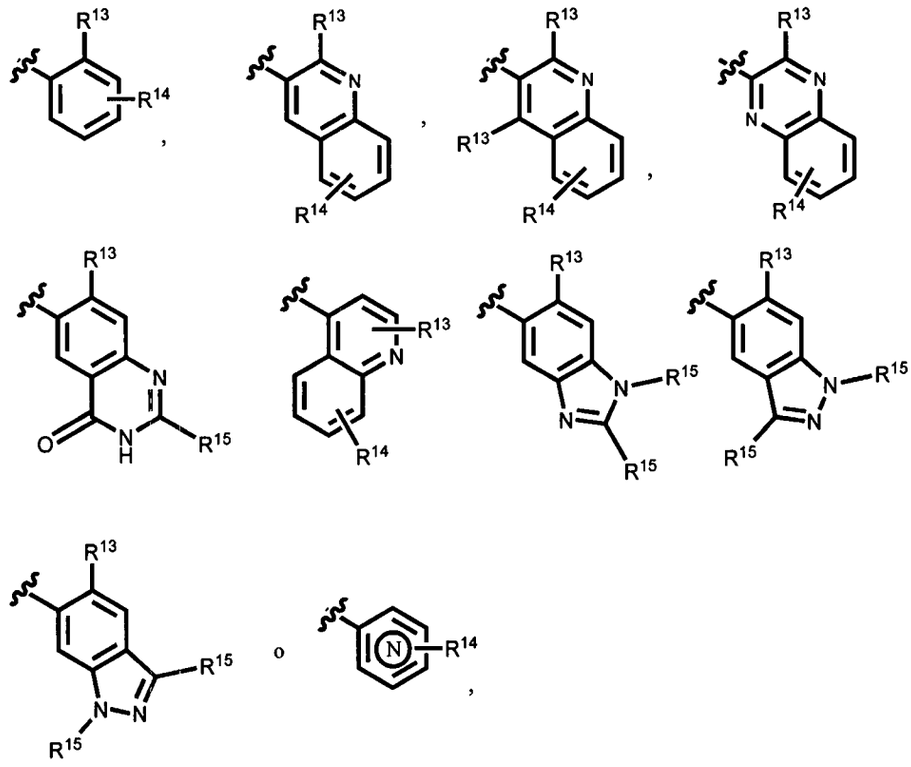
En otra realización, $-R^1-R^{10}$ es haloalquilo.

En una realización adicional, $-R^1-R^{10}$ es $-CH_2-$cicloalquilo.

En otra realización, $-R^1-R^{10}$ es distinto de H.

En otra realización, R^1 es $-CH_2-$ y R^{10} es alquilo o cicloalquilo.

En otra realización, R^1 es $-CH_2-$ y R^{10} es



en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

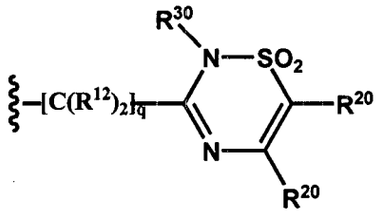
En una realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$.

En otra realización, R^2 es -$[C(R^{12})_2]_q$–$C(O)N(R^9)SO_2R^{11}$.

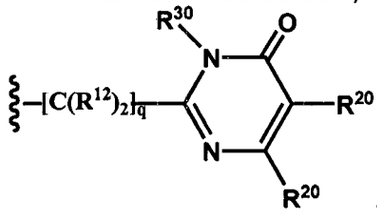
En otra realización, R^2 es -$[C(R^{12})_2]_q$–$C(O)N(R^9)SOR^{11}$.

Incluso en otra realización, R^2 es -$[C(R^{12})_2]_q$–$C(O)N(R^9)SO_2N(R^{11})_2$.

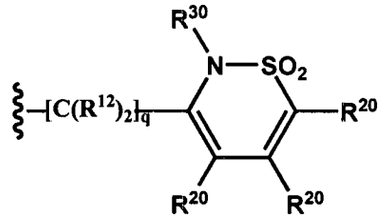
En otra realización, R^2 es



En otra realización, R^2 es



Además en otra realización, R^2 es



En otra realización, R^2 es $-C(O)N(R^9)SO_2R^{11}$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$alquilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$arilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$cicloalquilo.

En una realización adicional, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$heteroarilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$haloalquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$hidroxialquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es alquilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es arilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es cicloalquilo.

En una realización adicional, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es heteroarilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es haloalquilo.

Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es hidroxialquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-$fenilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es bencilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es naftilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-NH_2$ o $-N(CH_3)_2$.

En otra realización, R^2 es $-C(O)NHSO_2CH_3$.

En otra realización, R^2 es $-C(O)NHSO_2CH_2CH_3$.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$, y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

En una realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es alquilo, cicloalquilo o arilo.

En una realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, alquilo o cicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es metilo, etilo, isopropilo, ciclopropilo o fenilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H, metilo, etilo o ciclopropilo.

Además en otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es $-[C(R^{12})_2]_q-O-$alquilo o $-[C(R^{12})_2]_q-N(alquil)_2$.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es $-(CH_2)_2-N(CH_3)_2$ o $-(CH_2)_3-N(CH_3)_2$.

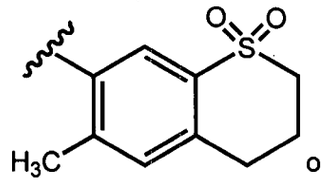
Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es ciclopropilo.

En otra realización, R^2 es $-C(O)NHSO_2N(R^9)_2$ y R^9 es H o metilo.

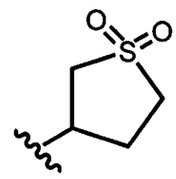
Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, $-COOH$, $-[C(R^{12})_2]_q-C(O)O-$alquilo, $-OH$, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, $-CN$, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es $-[C(R^{12})_2]_q-NHSO_2-$alquilo, $-[C(R^{12})_2]-O-$alquilo, o $-[C(R^{12})_2]-$alquilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es imidazolilo, piridilo, tienilo, furanilo, benzofuranilo, benzo[1,3]dioxolilo, tetrahidropiranilo,

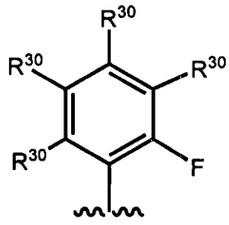


o

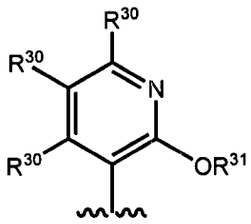


Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ y R^{11} es ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

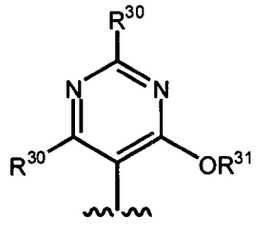
En una realización, R^3 es



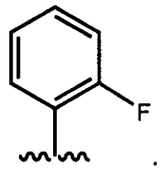
En otra realización, R^3 es



En otra realización, R^3 es



En otra realización, R^3 es



En una realización, R^4 es H.

En otra realización, R^4 es H o F.

En otra realización, R^4 es F.

En otra realización, R^5 es H.

En otra realización, R^5 es distinto de H.

Además en otra realización, R^6 es H.

En otra realización, R^6 es distinto de H.

En otra realización, R^6 es H o F.

En una realización adicional, R^6 es F.

En una realización, R^9 es H y R^{11} es metilo o etilo.

En otra realización, R^9 es H y R^{11} es ciclopropilo.

Incluso en otra realización, R^7 es H.

En otra realización, R^4 y R^7 son cada uno en forma independiente H, halo o hidroxi.

En otra realización, R^4 y R^7 son cada uno en forma independiente H, F o hidroxi.

En otra realización, R^4 y R^7 son cada uno H.

Además en otra realización, R^4, R^6 y R^7 son cada uno H.

En otra realización, R^4, R^5, R^6 y R^7 son cada uno H.

En una realización adicional, R^4, R^6 y R^7 son cada uno H y R^5 es distinto de H.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es alquilo.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es halo.

En otra realización, R^4, R^6 y R^7 son cada uno H y R^5 es metilo.

En una realización adicional, R^4, R^6 y R^7 son cada uno H y R^5 es Cl.

En otra realización, R^4 y R^7 son cada uno H y R^5 y R^6 son distintos de H.

En otra realización, R^5 es distinto de H.

Incluso en otra realización, R^5 es alquilo.

Además en otra realización, R^5 es halo.

Incluso en otra realización, R^5 es metilo.

En otra realización, R^5 es etilo.

En otra realización, R^6 es H.

En otra realización, R^6 es distinto de H.

En una realización adicional, R^6 es alquilo.

Además en otra realización, R^6 es halo.

Incluso en otra realización, R^6 es metilo.

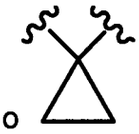
En otra realización, R^6 es F.

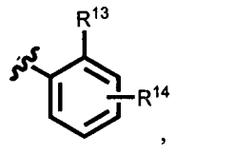
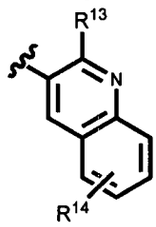
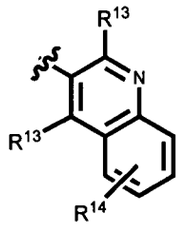
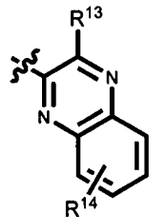
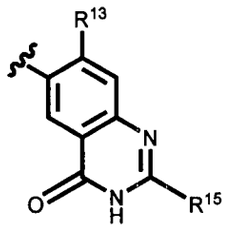
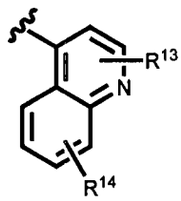
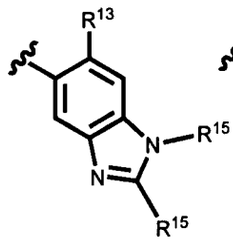
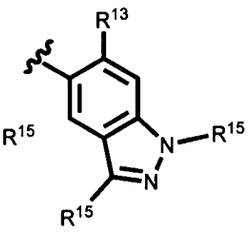
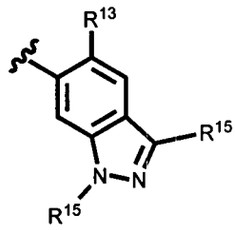
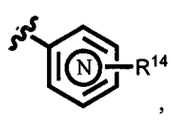
En una realización, R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2$–alquilo,

haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; y R^2 es –$C(O)NHSO_2R^{11}$.

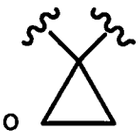
En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; y R^2 es –$C(O)NHSO_2CH_3$.

En otra realización, R^1 es -CH_2–, –CH_2CH_2–, –$CH(CH_3)$— o  ; R^2 es –$C(O)N(R^9)SO_2R^{11}$; y R^{10} es:

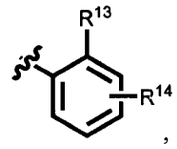
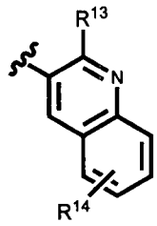
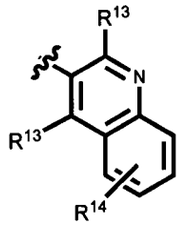
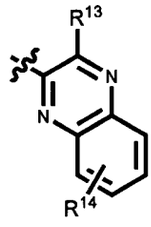
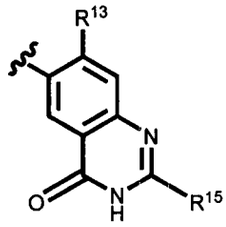
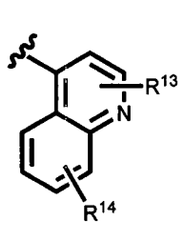
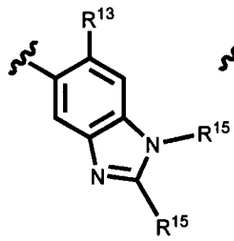
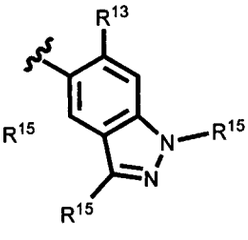
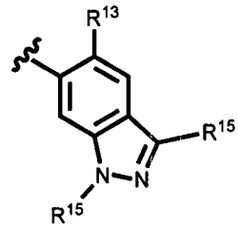
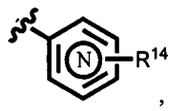

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en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –

C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

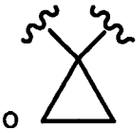
En otra realización, R^1 es $-CH_2–$, $–CH_2CH_2–$, $–CH(CH_3)–$ o  ; R^2 es $–C(O)N(R^9)SO_2R^{11}$; R^5 es alquilo, cicloalquilo, halo o –OH; R^6 es H, halo o –OH; y

R^{10} es:

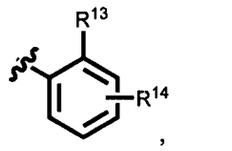
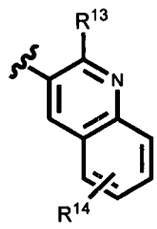
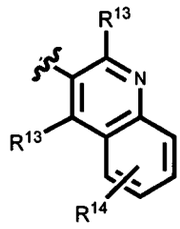
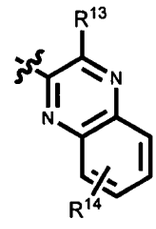
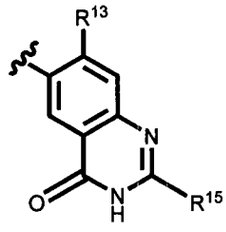
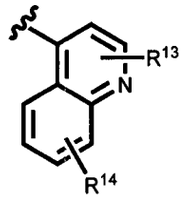
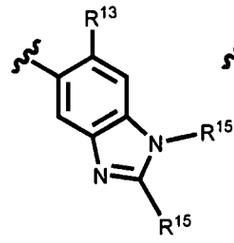
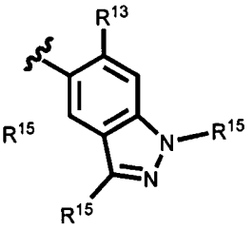
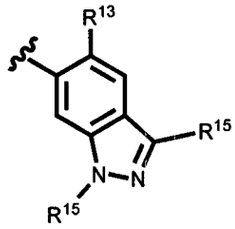
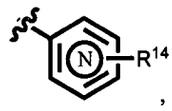

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en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –

C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

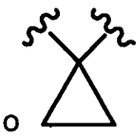
En otra realización, R^1 es $-CH_2–$, $–CH_2CH_2–$, $–CH(CH_3)–$ o  ; R^2 es $–C(O)N(R^9)SO_2R^{11}$; R^5 es metilo o etilo; R^6 es H, F o Cl; y

R^{10} es:

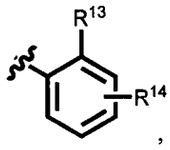
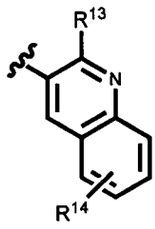
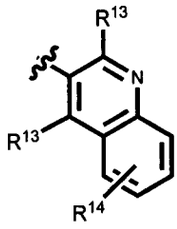
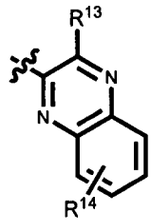
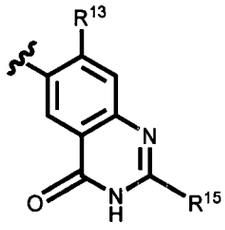
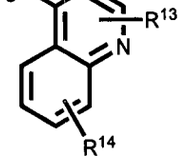
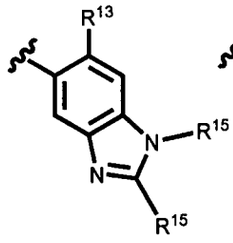
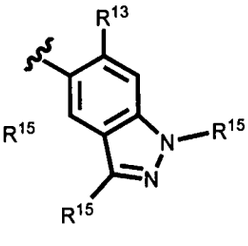
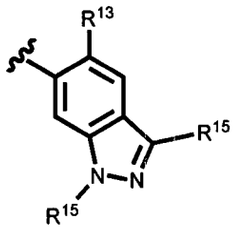
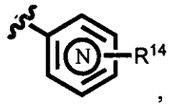

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en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma

independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es $-CH_2–$, $–CH_2CH_2–$, $–CH(CH_3)–$ o  ; R^2 es $–C(O)N(R^9)SO_2R^{11}$; R^5 es metilo o etilo; R^6 es H, F o Cl; R^9 es H;

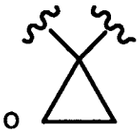
R^{10} es:


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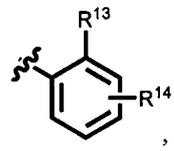
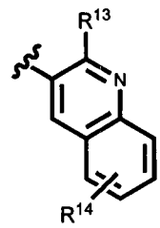
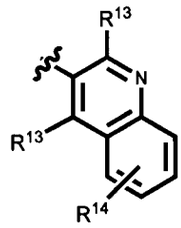
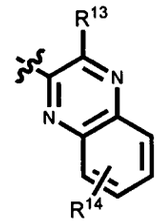
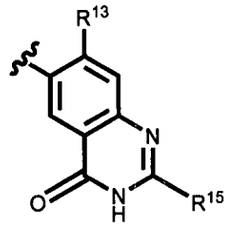
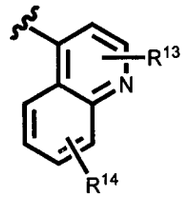
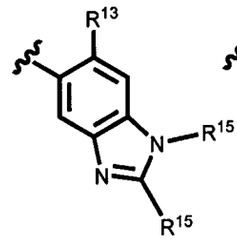
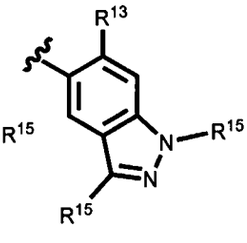
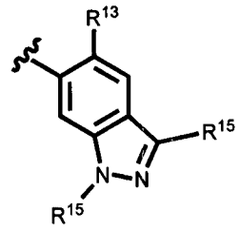
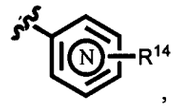
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R^{11} es metilo; R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$

alquilo, –NO_2, –C(O)NH_2, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es -CH_2–, –CH_2CH_2–, –$CH(CH_3)$— o  ; R^2 es –C(O)N(R^9)SO_2R^{11}; R^5 es metilo o etilo; R^6 es H, F o Cl; R^9 es H;

R^{10} es:

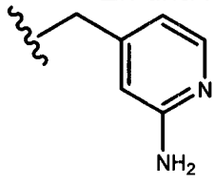

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R^{11} es ciclopropilo; R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –C(O)NH_2, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –C(O)NH_2, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo,

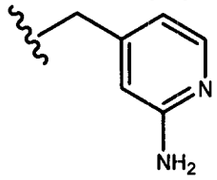
–SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En una realización, R^1–R^{10} es



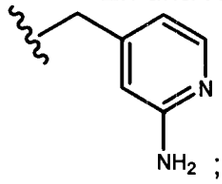
y R^2 es –$C(O)NHSO_2R^1$.

En una realización, R^1–R^{10} es



y R^2 es –$C(O)NHSO_2CH_3$.

En una realización, R^1–R^{10} es



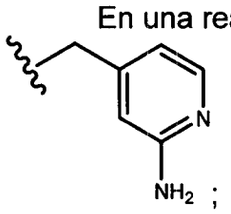
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R^2 es –$C(O)NHSO_2R^{11}$; y R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$.

En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$; y R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma

independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$.

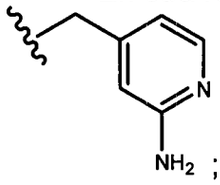
En una realización, R^1–R^{10} es



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R^2 es –$C(O)NHSO_2R^{11}$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

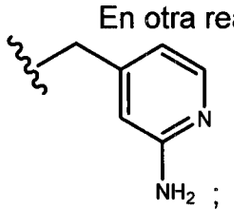
En otra realización, R^1–R^{10} es



;

R^2 es –$C(O)NHSO_2CH_3$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es



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R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)alquilo, pirazolilo o –$OCH_2C(O)NH_2$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

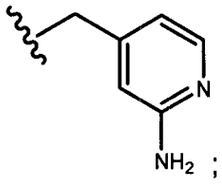
En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo,

haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2CH_3$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$; R^4, R^6 y R^7 son cada uno H; y R^5 es distinto de H.

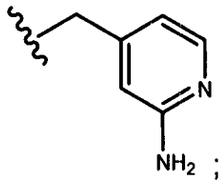
En una realización, R^1–R^{10} es



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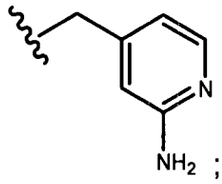
R^2 es –$C(O)NHSO_2R^{11}$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es



R^2 es $-C(O)NHSO_2CH_3$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es



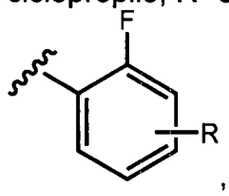
R^2 es $-C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, $-NH_2$, $-NO_2$, metoxi, $-SO_2NH_2$, –COOH, $-[C(R^{12})_2]_q-C(O)O-$alquilo, –OH, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-SO_2-$alquilo, $-CF_3$, –CN, tiazolilo, $-C(O)NH-$alquilo, $-NHSO_2-$fenilo, $-NHSO_2-$ciclopropilo, $-NHSO_2-$alquilo, $-[C(R^{12})_2]_q-NHC(O)-$alquilo, pirazolilo o $-OCH_2C(O)NH_2$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En una realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2-$alquilo, haloalquilo, metoxi, –O–haloalquilo, $-[C(R^{12})_2]_q-NHC(O)NH-$alquilo, alquilo, –OH, –CN, $-C(O)NH_2$ o $-[C(R^{12})_2]_q-NH_2$; R^2 es $-C(O)NHSO_2R^{11}$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, $-NH_2$, $-NHSO_2-$alquilo, haloalquilo, metoxi, –O–haloalquilo, $-[C(R^{12})_2]_q-NHC(O)NH-$alquilo, alquilo, –OH, –CN, $-C(O)NH_2$ o $-[C(R^{12})_2]_q-NH_2$; R^2 es $-C(O)NHSO_2CH_3$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

En otra realización, R^1–R^{10} es bencilo, en los cuales el resto fenilo del grupo bencilo está sustituido en forma opcional con desde 1–4 grupos seleccionados en forma independiente de: halo, –NH_2, –$NHSO_2$–alquilo, haloalquilo, metoxi, –O–haloalquilo, –$[C(R^{12})_2]_q$–NHC(O)NH–alquilo, alquilo, –OH, –CN, –$C(O)NH_2$ o –$[C(R^{12})_2]_q$–NH_2; R^2 es –$C(O)NHSO_2R^{11}$, R^{11} es fenilo, que está sustituido en forma opcional con hasta 3 grupos seleccionados en forma independiente de: alquilo, F, Cl, metilo, –NH_2, –NO_2, metoxi, –SO_2NH_2, –COOH, –$[C(R^{12})_2]_q$–C(O)O–alquilo, –OH, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–SO_2–alquilo, –CF_3, –CN, tiazolilo, –C(O)NH–alquilo, –$NHSO_2$–fenilo, –$NHSO_2$–ciclopropilo, –$NHSO_2$–alquilo, –$[C(R^{12})_2]_q$–NHC(O)–alquilo, pirazolilo o –$OCH_2C(O)NH_2$; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; y R^7 es H.

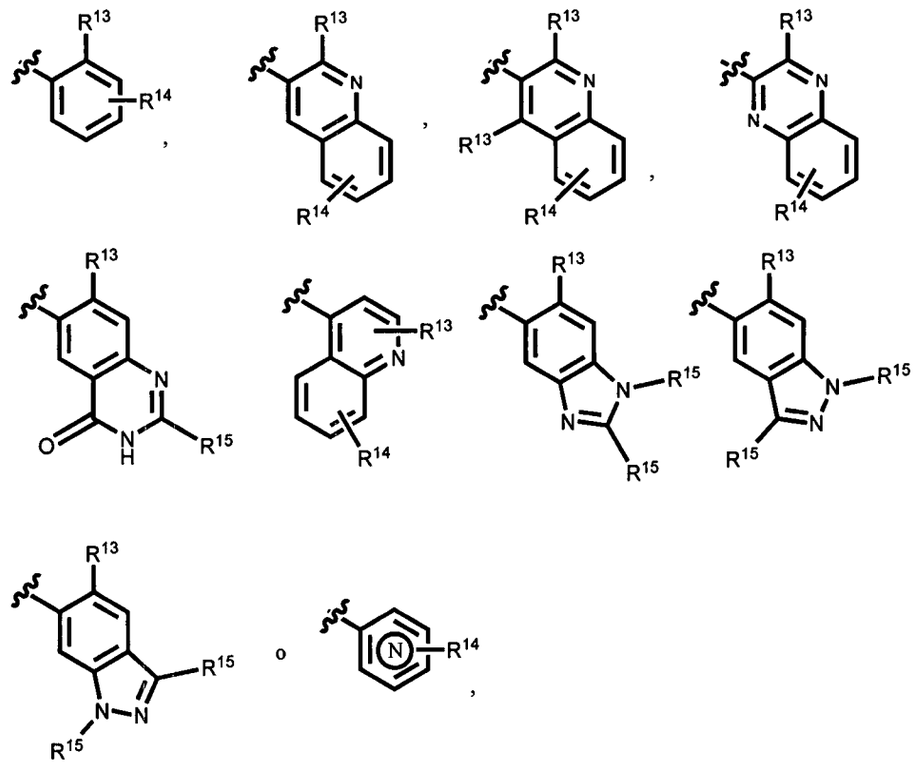
En una realización, R^1 es -CH_2–; R^2 es -$C(O)NHSO_2CH_3$ o –$C(O)NHSO_2$–ciclopropilo; R^4 es H o F; R^5 es metilo o etilo; R^6 es H o F; R^7 es H; y –R^{10} es:



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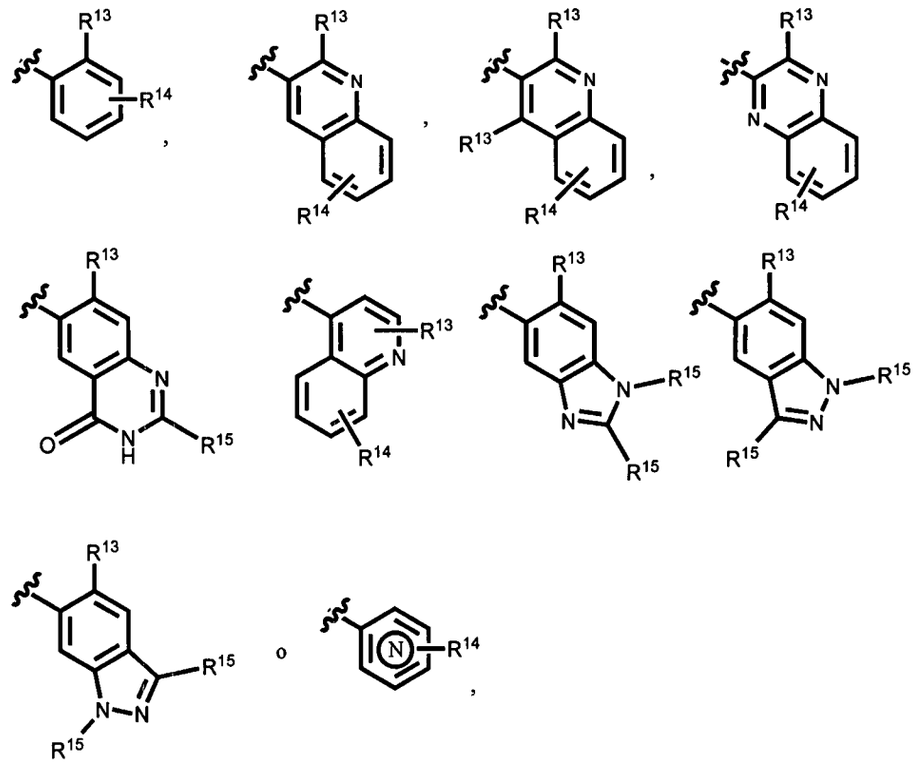
donde R representa hasta 2 sustituyentes fenilo opcionales y adicionales, cada uno seleccionado en forma independiente de halo, –O–alquilo, alquilo, –CF_3, –CN, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)OH, –NH_2, –SO_2–alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo.

En otra realización, R^1 es -CH_2–; R^5 es alquilo, cicloalquilo, halo o –OH; R^6 es H, halo o –OH; y R^{10} es



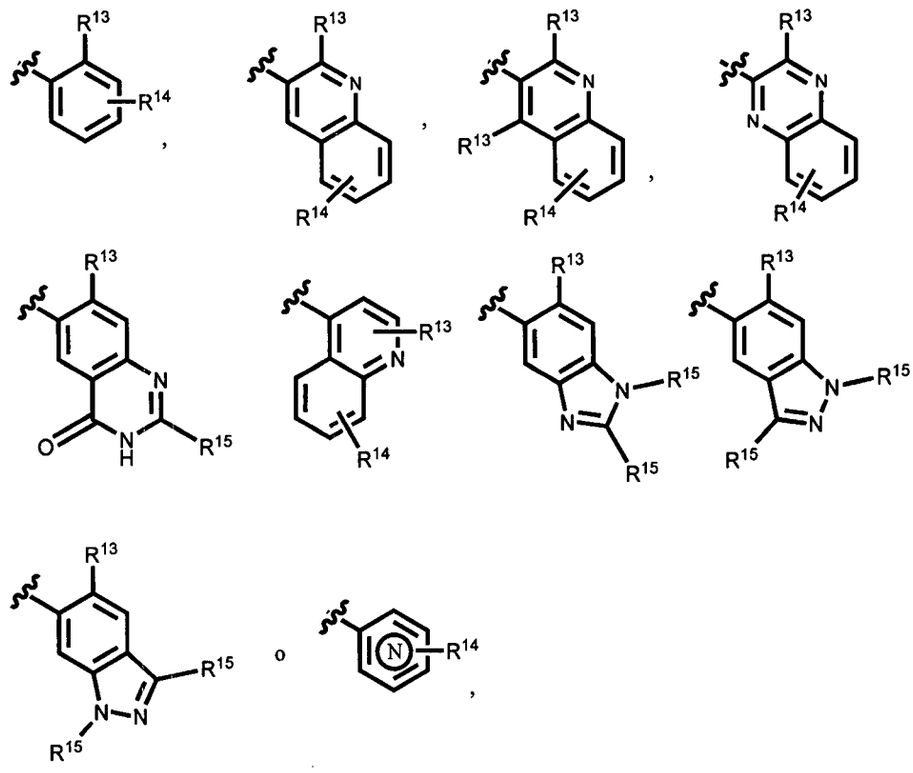
en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

En otra realización, R^1 es -CH_2–; R^5 es metilo o etilo; R^6 es H o F; y R^{10} es



en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $-NHSO_2$–alquilo, $-NO_2$, $-C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $-NH_2$, $-SO_2$alquilo, $-SO_2NH$–alquilo, –S–alquilo, $-CH_2NH_2$, $-CH_2OH$, $-SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

Incluso en otra realización, R^1 es $-CH_2-$; R^9 es H; R^{10} es



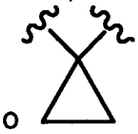
en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

R^{11} es metilo.

En otra realización, R^1 es $-CH_2–$; R^9 es H; R^{10} es

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, $-N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^1 es $-[C(R^{12})_2]_r-$.

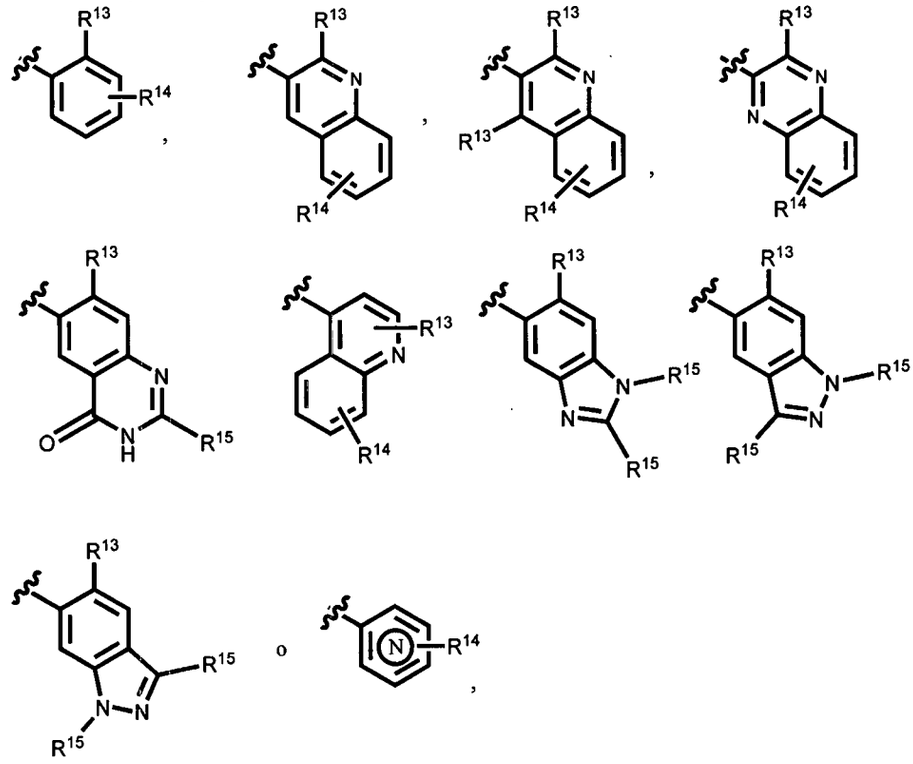
Incluso en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  .

En otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y en los cuales R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH, R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN, y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN.

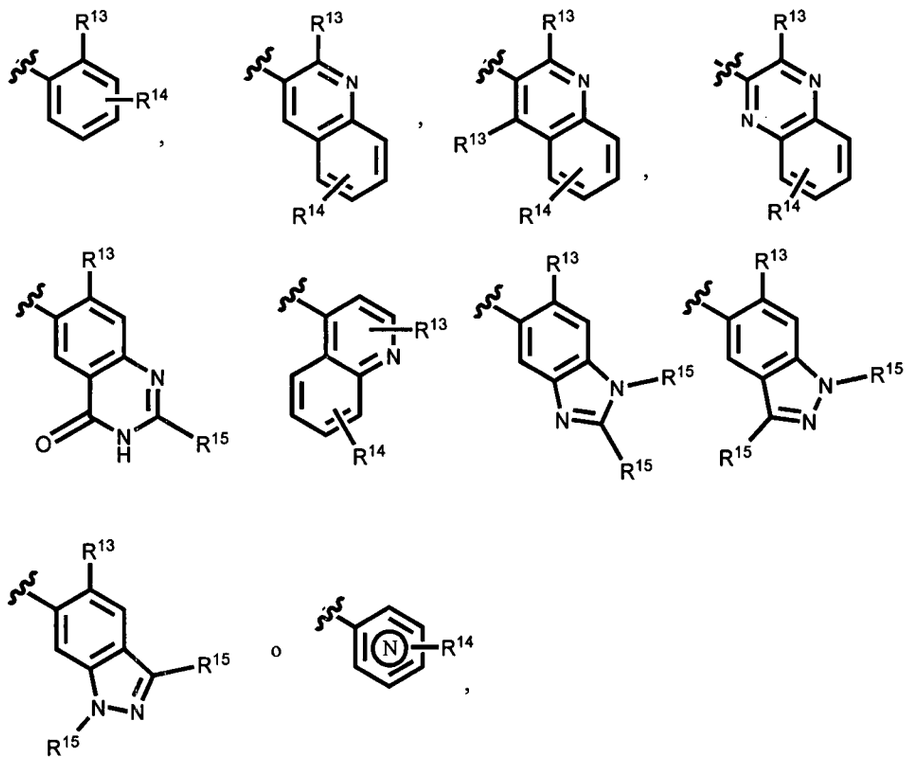
Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y

R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^{10} es arilo o heteroarilo.

Además en otra realización, R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y R^{10} es:



en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo,

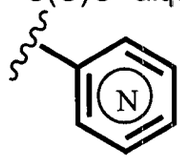


en los cuales R^{13} es F o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo.

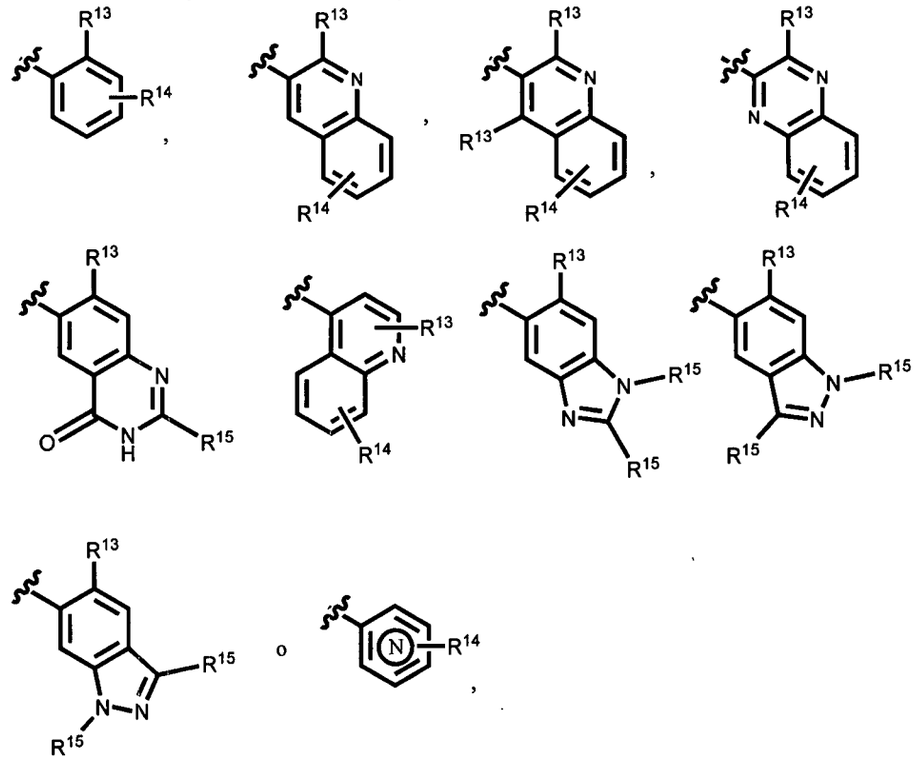
R^{11} es ciclopropilo.

En una realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

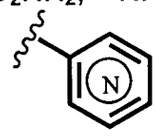
–C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y



representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos. Además en otra realización, R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; R^{10} es:

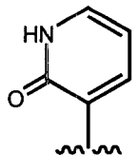


en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en

forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo;  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos; y R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN; y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, –NH_2 o –CN.

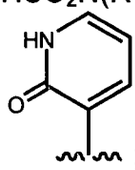
En una realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

En otra realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, –$N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$; R^3 es :  ; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma

independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

Incluso en otra realización, R^1 es -[C(R^{12})$_2$]$_r$–; R^2 es –C(O)NHSO$_2$$R^{11}$ o –C(O)NHSO$_2$N(R^9)$_2$; R^3 es :

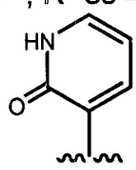


; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En otra realización, R^1 es -CH_2–, –CH_2CH_2–, –CH(CH_3)— o

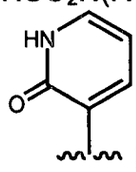


; R^2 es –C(O)NHSO$_2$$R^{11}$ o –C(O)NHSO$_2$N(R^9)$_2$; R^3 es :



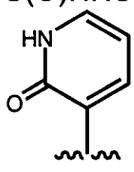
; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

Además en otra realización, R^1 es $-CH_2-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :



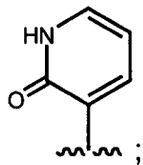
; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, $-N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En una realización adicional, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :



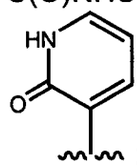
; R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, $-N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

En una realización, R^1 es $-[C(R^{12})_2]_r-$; R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$; R^3 es :

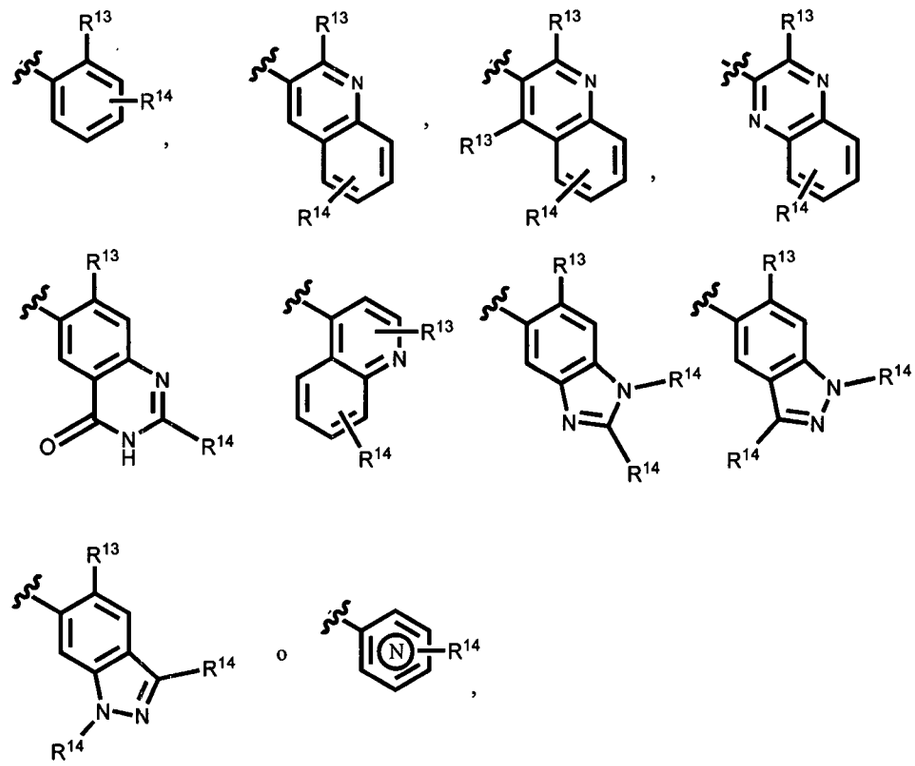


; R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, $–N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo; y R^{10} es arilo o heteroarilo.

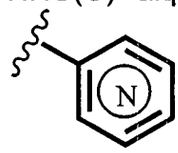
En otra realización, R^1 es $-[C(R^{12})_2]–$; R^2 es $–C(O)NHSO_2R^{11}$ o $–C(O)NHSO_2N(R^9)_2$; R^3 es :



; R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $–NH_2$ o –CN; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, $–N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo; y R^{10} es:

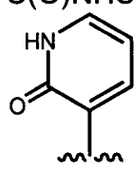


en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2–$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y

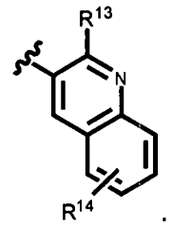


representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

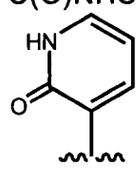
En otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —$C(O)NHSO_2R^{11}$ o —$C(O)NHSO_2N(R^9)_2$; R^3 es :



; R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o –CN; R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o –CN; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre R^{30} es en forma independiente, H, halo, —$N(alquil)_2$, —OH, —O—alquilo, —O—haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo; y R^{10} es:

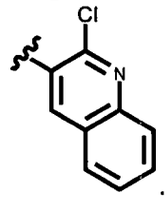


Incluso en otra realización, R^1 es -$[C(R^{12})_2]_r$—; R^2 es —$C(O)NHSO_2R^{11}$ o —$C(O)NHSO_2N(R^9)_2$; R^3 es :



; R^4 y R^7 son cada uno en forma independiente H, halo o –OH; R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o –CN; R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o –CN; R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo; R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo; y cada vez que ocurre

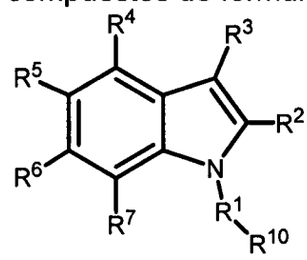
R^{30} es en forma independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo; y R^{10} es:



En una realización, para los compuestos de fórmula (II), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 y R^{10} se seleccionan en forma independiente entre sí.

En otra realización, los compuestos de fórmula (II) están en forma purificada.

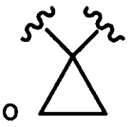
En una realización, los compuestos de fórmula (II) tienen la fórmula (IIa):



(IIa)

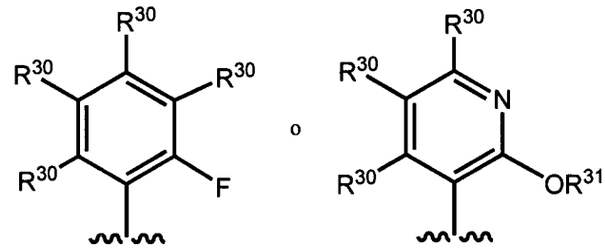
o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico,

en los cuales:

R^1 es -CH_2–, –CH_2CH_2–, –CH(CH_3)— o  ;

R^2 es –C(O)NHSO_2R^{11}, –C(O)NHSO_2N(R^9)$_2$, –C(O)N(alquil)SO_2R^{11} o –C(O)N(alquil)SO_2N(R^9)$_2$;

R^3 es:

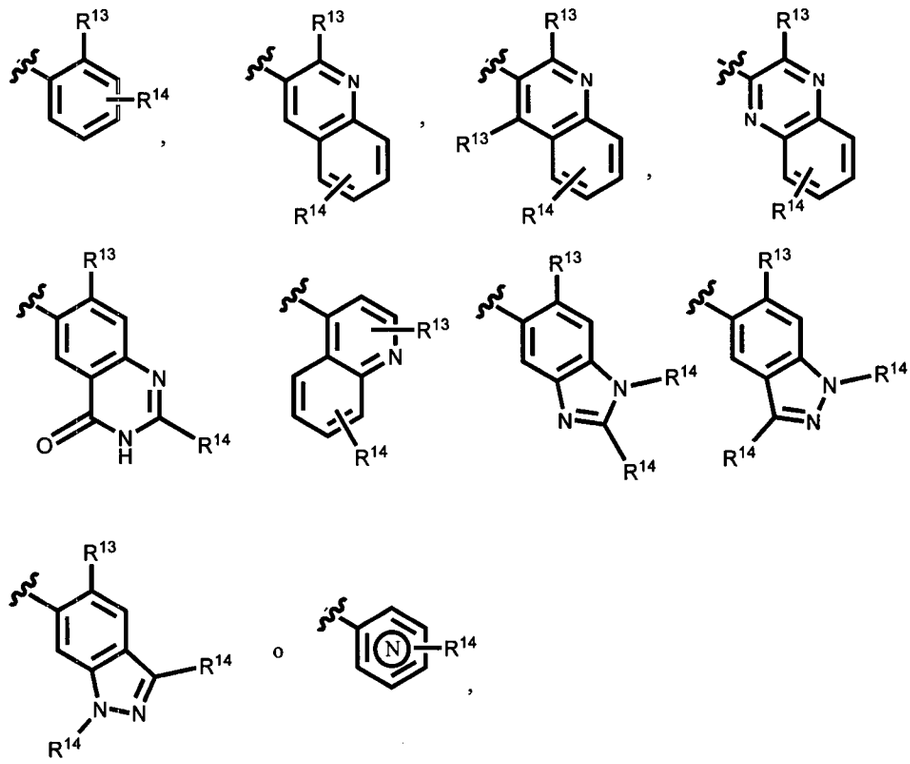


;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo, halo, –OH, –OH, –O–alquilo, –O–haloalquilo, $–NH_2$, –NH–alquilo o $–N(alquil)_2$;

cada vez que ocurre R^9 es en forma independiente H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo;

R^{10} es:



de manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo;

R^{13} es H, F, Br o Cl;

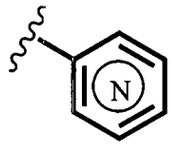
R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo;

cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, $–NHSO_2–$alquilo, $–NO_2$, $–C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, $–NH_2$, $–SO_2$alquilo, $–SO_2NH–$alquilo, –S–alquilo, $–CH_2NH_2$, $–CH_2OH$, $–SO_2NH_2$, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo;

cada vez que ocurre R^{30} es en forma independiente, H, halo, $–N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4;

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4; y

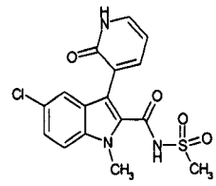
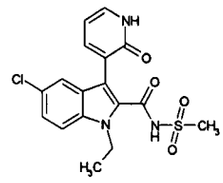
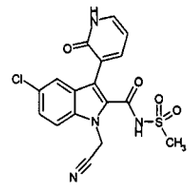
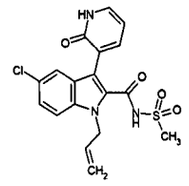
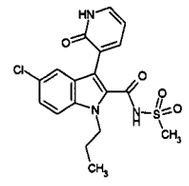


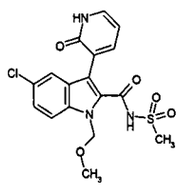
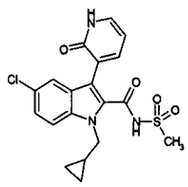
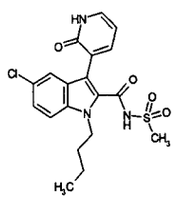
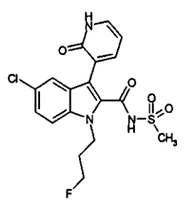
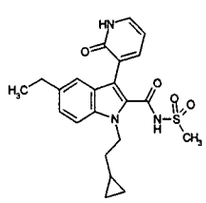
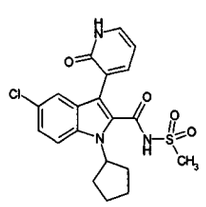
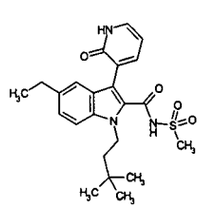
representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

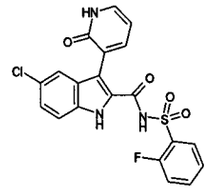
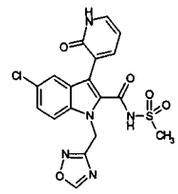
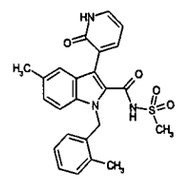
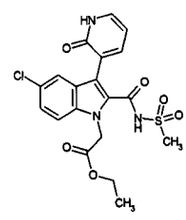
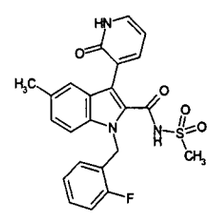
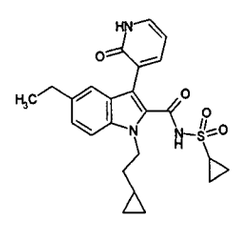
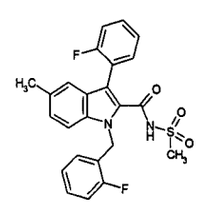
En una realización, para los compuestos de fórmula (IIa), variables R^1, R^2, R^3, R^4, R^5, R^5, R^6, R^7 y R^{10} se seleccionan en forma independiente entre sí.

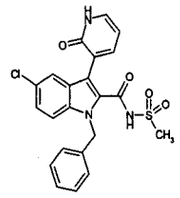
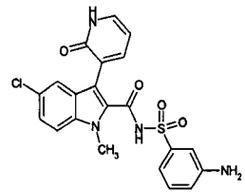
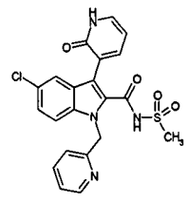
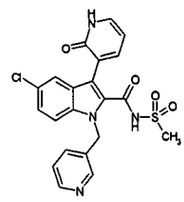
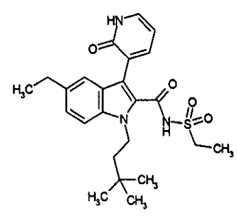
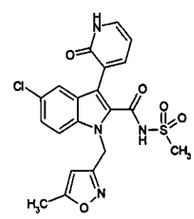
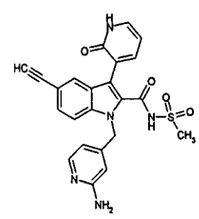
En otra realización, los compuestos de fórmula (IIa) están en forma purificada.

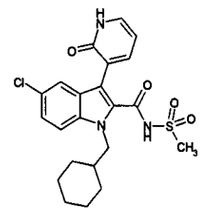
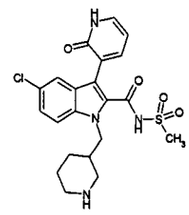
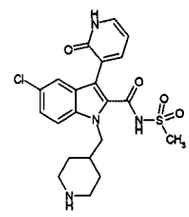
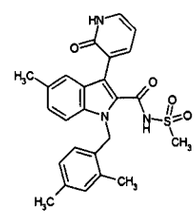
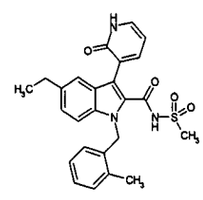
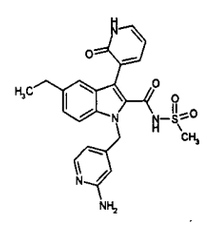
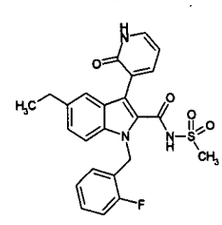
Algunos ejemplos no limitativos de los derivados indólicos 2,3 sustituidos incluyen los compuestos 1–641 como se indica en la siguiente tabla y en la sección Ejemplos más adelante.

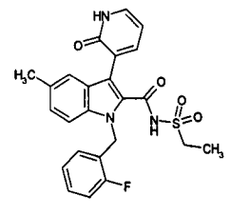
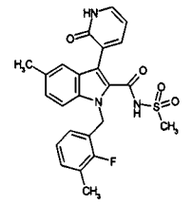
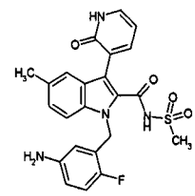
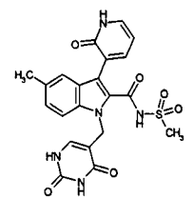
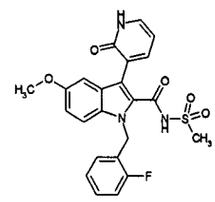
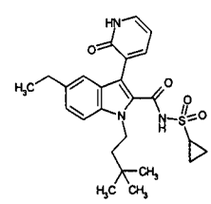
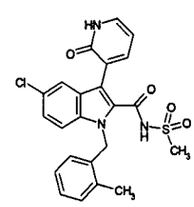
Compuesto No.	ESTRUCTURA	M+H
1		380,8
2		394,9
3		405,8
4		406,9
5		408,9

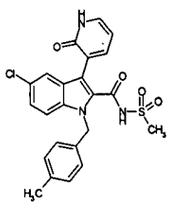
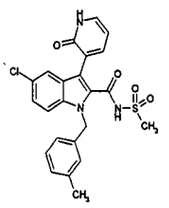
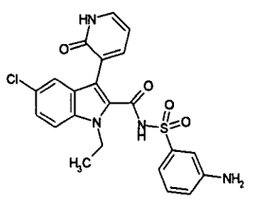
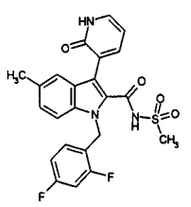
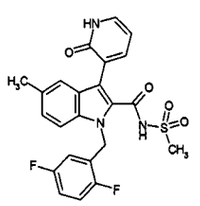
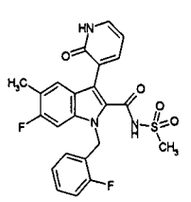
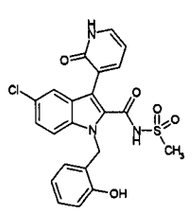
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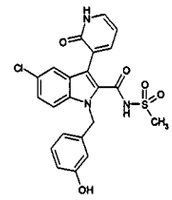
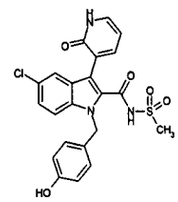
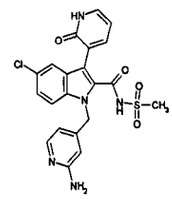
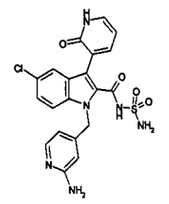
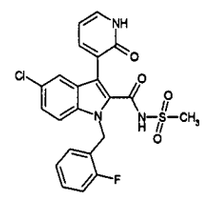
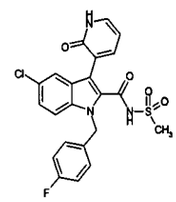
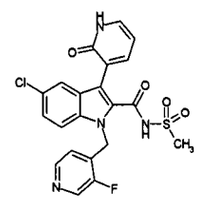
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19		455,5

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26		462,5

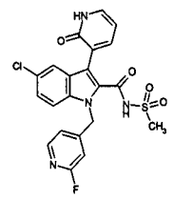
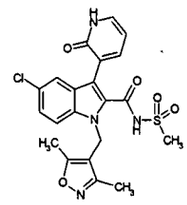
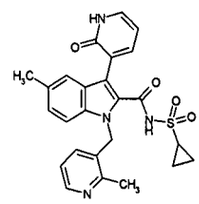
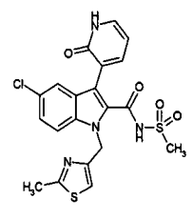
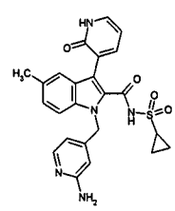
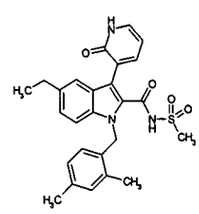
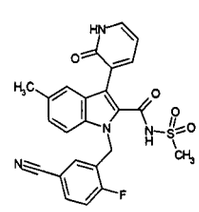
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33		468,5

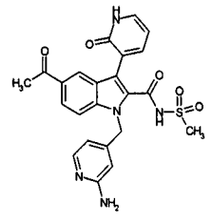
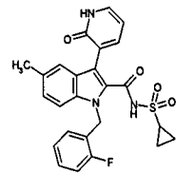
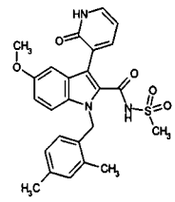
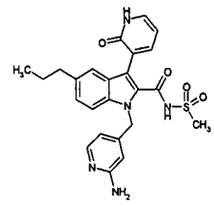
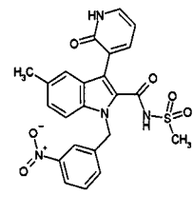
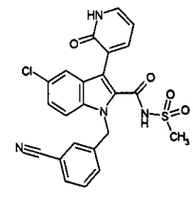
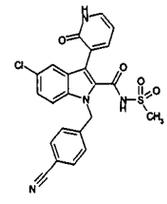
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40		471,0

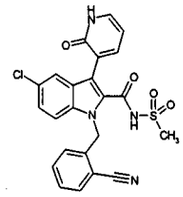
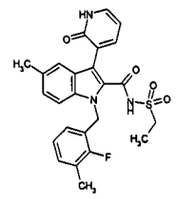
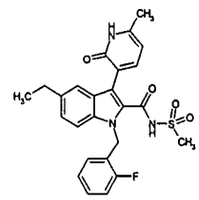
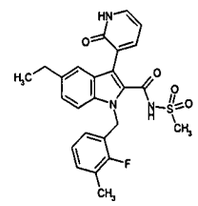
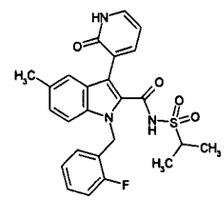
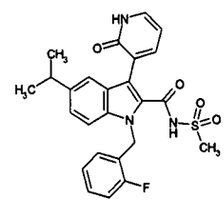
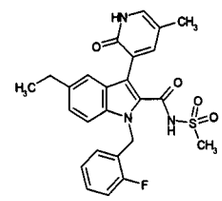
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47		472,9

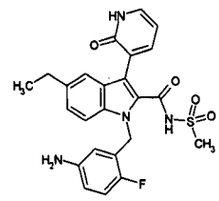
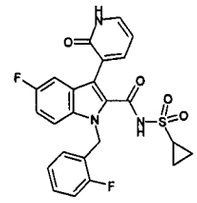
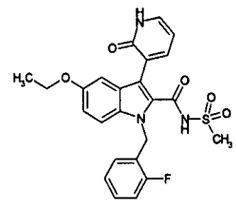
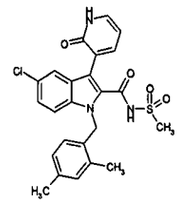
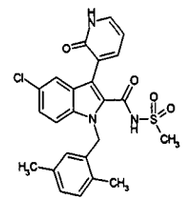
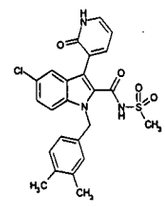
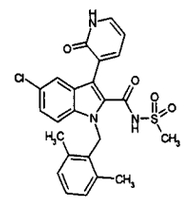
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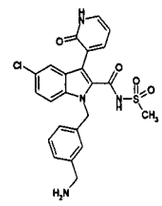
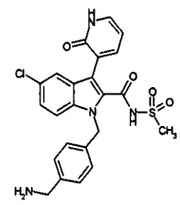
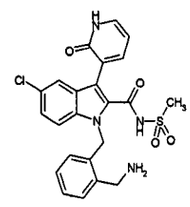
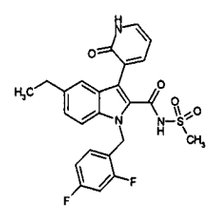
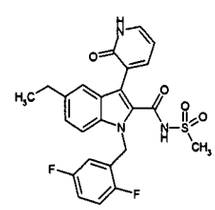
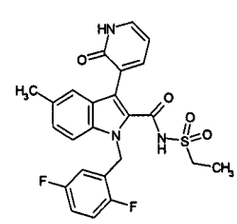
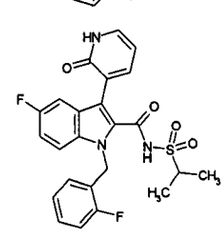
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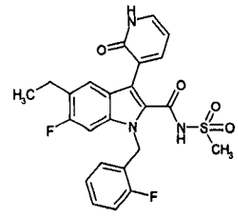
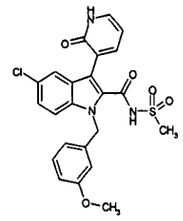
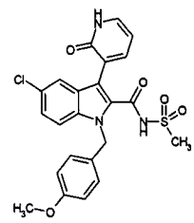
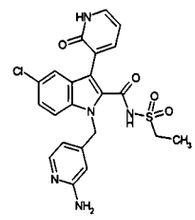
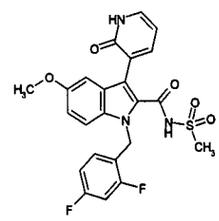
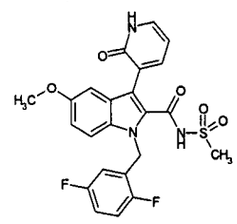
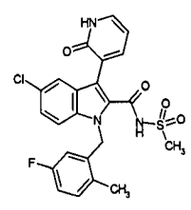
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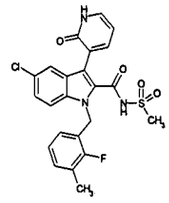
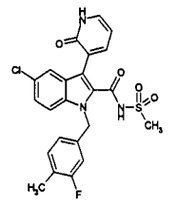
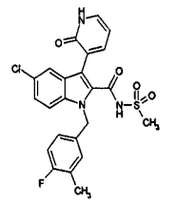
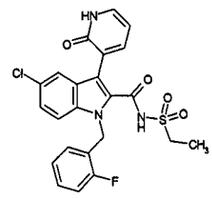
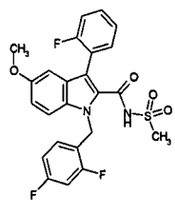
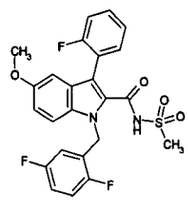
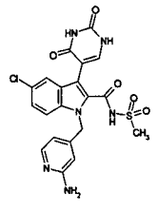
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68		481,9

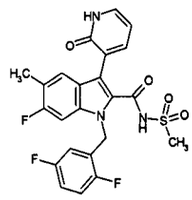
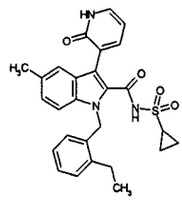
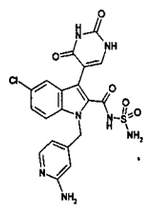
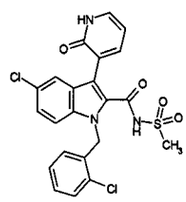
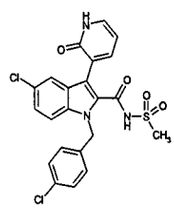
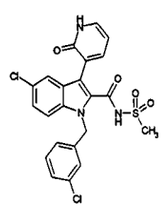
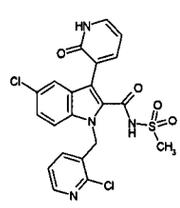
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82		485,0

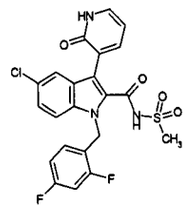
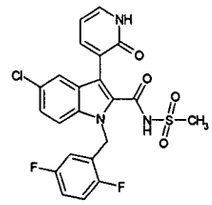
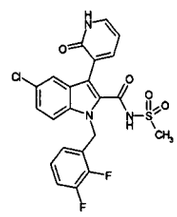
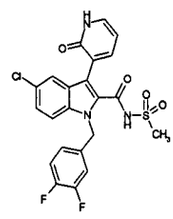
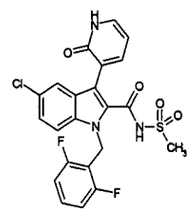
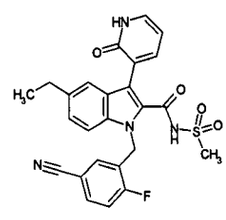
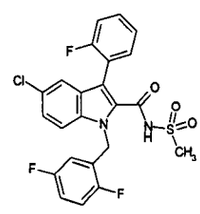
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96		488,9

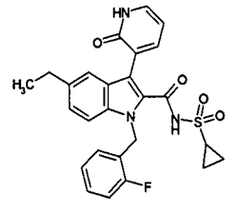
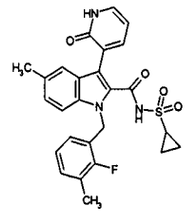
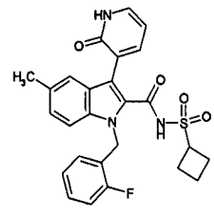
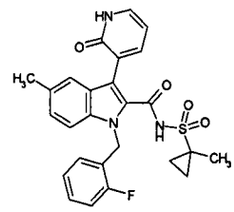
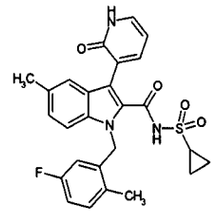
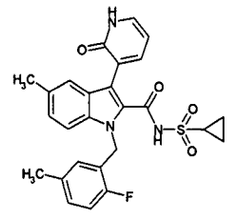
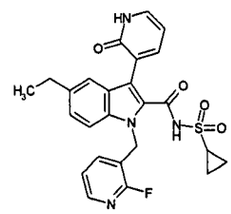
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110		492,4

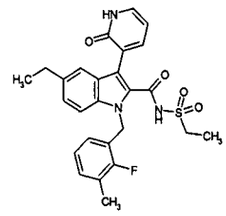
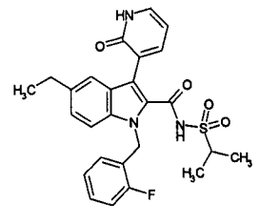
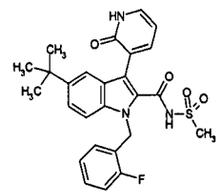
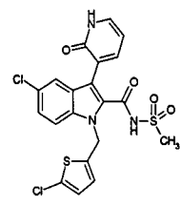
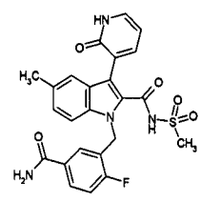
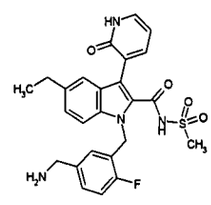
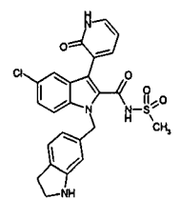
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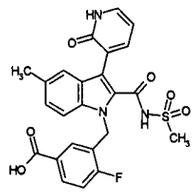
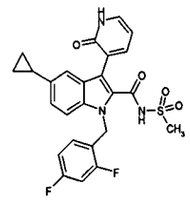
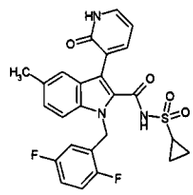
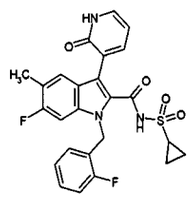
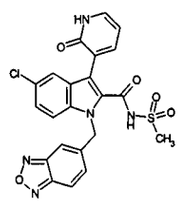
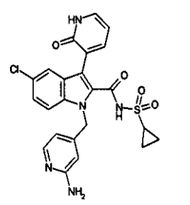
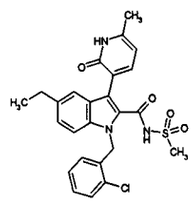
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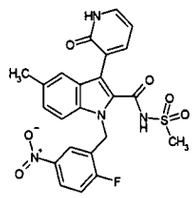
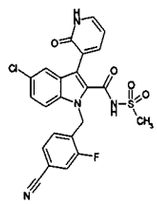
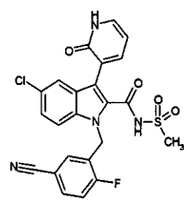
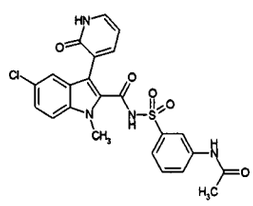
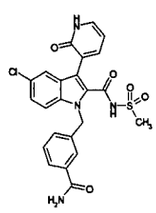
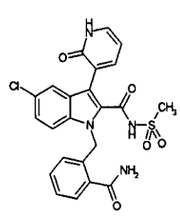
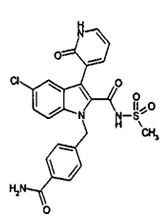
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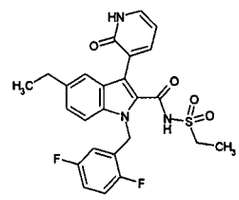
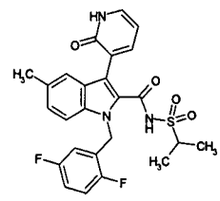
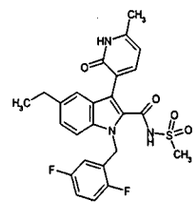
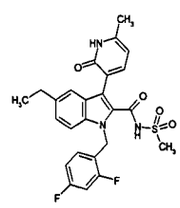
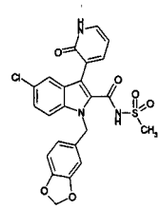
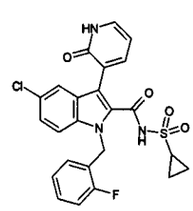
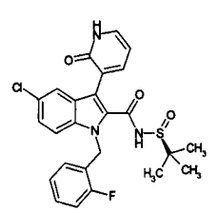
526

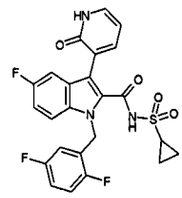
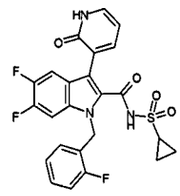
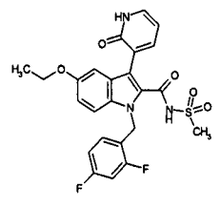
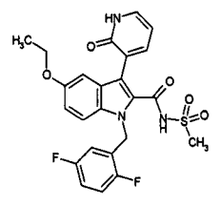
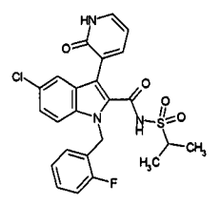
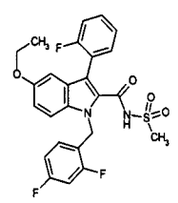
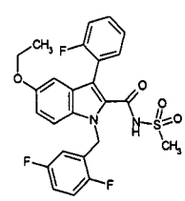
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131		498,0

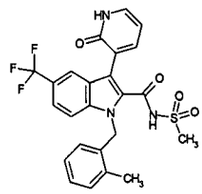
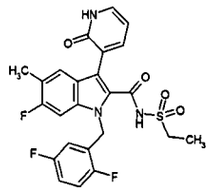
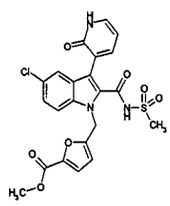
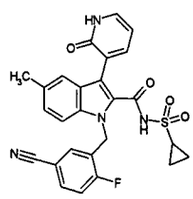
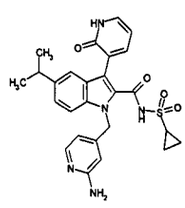
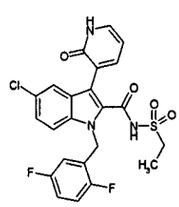
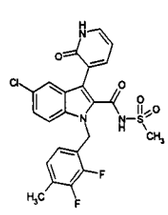
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138		499,0

528

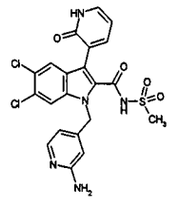
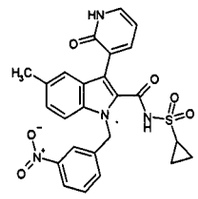
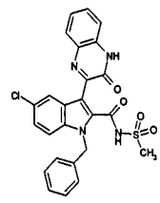
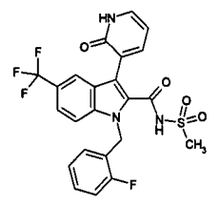
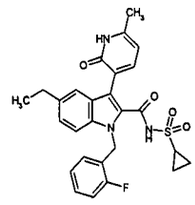
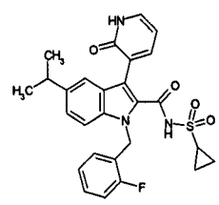
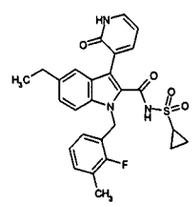
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145		499,9

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152		501,0

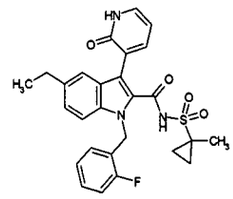
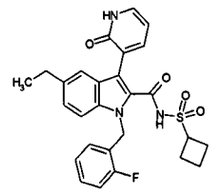
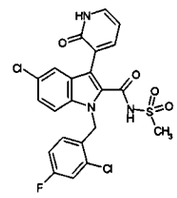
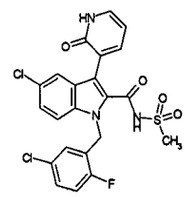
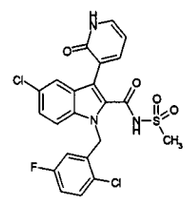
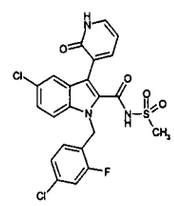
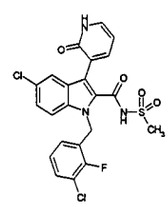
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159		503,5

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163		505,5
164		506,6
165		506,9
166		506,9

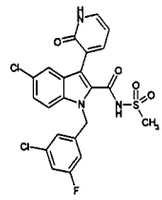
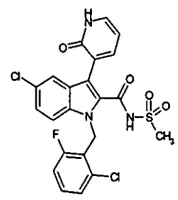
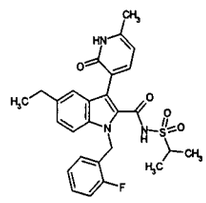
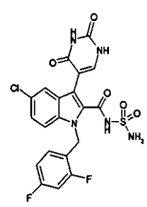
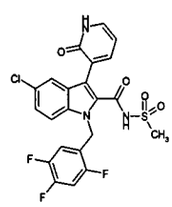
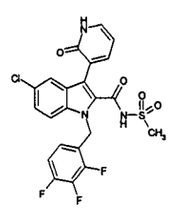
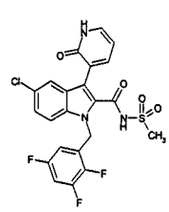
532

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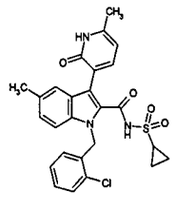
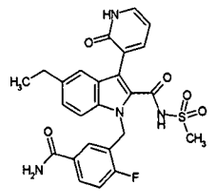
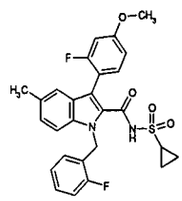
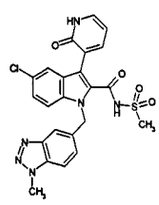
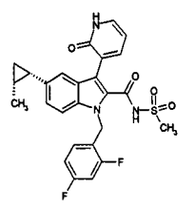
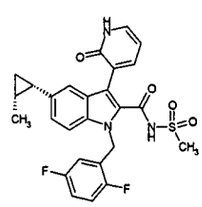
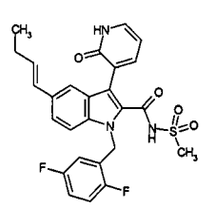
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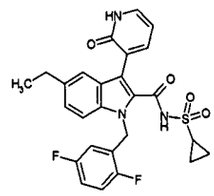
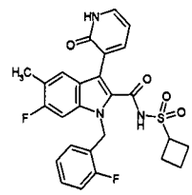
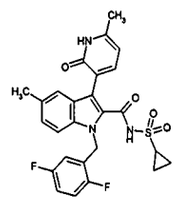
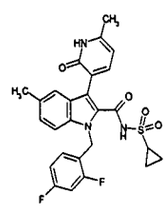
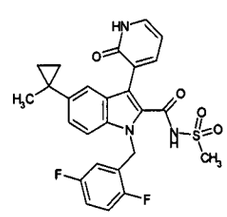
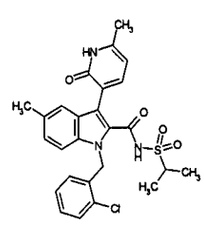
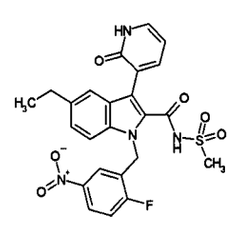
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534

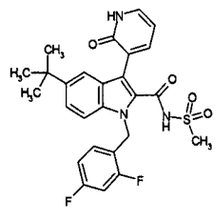
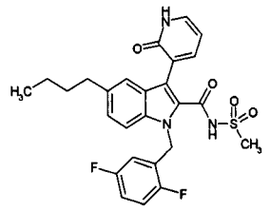
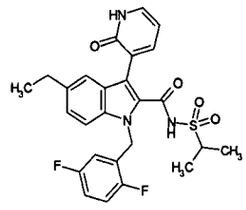
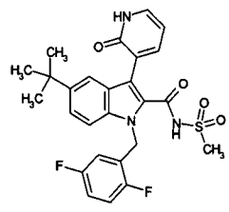
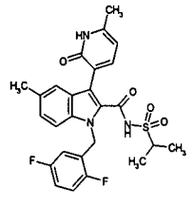
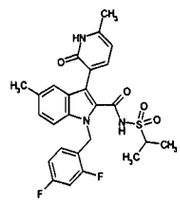
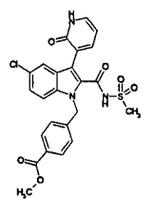
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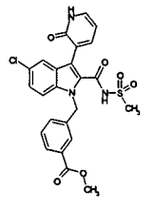
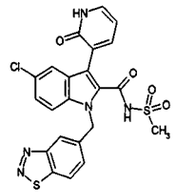
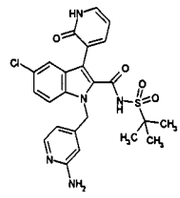
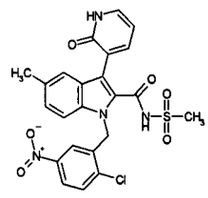
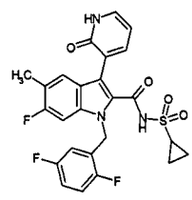
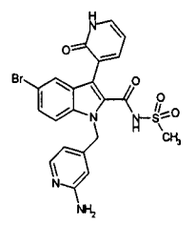
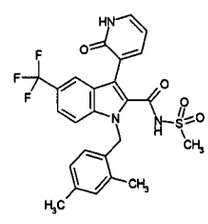
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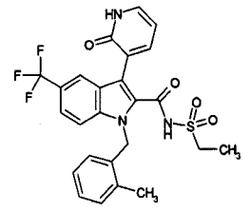
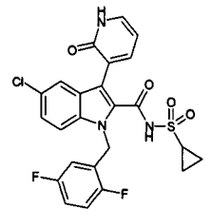
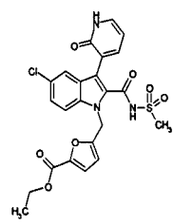
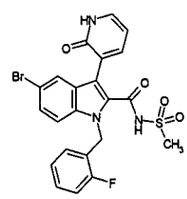
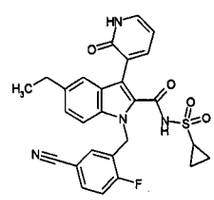
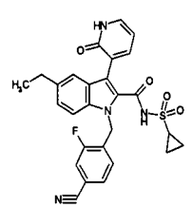
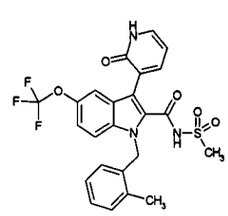
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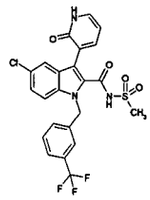
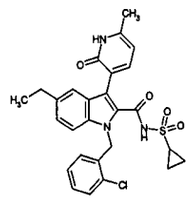
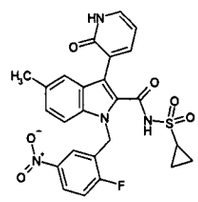
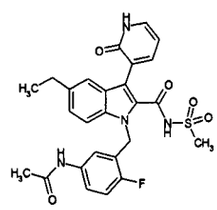
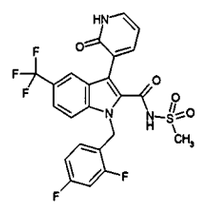
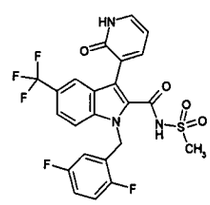
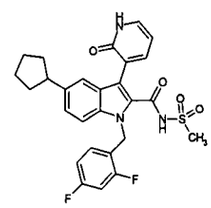
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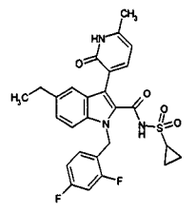
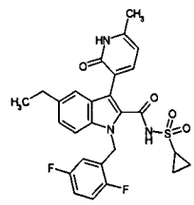
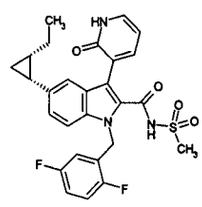
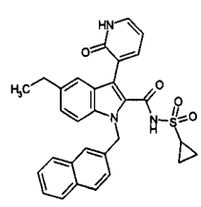
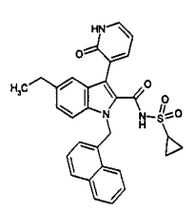
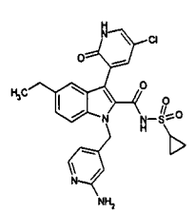
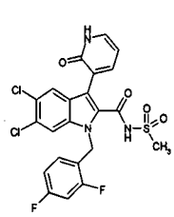
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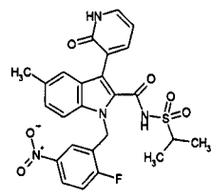
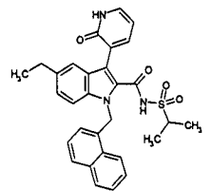
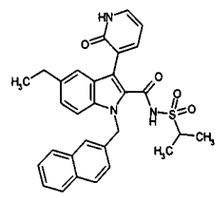
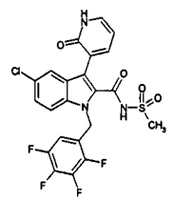
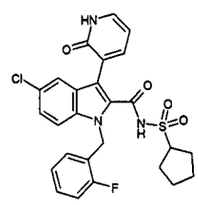
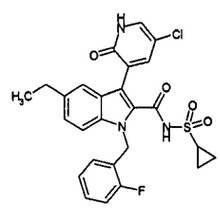
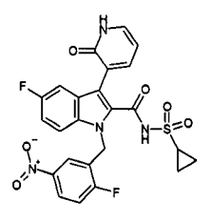
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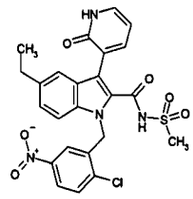
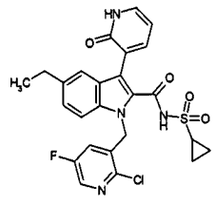
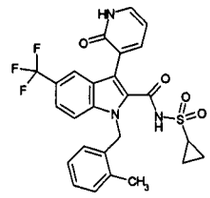
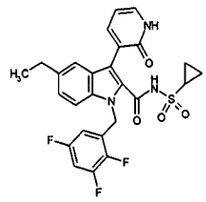
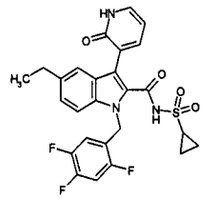
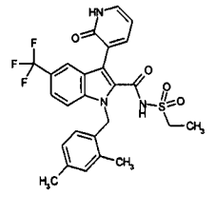
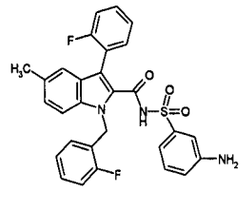
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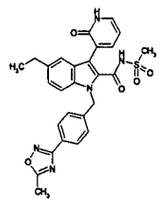
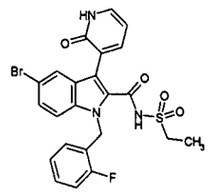
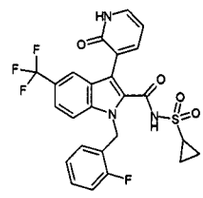
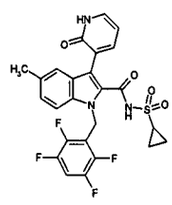
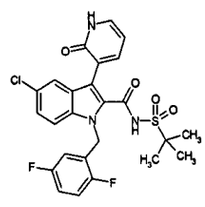
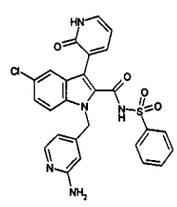
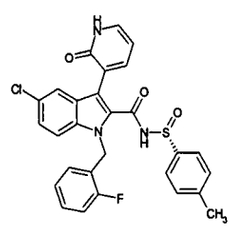
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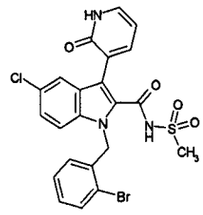
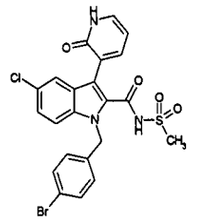
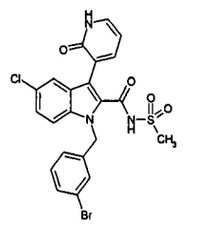
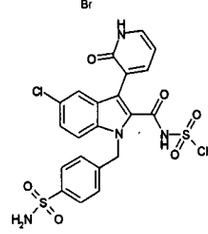
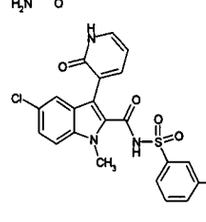
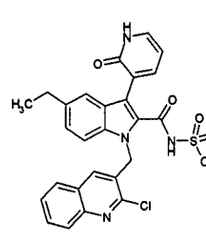
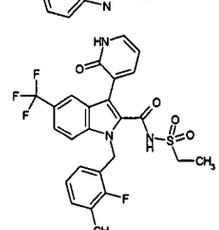
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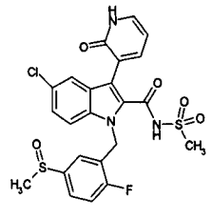
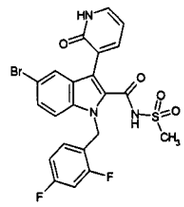
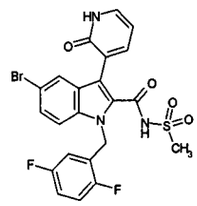
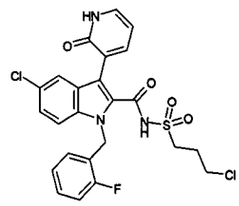
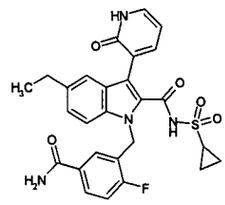
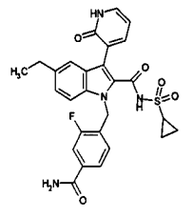
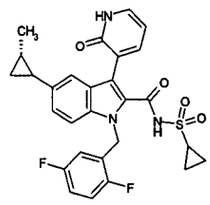
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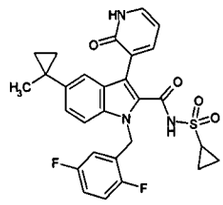
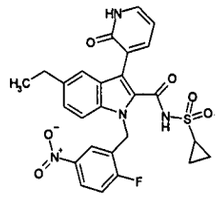
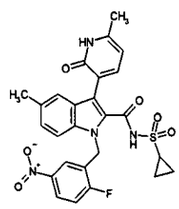
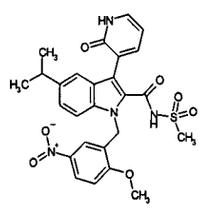
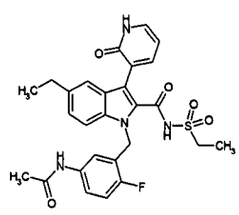
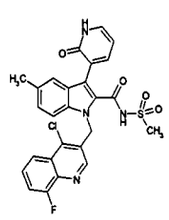
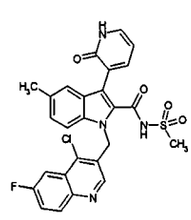
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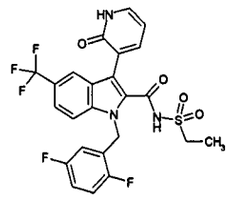
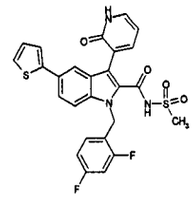
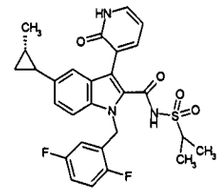
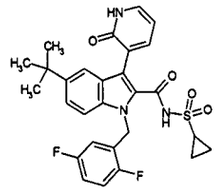
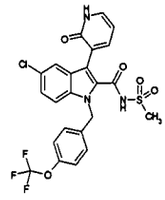
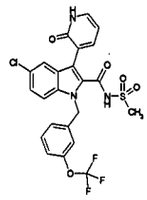
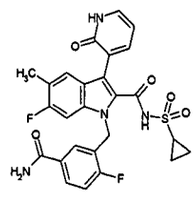
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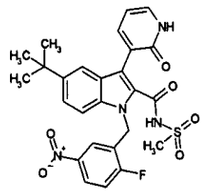
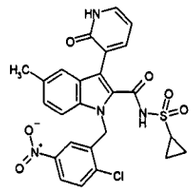
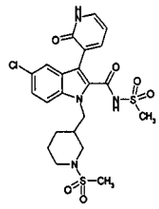
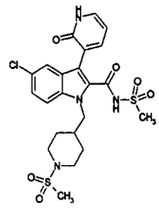
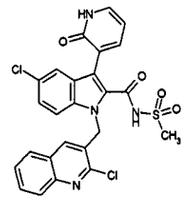
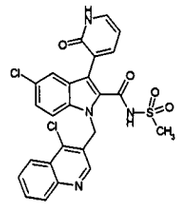
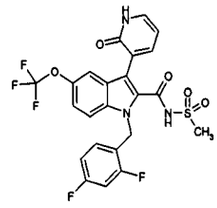
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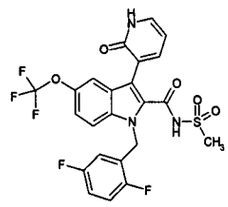
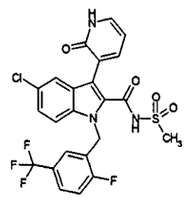
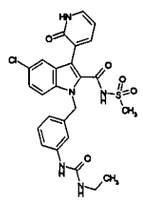
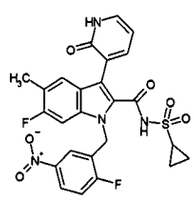
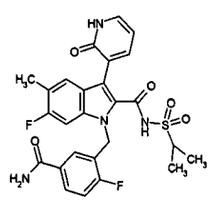
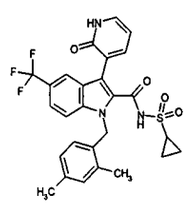
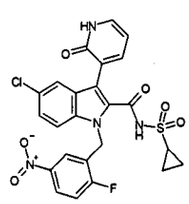
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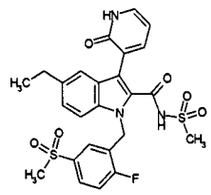
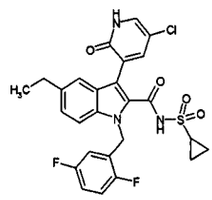
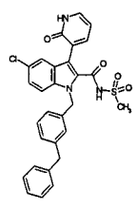
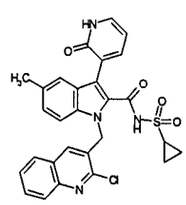
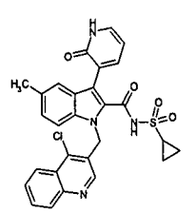
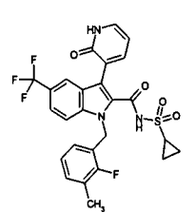
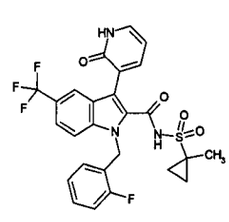
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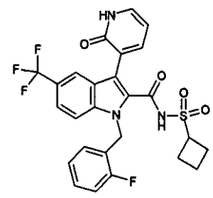
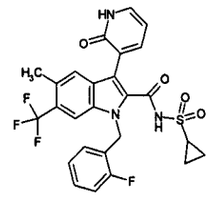
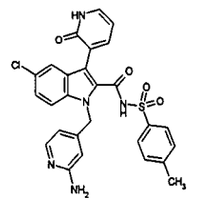
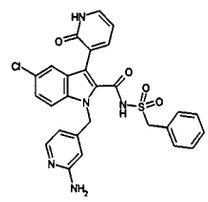
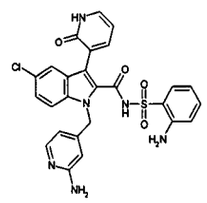
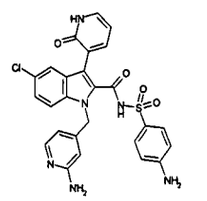
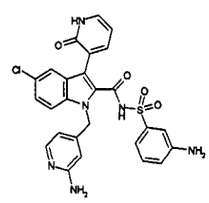
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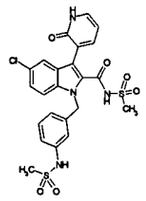
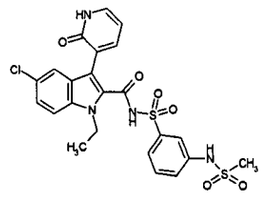
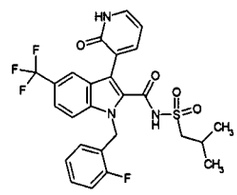
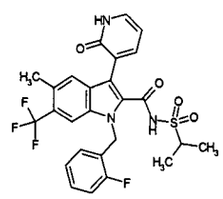
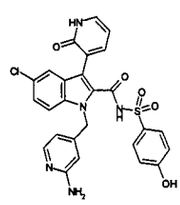
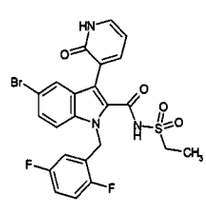
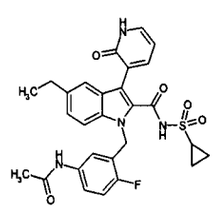
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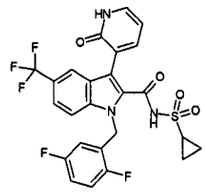
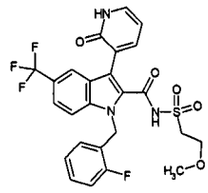
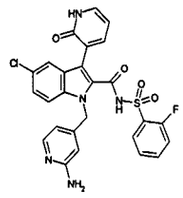
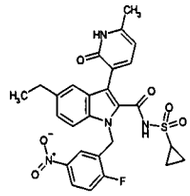
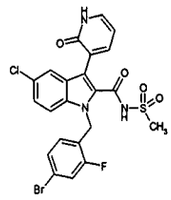
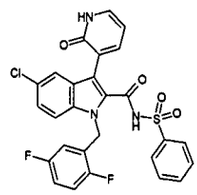
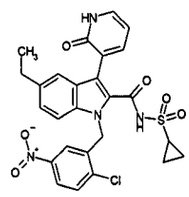
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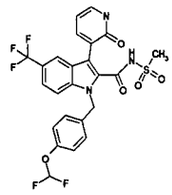
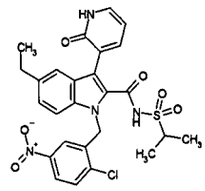
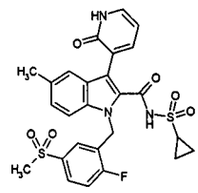
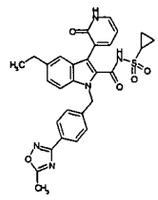
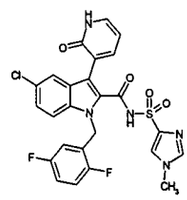
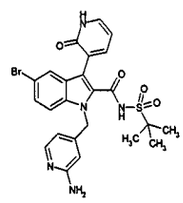
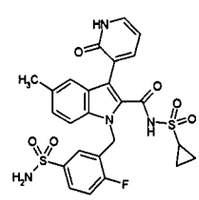
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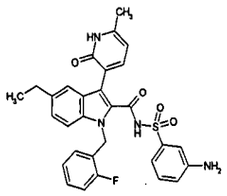
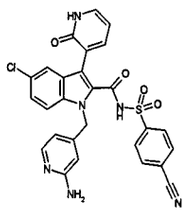
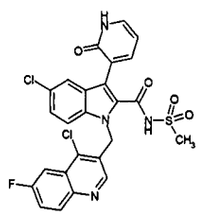
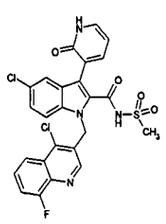
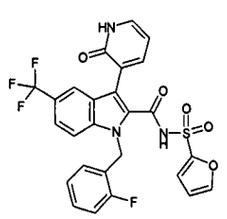
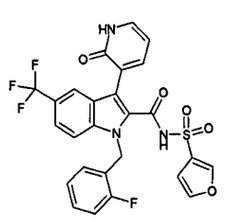
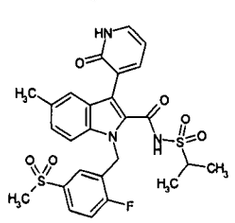
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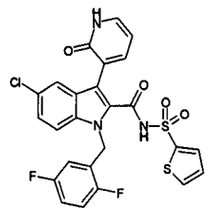
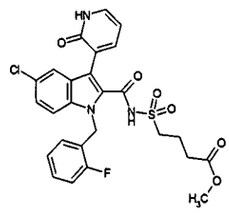
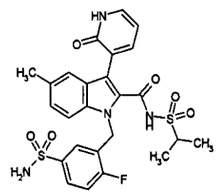
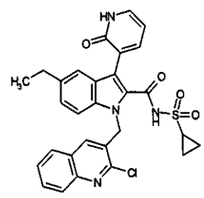
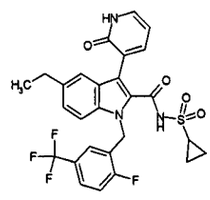
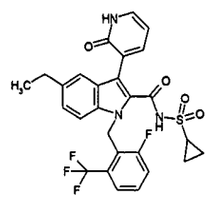
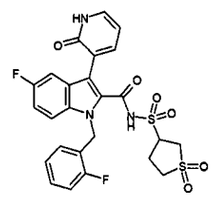
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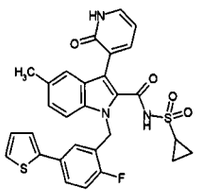
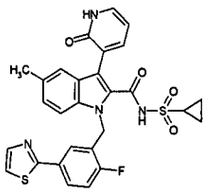
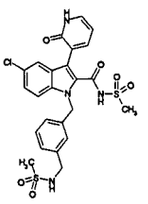
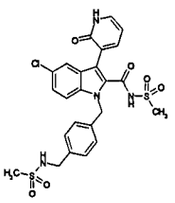
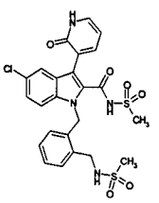
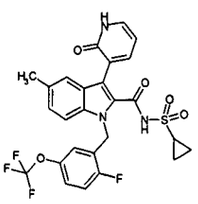
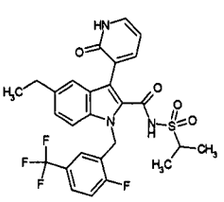
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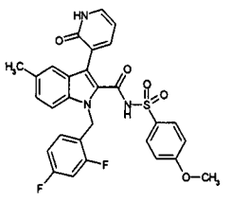
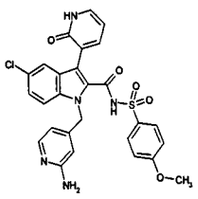
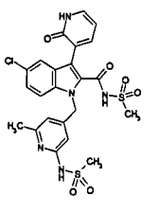
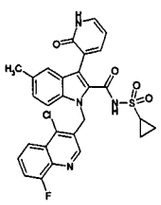
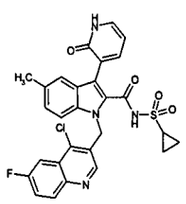
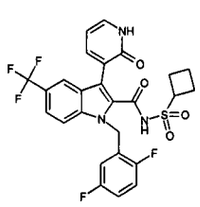
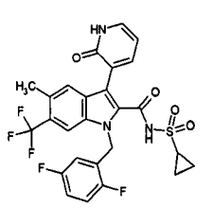
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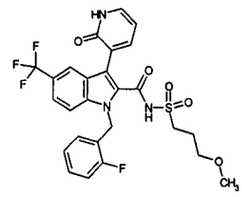
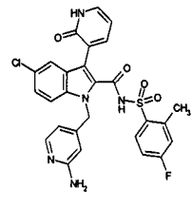
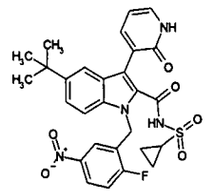
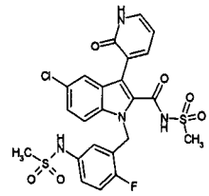
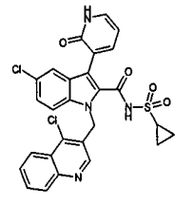
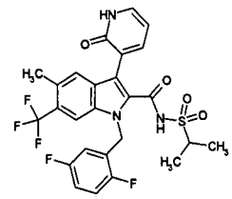
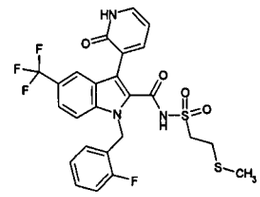
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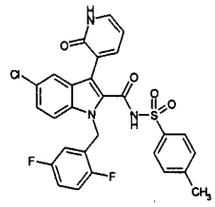
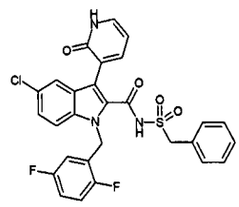
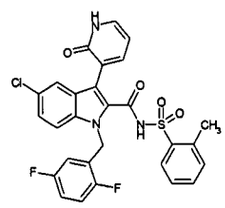
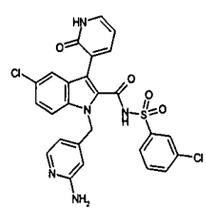
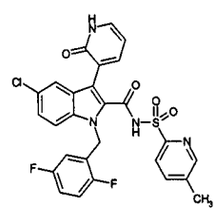
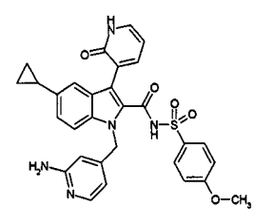
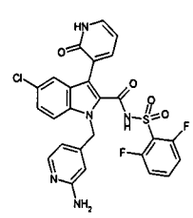
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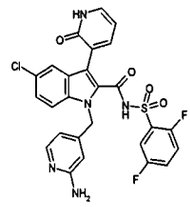
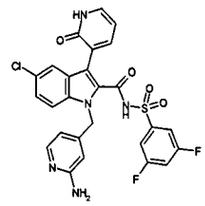
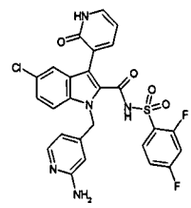
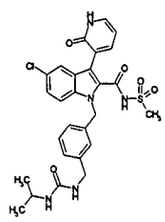
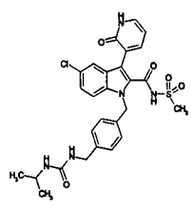
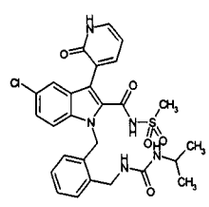
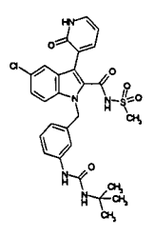
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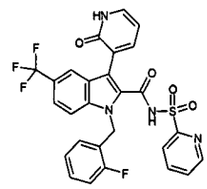
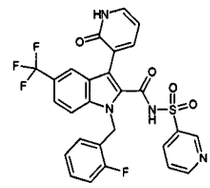
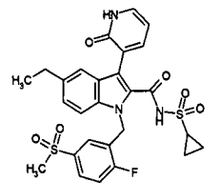
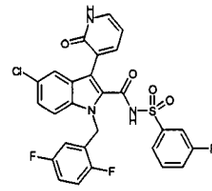
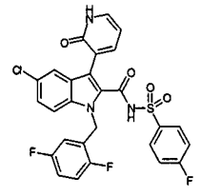
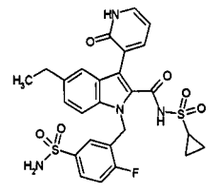
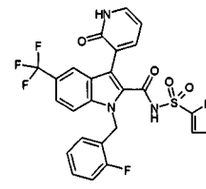
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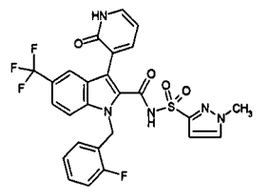
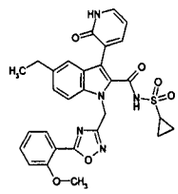
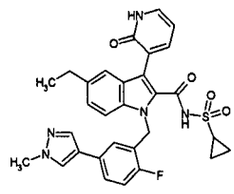
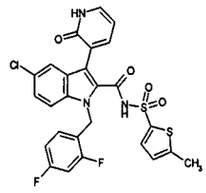
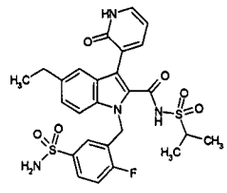
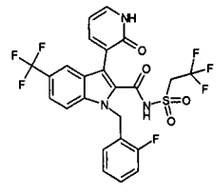
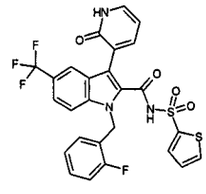
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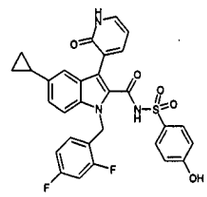
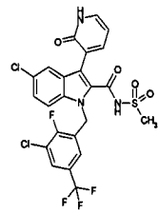
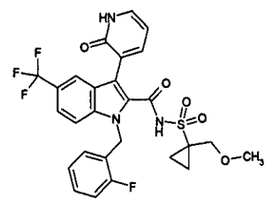
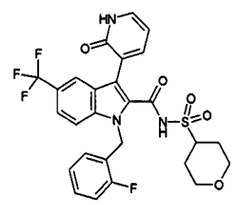
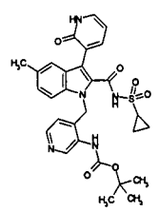
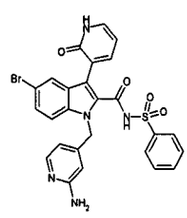
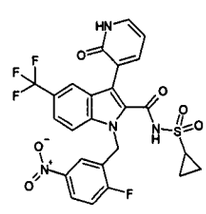
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397		571,0

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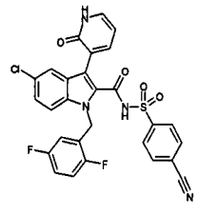
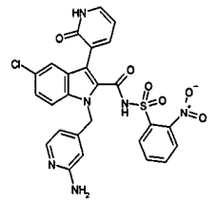
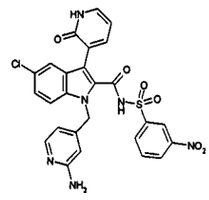
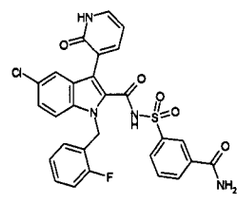
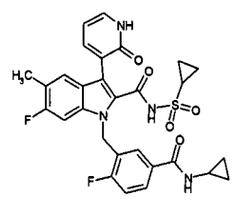
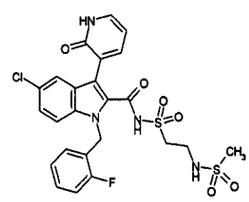
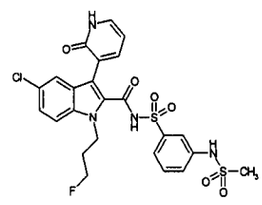
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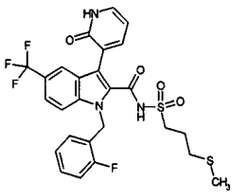
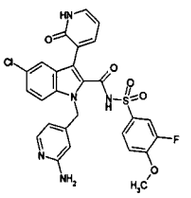
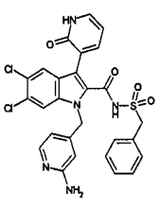
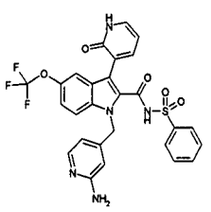
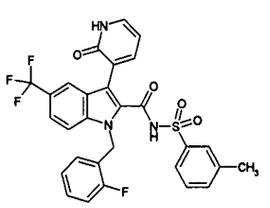
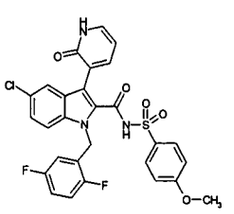
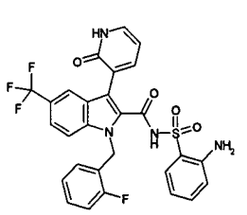
564

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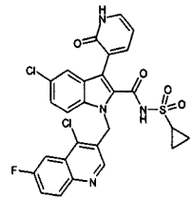
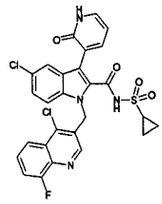
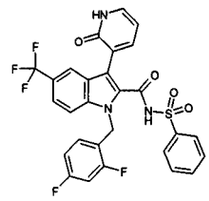
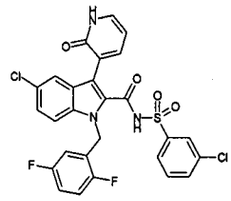
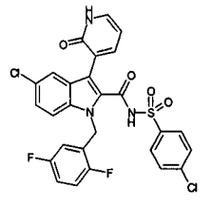
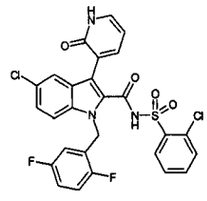
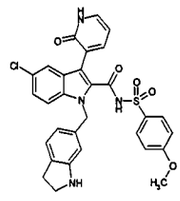
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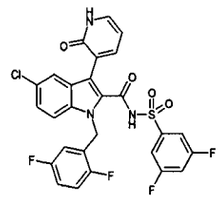
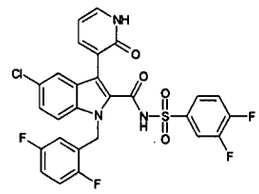
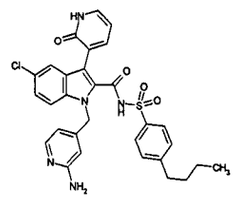
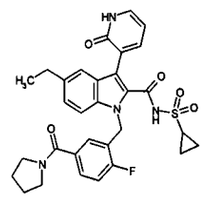
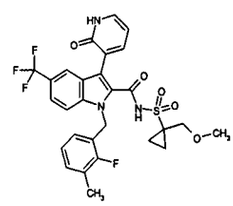
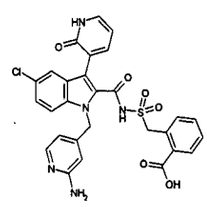
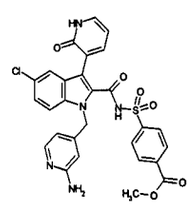
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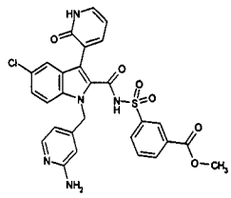
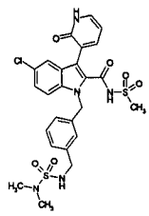
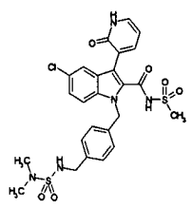
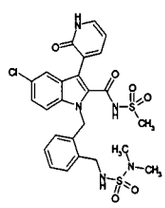
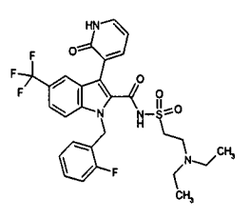
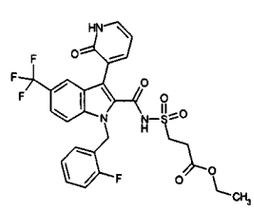
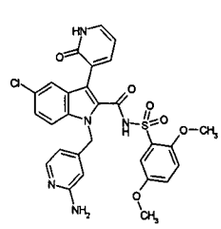
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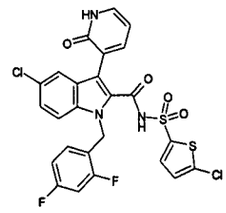
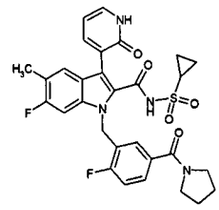
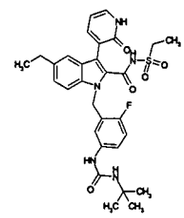
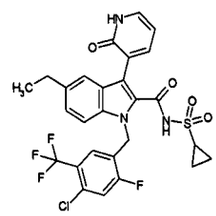
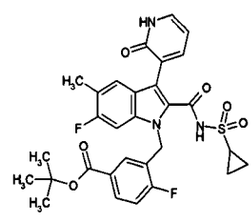
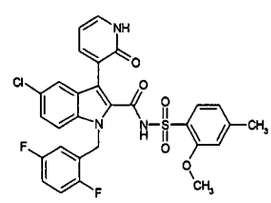
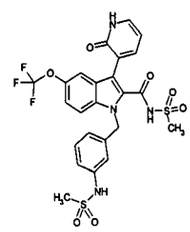
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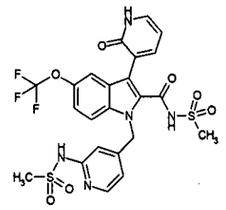
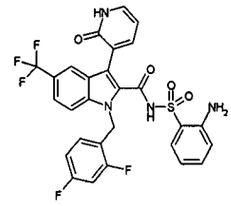
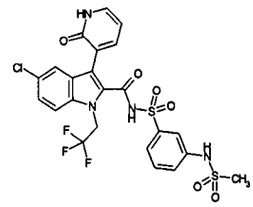
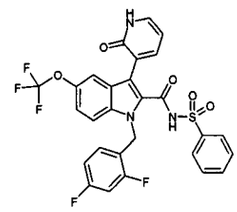
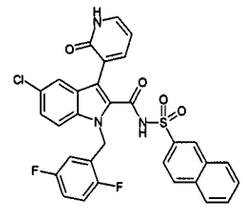
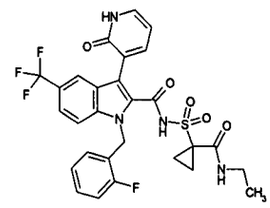
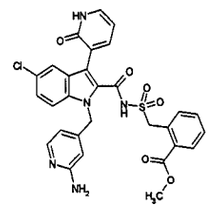
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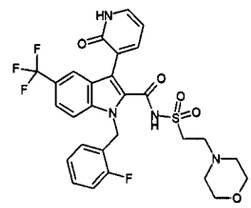
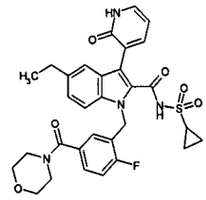
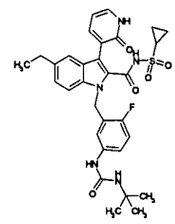
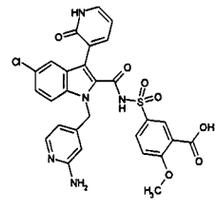
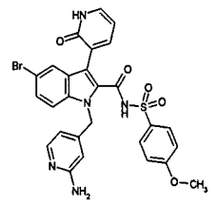
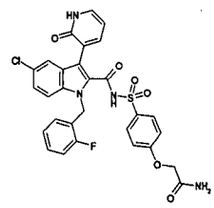
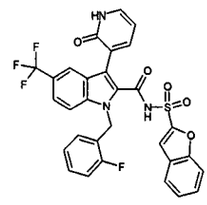
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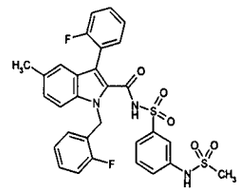
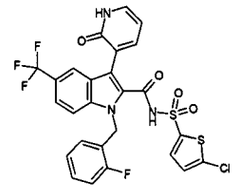
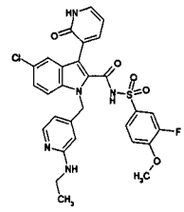
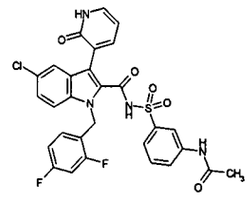
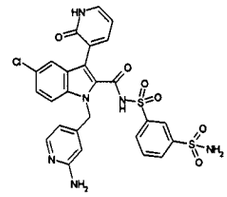
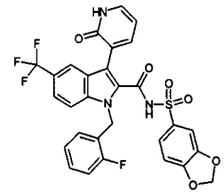
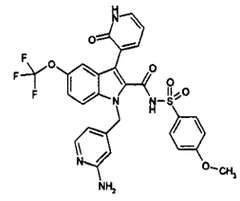
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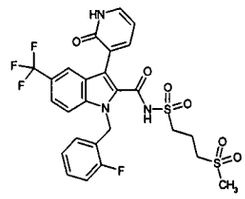
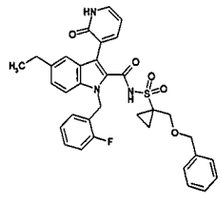
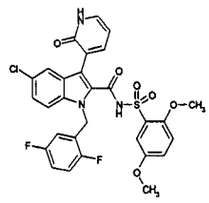
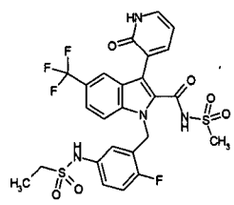
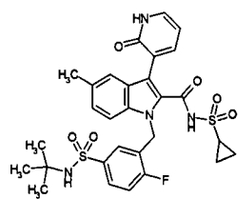
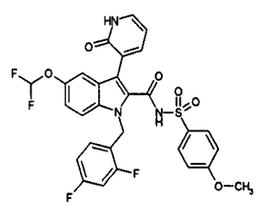
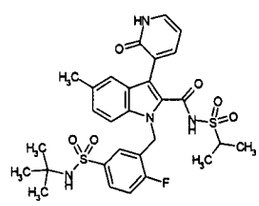
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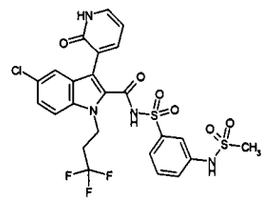
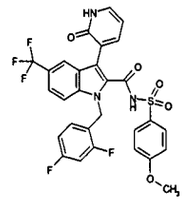
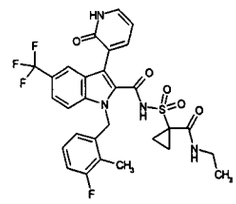
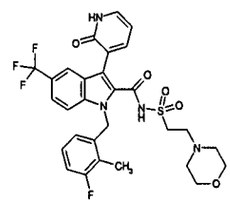
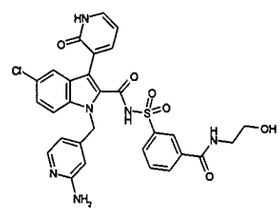
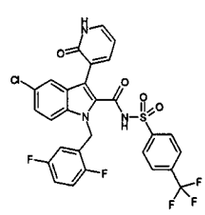
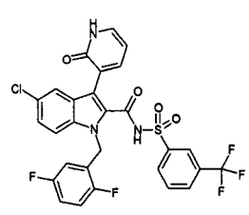
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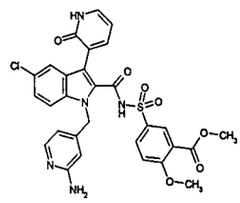
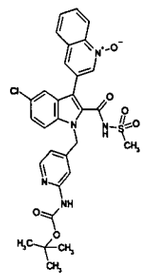
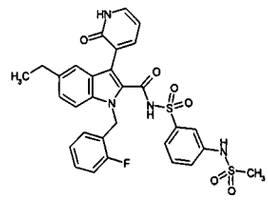
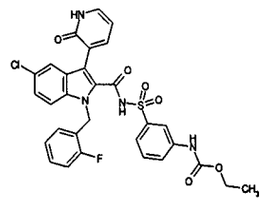
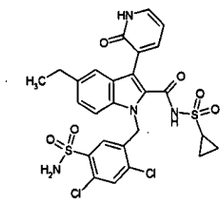
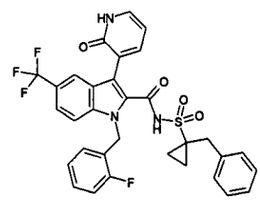
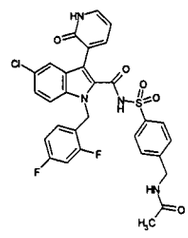
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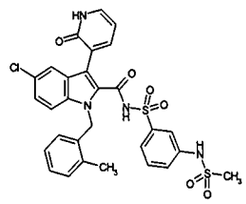
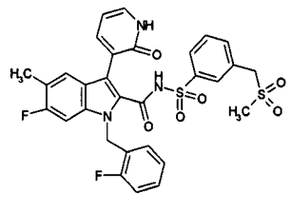
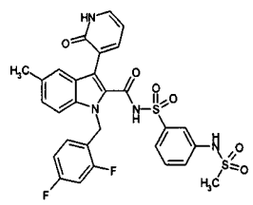
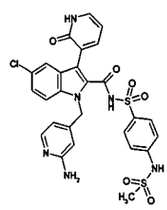
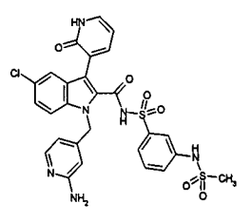
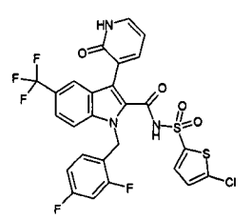
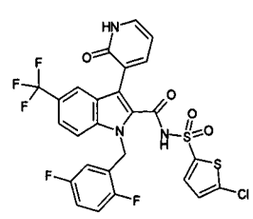
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481		610,6

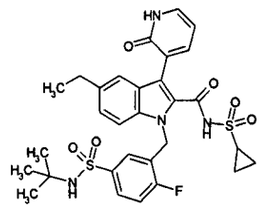
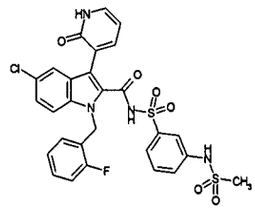
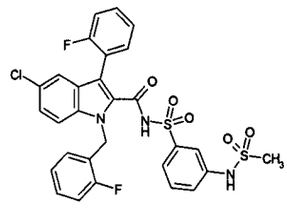
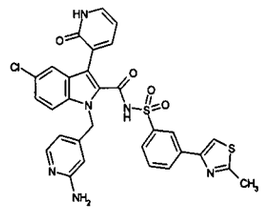
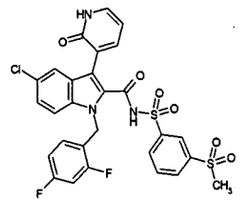
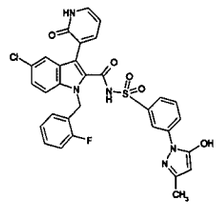
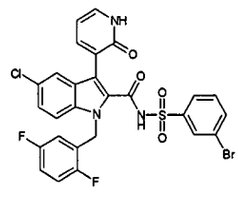
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488		614,6

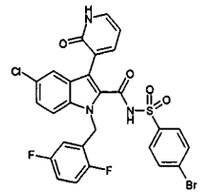
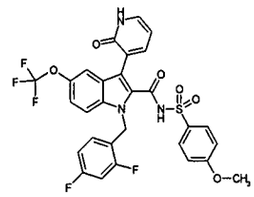
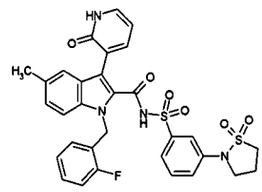
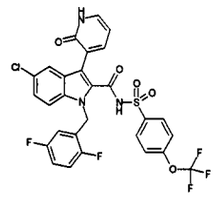
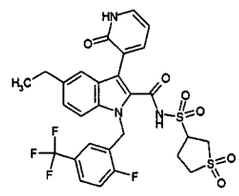
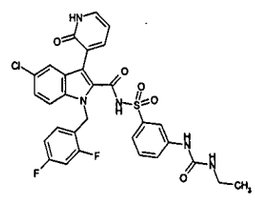
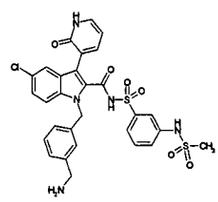
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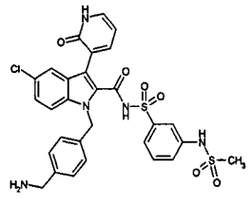
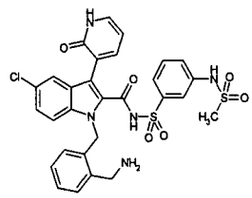
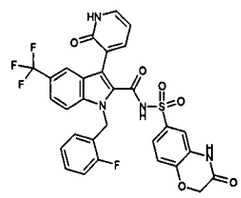
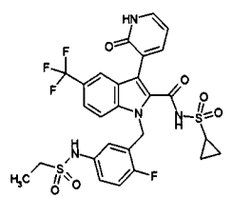
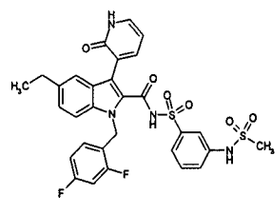
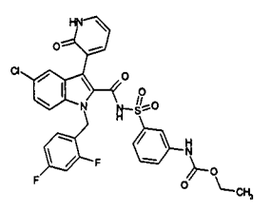
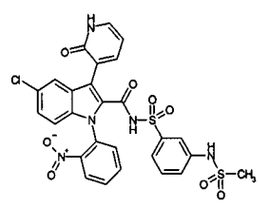
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509		626,1

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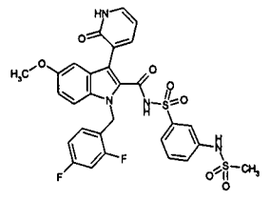
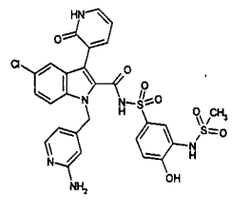
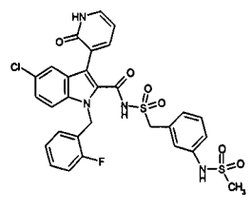
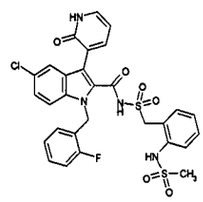
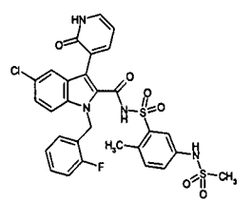
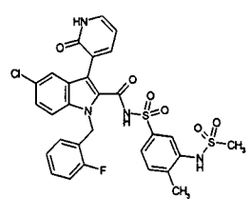
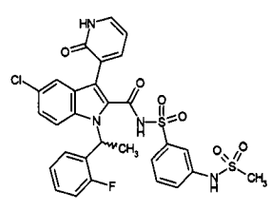
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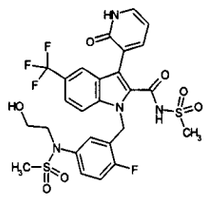
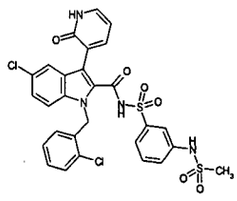
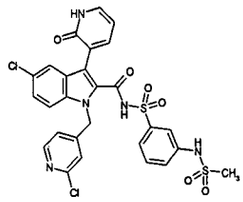
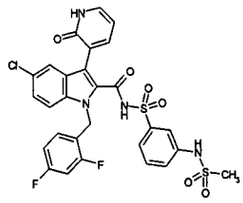
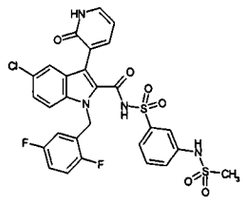
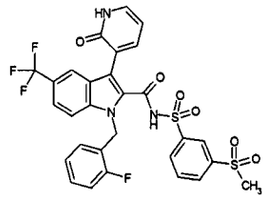
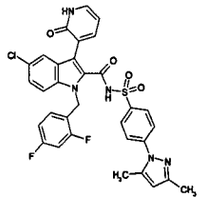
581

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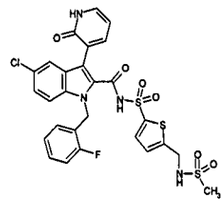
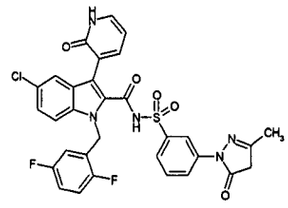
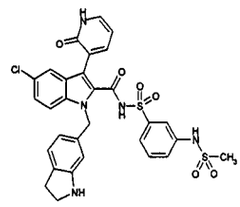
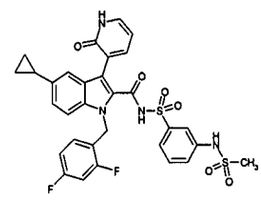
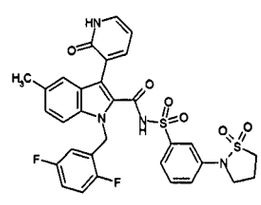
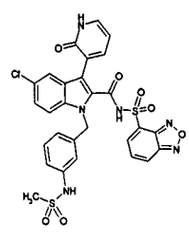
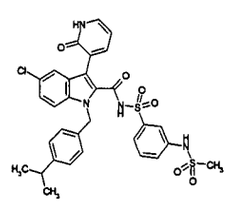
582

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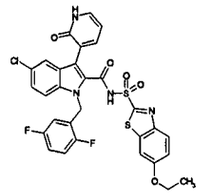
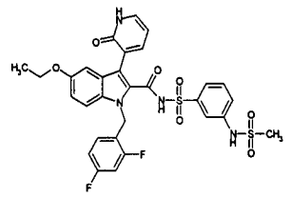
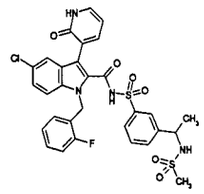
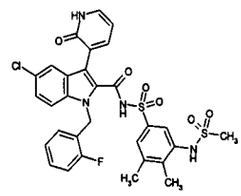
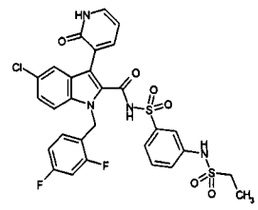
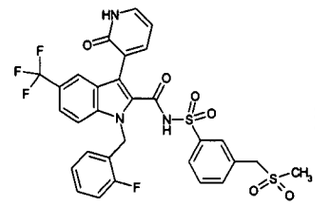
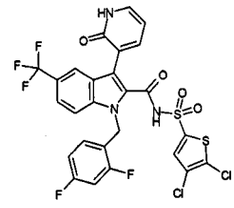
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551		649,1

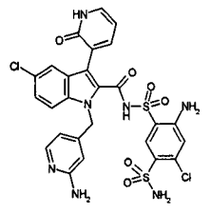
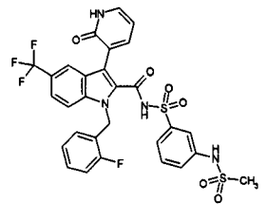
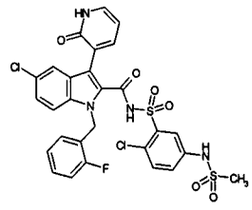
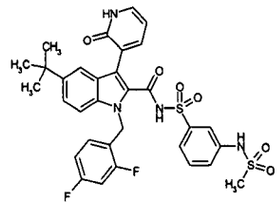
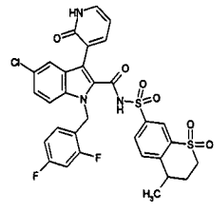
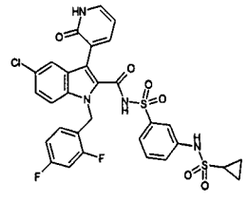
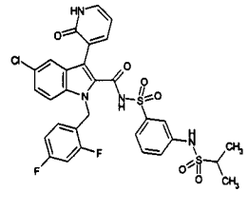
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558		654,2

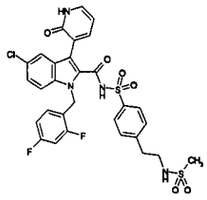
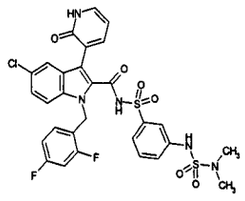
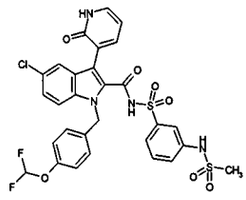
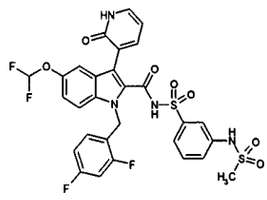
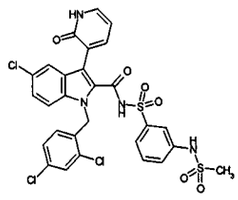
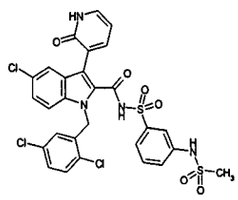
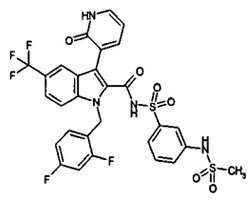
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564		662,7
565		663,4

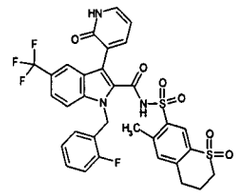
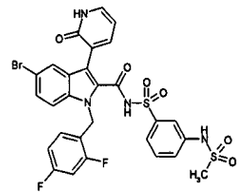
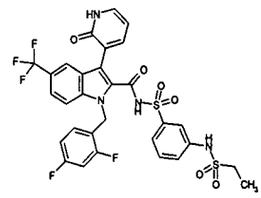
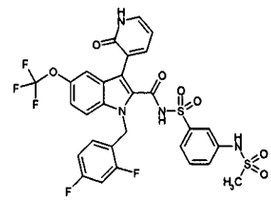
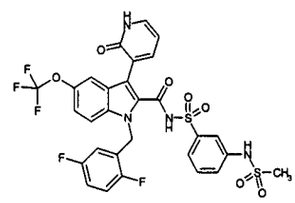
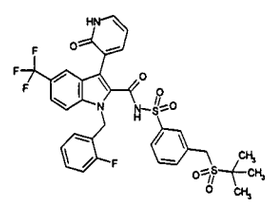
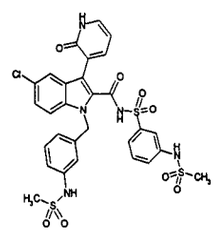
586

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569		669,7
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572		676,1

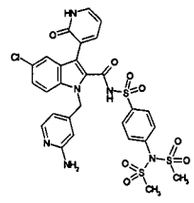
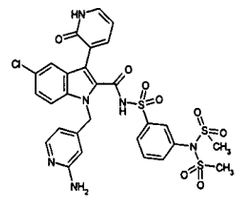
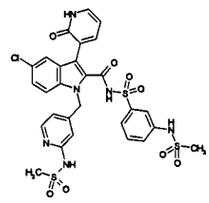
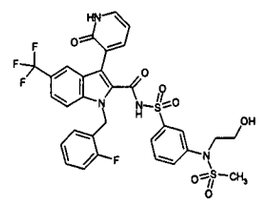
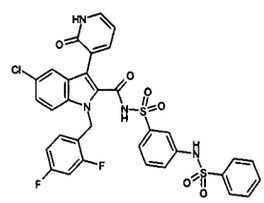
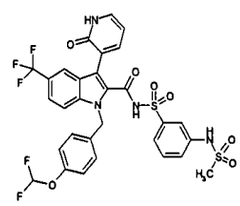
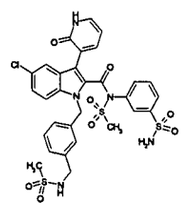
587

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579		681,6

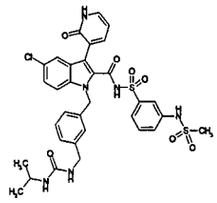
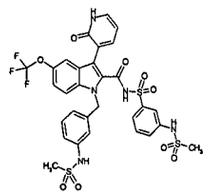
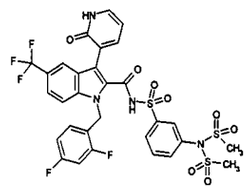
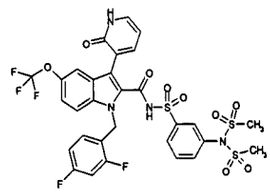
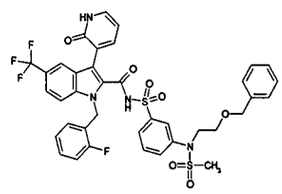
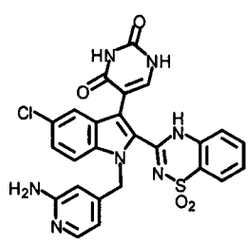
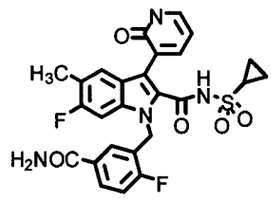
588

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585		704,7
586		705,2

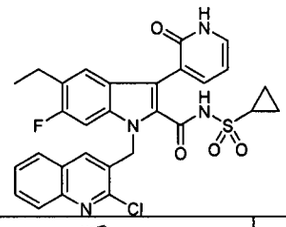
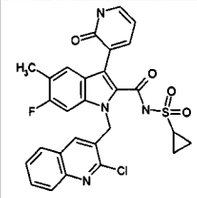
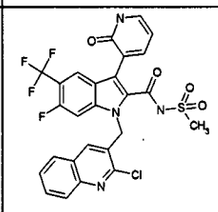
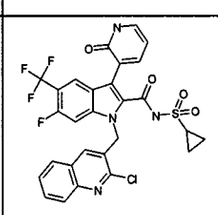
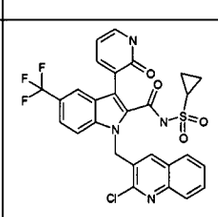
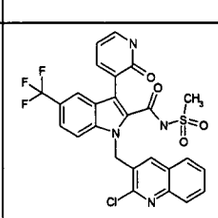
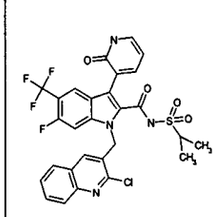
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591		710,2
592		711,7
593		719,2

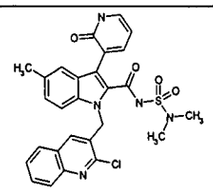
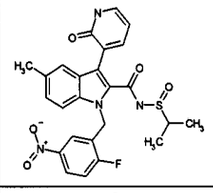
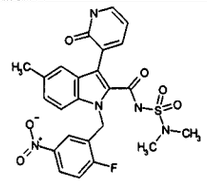
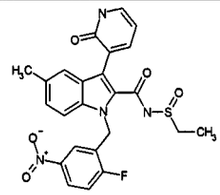
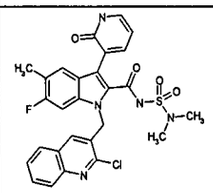
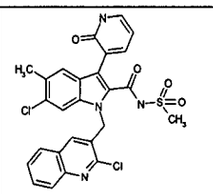
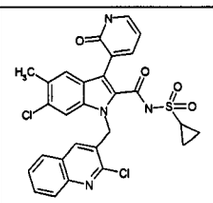
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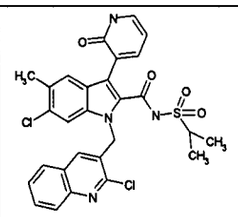
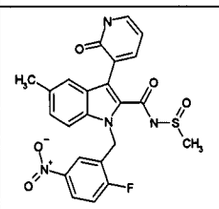
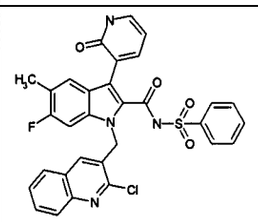
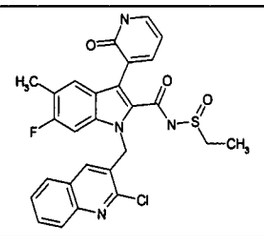
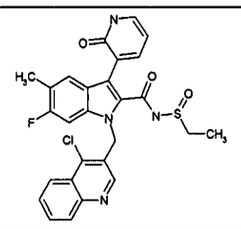
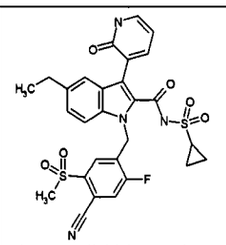
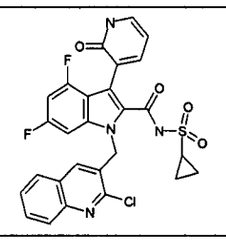
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596		759,7
597		775,7
598		797,8
599		548,3
600		
		541,3

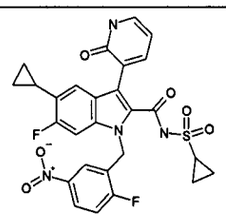
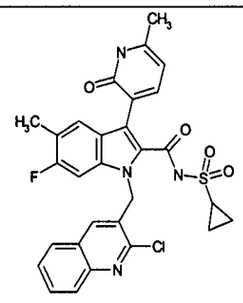
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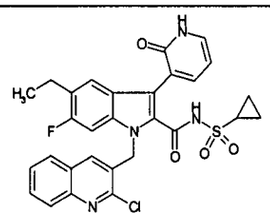
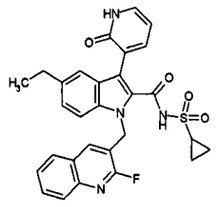
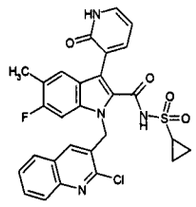
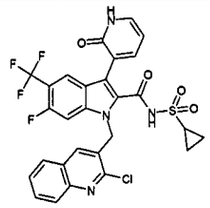
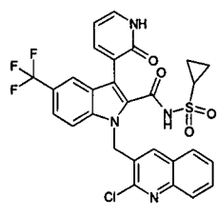
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603		594,0
604		620,0
605		602,0
606		576,0
607		622,0

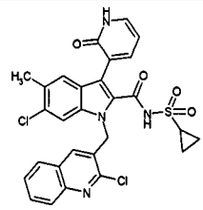
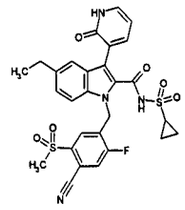
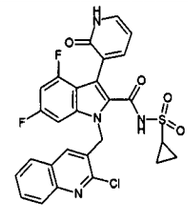
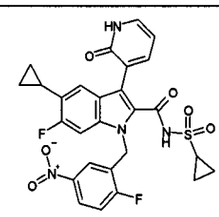
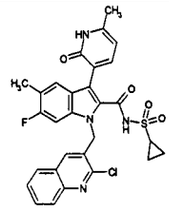
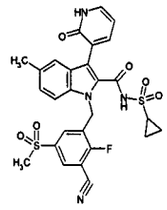
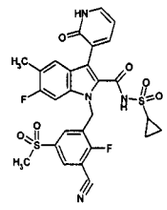
592

608		551,0
609		511,5
610		528,5
611		497,5
612		569,0
613		556,4
614		582,5

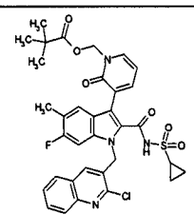
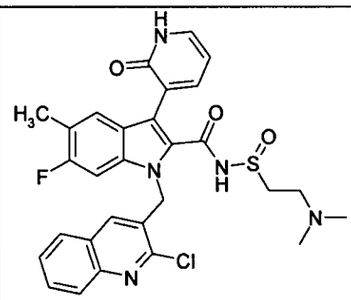
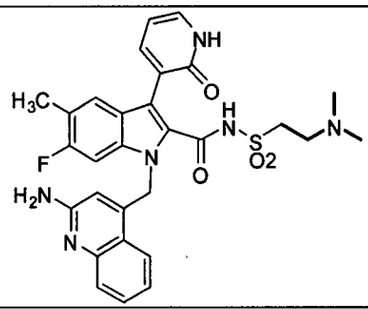
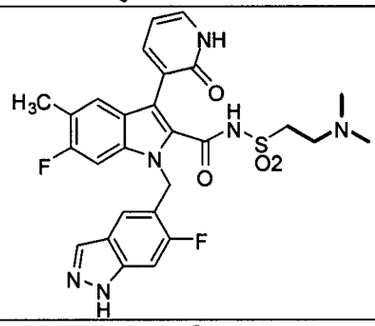
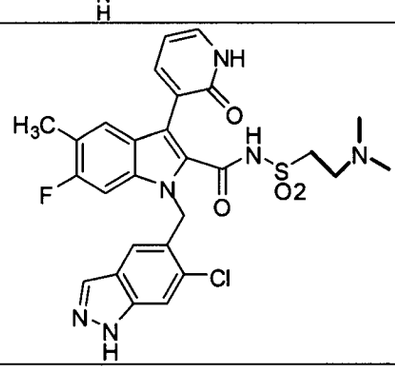
615		584,5
616		483,5
617		602,1
618		538,0
619		538,0
620		597,7
621		570,0

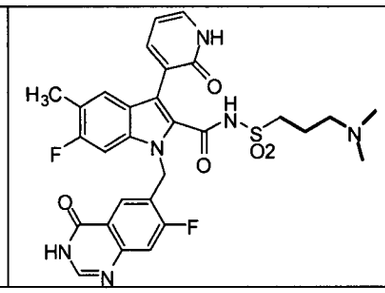
622		569,6
623		580,1

624		580,1
625		545,6
626		566,0
627		620,0
628		602,0

629		582,5
630		597,7
631		570,0
632		569,6
633		580,1
634		583,6
635		601,6

596

636		680,2
637		NA
638		NA
639		NA
640		NA

641		NA

NA = no disponible

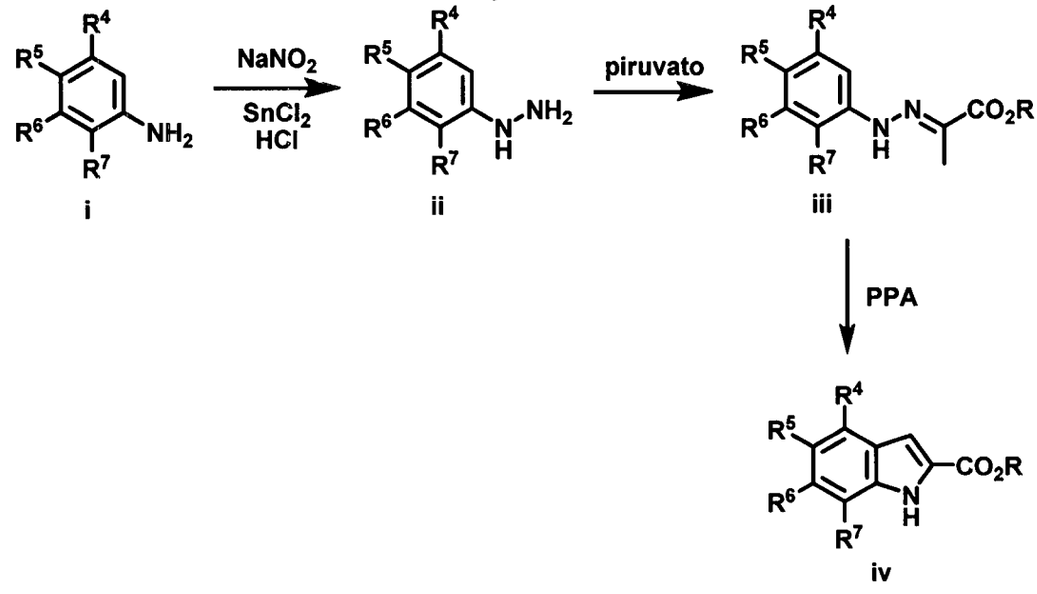
y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico.

Métodos para producir los derivados indólicos 2,3 sustituidos

Los métodos útiles para producir los derivados indólicos 2,3 sustituidos se indican en los Ejemplos que siguen y se generalizan en los Esquemas 1–6. Los ejemplos de metodologías comúnmente conocidas útiles para la síntesis de índoles se indican, por ejemplo, en G. R. Humphrey and J. T. Kuete, *Chemical Reviews* 106:2875–2911, **2006**.

El Esquema 1 muestra un método útil para producir compuestos de fórmula **iv**, que son intermediarios útiles para producir los derivados indólicos 2,3 sustituidos.

Esquema 1

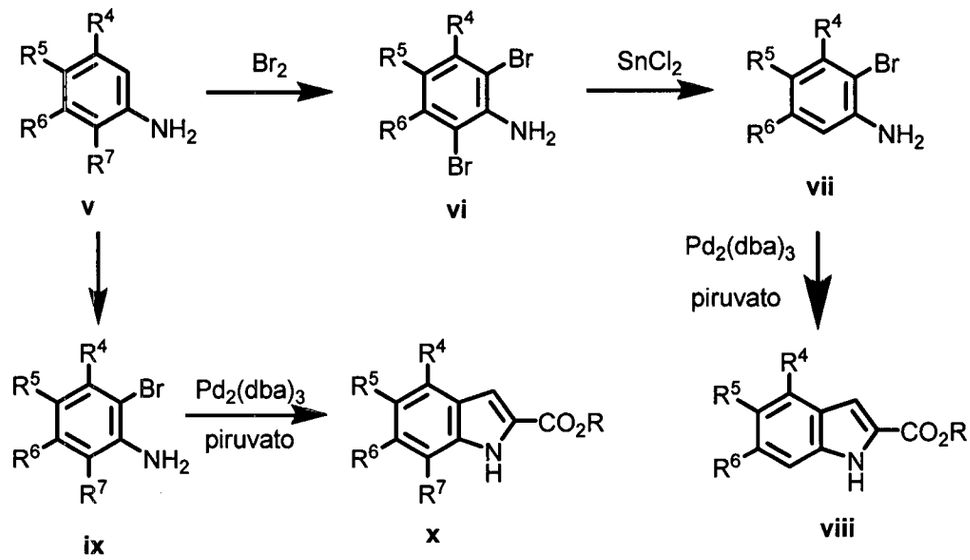


en los cuales R^4–R^7 se definió con anterioridad para los compuestos de fórmula (I) y R es H, alquilo o arilo.

Un compuesto con estructura de anilina de Fórmula **i** puede convertirse en un compuesto indólico de Fórmula **iv** usando varias síntesis de indoles que resultan conocidas para aquellas personas con experiencia en el arte de la síntesis orgánica, incluyendo sin carácter limitativo, una síntesis indólica de Fischer a través de los intermediarios del tipo **ii y iii**, el método se menciona en Nazare *et al.*, *Angew. Chem.*, 116:4626–4629 (2004). Los compuestos de fórmula **iv** pueden elaborarse, en forma tal que se proporcionen los derivados indólicos 2,3 sustituidos usando el método descrito más adelante en el Esquema 4.

El Esquema 2 muestra métodos útiles para producir compuestos de fórmulas **viii** y **x**, que son intermediarios útiles para producir los derivados indólicos 2,3 sustituidos.

Esquema 2

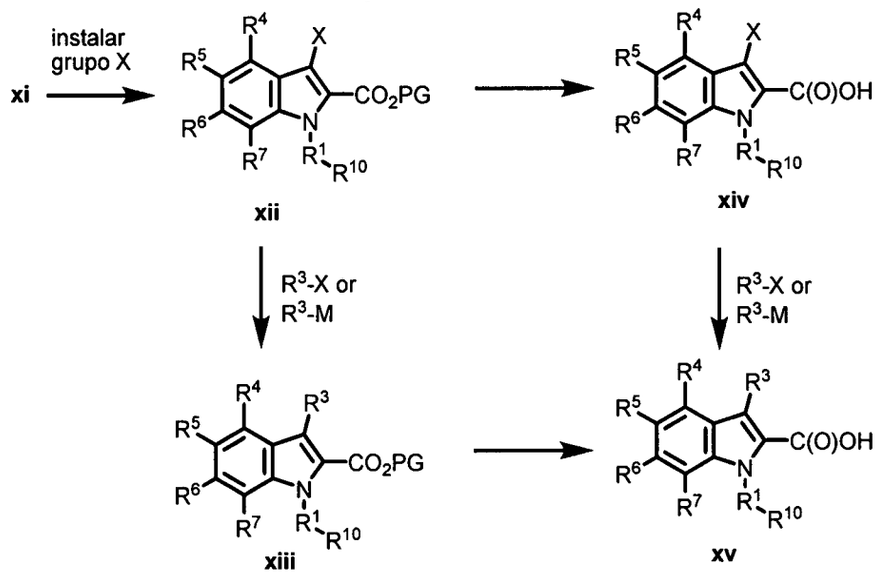


en los cuales R^4–R^7 se definió con anterioridad para los compuestos de fórmula (I) y R es H, alquilo o arilo.

Un derivado bencénico de Fórmula **v**, en el cual R^7 es H, puede di–bromarse para proporcionar el compuesto **vi**. La des-bromación selectiva provee el correspondiente análogo monobromo **vii**, el cual ajo condiciones de ciclación catalizada con paladio provee el intermediario deseado **viii**, en los cuales R^7 es H. En forma alternativa un compuesto de Fórmula **v**, en los cuales R^7 es distinto de H, puede monobromarse para proporcionar el compuesto **ix**. Un compuesto de Fórmula **ix** puede luego someterse a condiciones de ciclación catalizada por paladio proveer el intermediario deseado **x**, en los cuales R^7 es distinto de H.

El Esquema 3 ilustra métodos por los cuales los compuestos intermediarios de fórmula **xi** pueden derivarse en forma adicional para proporcionar los derivados indólicos 2,3 sustituidos, que son intermediarios para los derivados indólicos 2,3 sustituidos del título.

Esquema 3



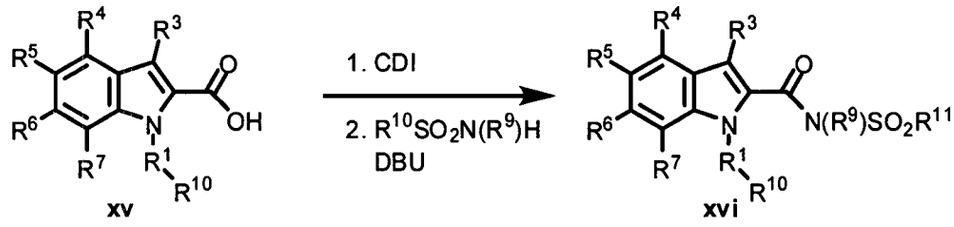
en los cuales R^1, R^3, R^4–R^7 y R^{10} se definió con anterioridad para los compuestos de fórmula (I); PG es un grupo protector de carboxilos; y X es halo, –O–triflato, –$B(OH)_2$, –$Si(alquil)_2OH$, –$Sn(alquil)_3$, –MgBr, –MgCl, –ZnBr, o –ZnCl; y M es cualquier metal que puede participar en la reacción de acoplamiento cruzado organometálica.

Un compuesto intermediario de Fórmula **xi** puede convertirse en un indol 3 sustituido de Fórmula **xii** usando métodos muy conocidos por aquellos expertos en el arte de la síntesis orgánica. Un compuesto de Fórmula **xii**, en el cual X es halo o –O–triflato pueden acoplarse luego con un compuesto apropiado de Fórmula R^3–M' (en el cual M es –$B(OH)_2$, –$Si(alquil)_2OH$, –$Sn(alquil)_3$, –MgBr, –MgCl, –ZnBr, –ZnCl, o cualquier metal que puede participar en la reacción de acoplamiento cruzado organometálico) usando un método de acoplamiento cruzado organometálico. En forma alternativa, un compuesto de Fórmula **xii**, en el cual X es –$B(OH)_2$, –$Si(alquil)_2OH$, –$Sn(alquil)_3$, –MgBr, –MgCl, –ZnBr, –ZnCl, o cualquier metal que puede participar en la reacción de acoplamiento cruzado organometálico, puede acoplarse luego con un compuesto apropiado de Fórmula R^3–M (en los cuales M es halo o –O–triflato) usando un método de acoplamiento cruzado organometálico. Los métodos de acoplamiento cruzado apropiados incluyen, sin carácter limitativo, un acoplamiento de 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 de Suzuki (ver Miyaura *et al.*, *Chem. Rev.*, 95:2457 (1995)), un acoplamiento de Negishi (ver Zhou *et al.*, *J. Am. Chem. Soc.*, 127:12537–12530 (2003)), un acoplamiento basado en silanoato (ver Denmark *et al.*, *Chem. Eur. J.* 12:4954–4963 (2006)) y un acoplamiento de Kumada (ver Kumada, *Pure Appl. Chem.*, 52:669 (1980) y Fu *et al.*, *Angew. Chem.* 114:4363 (2002)) para proporcionar un compuesto de Fórmula **F**. El grupo protector de carboxilos, PG, puede eliminarse entonces del compuesto de Fórmula **xiv** y el ácido carboxílico resultante puede derivarse usando los métodos descritos a continuación para realizar los grupos R^2 apropiados y producir los compuestos de fórmula **xv**, que corresponden a los compuestos de fórmula (I), en los cuales R^2 es -C(O)OH. En forma alternativa, un compuesto de Fórmula **xii** primero puede desprotegerse y el grupo R^2 unido usando los métodos anteriores para

proporcionar un compuesto de Fórmula **xiii**. Un compuesto de Fórmula **xiii** puede sufrir acoplamiento cruzado con un compuesto de R^3–X o R^3–M como se describió con anterioridad para proporcionar los compuestos de fórmula **xv**.

El Esquema 4 muestra un método útil para producir los derivados indólicos 2,3 sustituidos, en los cuales R^2 es $-C(O)N(R^9)SO_2R^{11}$.

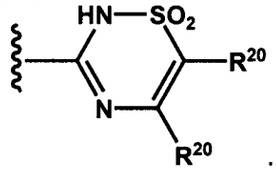
Esquema 4



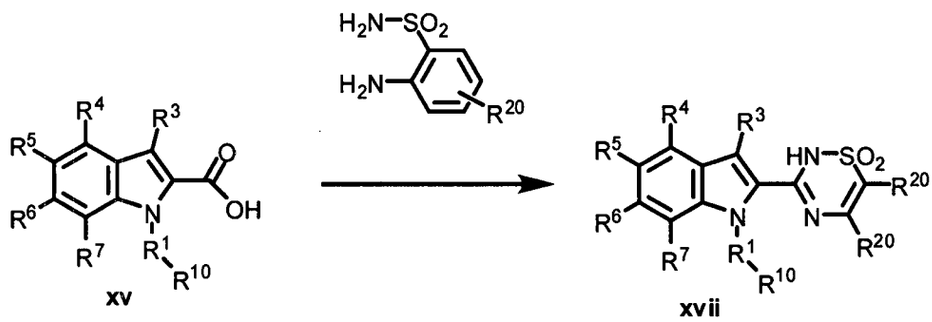
en los cuales R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10}, etc. y G son como se los definió para los derivados indólicos 2,3 sustituidos.

Un compuesto indólico 2–carboxi de Fórmula **xv** puede acoplarse con un compuesto de Fórmula $R^{11}SO_2NH(R^9)$ en presencia de carbonildiimidazol (CDI) y 1,8–diazabiciclo[5,4,0]undec–7–eno (DBU) para proporcionar los compuestos de fórmula **xvi**, que corresponden a los derivados indólicos 2,3 sustituidos en los cuales R^2 es $-C(O)NHSO_2R^{11}$.

El Esquema 5 muestra un método útil para producir los derivados indólicos 2,3 sustituidos, en los cuales R^2 es:



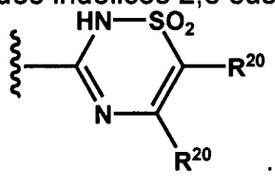
Esquema 5



xv xvii

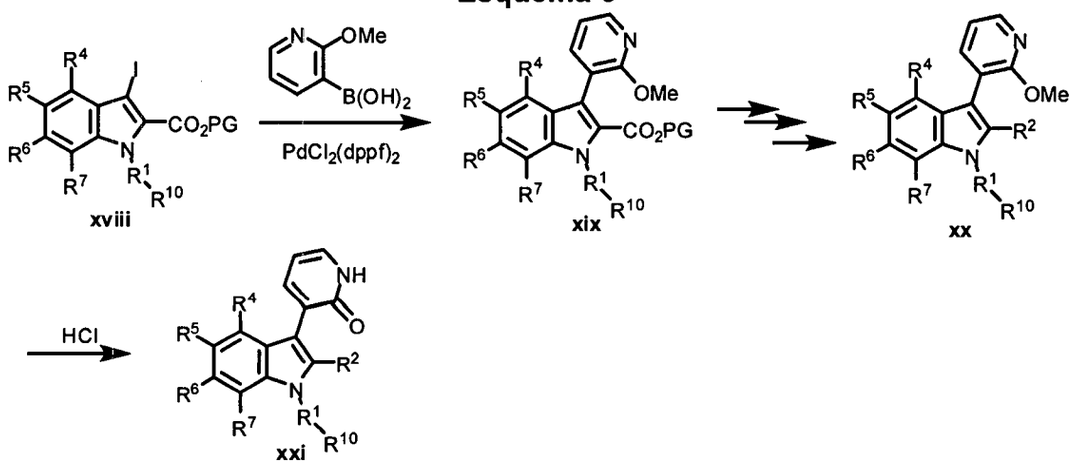
en los cuales R^1, R^3, R^4–R^7, R^{10} y R^{20} se definió con anterioridad para los compuestos de fórmulas (I) y (II).

Un compuesto indólico 2–carboxi de Fórmula **xv** puede hacerse reaccionar con una 2–amino sulfonamida para proporcionar los compuestos de fórmula **xvii**, que corresponden a los derivados indólicos 2,3 sustituidos en los cuales R^2 es:



El Esquema 6 muestra un método útil para producir los derivados indólicos 2,3 sustituidos, en los cuales R^3 es 1*H*–piridin–2–one–3–ilo.

Esquema 6



xviii xix xx xxi

en los cuales R^1, R^2, R^4–R^7 y R^{10} se definió con anterioridad para los compuestos de fórmulas (I) y (II).

Un compuesto 3–yodoindólico de Fórmula **xviii** puede acoplarse con ácido 2–hidroxipiridin–3–borónico usando una reacción de acoplamiento de Suzuki

para proporcionar los compuestos indólicos R^3 sustituidos de fórmula **xix**. Un compuesto de Fórmula **xix** puede elaborarse en forma adicional usando métodos indicados anteriormente en los Esquemas 1–6 para proporcionar los compuestos de fórmula **xx**. El resto 2–hidroxipiridilo de un compuesto de Fórmula **xx** puede hacerse reaccionar luego con un ácido fuerte, tal como ácido clorhídrico para proporcionar los compuestos de fórmula **xxi**, que corresponden a los derivados indólicos 2,3 sustituidos, en los cuales R^3 es 1*H*–piridin–2–ona–3–ilo.

El material de partida y los reactivos presentado en los Esquemas 1–6 se encuentran disponibles de proveedores comerciales tales como Sigma–Aldrich (St. Louis, MO) y Acros Organics Co. (Fair Lawn, NJ), o pueden prepararse usando métodos conocidos por aquellos con experiencia en el arte de la síntesis orgánica.

Una persona con experiencia en el arte reconocerá que la síntesis de los derivados indólicos 2,3 sustituidos puede requerir la necesidad de protección de ciertos grupos funcionales (*es decir*, derivación para fines de compatibilidad química con una condición de reacción particular). Los grupos protectores apropiados para los varios grupos funcionales de los derivados indólicos 2,3 sustituidos y métodos para su instalación y eliminación pueden encontrarse en Greene *et al.*, *Protective Grupos in Organic Synthesis*, Wiley–Interscience, New York, (1999).

Una persona con experiencia en el arte reconocerá que una vía será óptima dependiendo de la elección de los sustituyentes de anexos. Adicionalmente, una persona con experiencia en el arte reconocerá que en algunos casos el orden de los pasos tiene que controlarse para evitar incompatibilidades de grupos funcionales. Una persona con experiencia en el arte reconocerá que una vía más convergente (es decir no lineal o pre-montaje de ciertas porciones de la molécula) es un método más eficiente del montaje de los

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compuestos blanco. Los métodos apropiados para la preparación de los derivados indólicos 2,3 sustituidos se indicaron con anterioridad en los Esquemas 1–6.

Los materiales de partida e intermediarios preparados usando los métodos mencionados en los Esquemas 1–6 pueden aislarse y purificarse si se desea usando técnicas convencionales, incluyendo sin carácter limitativo filtración, destilación, cristalización, cromatografía y similares. Dichos materiales pueden caracterizarse usando medios convencionales, incluyendo constantes físicas y datos espectrales.

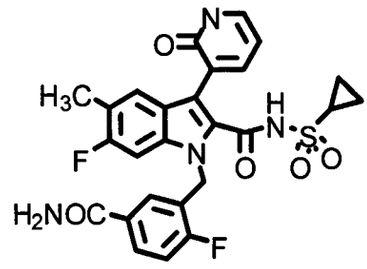
EJEMPLOS

Métodos Generales

Los solventes, reactivos e intermediarios que se encuentran disponibles en el mercado se usaron como se los recibió. Los reactivos e intermediarios que no se encuentran en el mercado se prepararon de un modo como se describe a continuación. Los espectros de ^{1}H RMN se obtuvieron en un instrumento Bruker Avance 500 (500 MHz) y se informan como ppm a partir de Me_4Si con número de protones, multiplicidades y constantes de acoplamiento en Hertz indicados entre paréntesis. Donde se presentan datos de CL/EM, el análisis se realizó un espectrómetro de masa Applied Biosystems API–100 y columna de CL Shimadzu SCL–10A: Altech platinum C18, 3 micrones, 33 mm x 7mm ID; flujo gradiente: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 5–7 min – 95% CH_3CN, 7 min – detención. Se incluyen el tiempo de retención y el ion progenitor observado. Se realizó la cromatografía flash en columna usando sílice de fase pre-empacada normal de Biotage, Inc. o sílice a granel de Fisher Scientific.

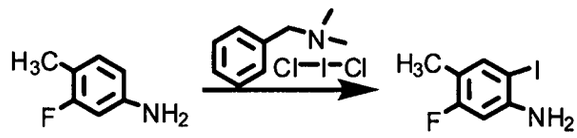
Ejemplo 1

Preparación del compuesto **600**



600

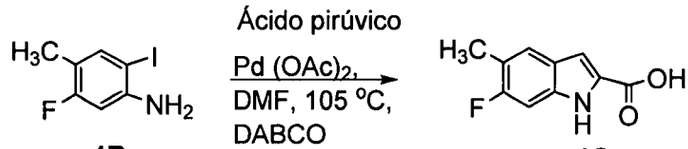
Paso 1:



1A **1B**

A una solución de 3–Fluoro–4–metil–fenilamina (**1A**) (8,0 g, 64 mmol) en diclorometano (500 ml) y MeOH (100 ml) se agregó dicloroyodato de benciltrimetilamonio (23,8 g, 67,4 mmol) y carbonato de calcio (12,8g, 133 mmol). Se dejó agitar la suspensión a temperatura ambiente durante 1h, los sólidos se retiraron por filtración y el filtrado se concentró. El producto en bruto concentrado se disolvió nuevamente en CH_2Cl_2, se lavó sucesivamente con 5% $NaHSO_4$, $NaHCO_3$ saturado, agua, salmuera y se secó sobre $MgSO_4$. La fase orgánica se concentró y el bruto se purificó usando cromatografía sobre SiO_2 (330 g, columna flash) usando 0 hasta 20% acetato de etilo en hexano para proporcionar el compuesto **1B** (13,4g, 87%). ^1H RMN (400 MHz, $CDCl_3$): δ 2,12 (s, 3H), 4,2 (s amplio, 2H), 6,51 (d, J = 10,8 Hz, 1H), 7,43 (d, J = 8,4 Hz, 1H).

Paso 2:



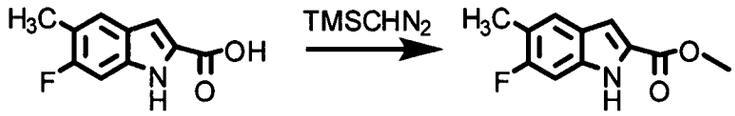
1B **1C**

Una solución del 5–fluoro, 4–metil yodo anilina (**1B**) (13,4g, 53,5 mmol), $Pd(OAc)_2$ (607 mg, 2,7 mmol), ácido pirúvico (14,28 g, 162,0 mmol) y DABCO

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(18,2g, 162 mmol) en DMF (120 ml) se desgasificó y se calentó hasta 105°C durante 4h, se enfrió hasta la temperatura ambiente y se repartió entre acetato de etilo y agua. La fase acuosa se extrajo dos veces más con acetato de etilo. La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se concentró y el sólido marrón se lavó con acetato de etilo/hexanos y se filtró para proporcionar el compuesto **1C** como un sólido blanco (8,3g, 83%) que se usó directamente en el paso siguiente. ^{1}H RMN (400 MHz, d_6–DMSO): δ 2,0 (s amplio, 1H), 2,25 (s, 3H), 7,0 (s, 1H), 7,15 (d, *J* = 11 Hz, 1H), 7,49 (d, J = 7,3 Hz, 1H), 11,7(s, 1H).

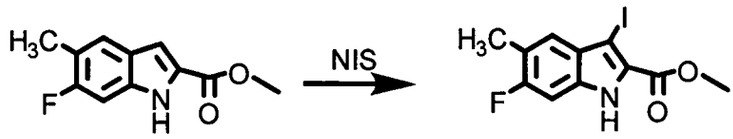
Paso :



1C **1D**

A una solución enfriada de ácido 6–Fluoro–5–Metil–1H–indol–2–carboxílico en MeOH/tolueno (**1C**)(200 ml, 1 : 1) se agregó TMS–diazometano (solución 2,0M en dietiléter, 1,05 eq.) gota a gota y la reacción se dejó entibiar hasta la temperatura ambiente durante 1h. La mezcla de reacción se concentró y se purificó triturando con CH_2Cl_2 y hexano y recolectando los sólidos por filtración para obtener metil éster del ácido 6–Fluoro–5–Metil–1*H*–indol–2–carboxílico **1D** (3,5 g). El filtrado concentrado se purificó usando cromatografía sobre SiO_2 usando 0 hasta 40% acetato de etilo en hexanos para proporcionar una cantidad adicional de metil éster del ácido 6–Fluoro–5–Metil–1*H*–indol–2–carboxílico **1D** (1,0 g). Rendimiento general (60%). ^{1}H RMN (400 MHz, d_6–DMSO): δ 2,26 (s, 3H), 3,83 (s, 3H), 7,07 (s, 1H), 7,08 (d, *J* = 10,2 Hz, 1H), 7,49 (d, *J* = 8,1 Hz, 1H), 11,9 (s, 1H).

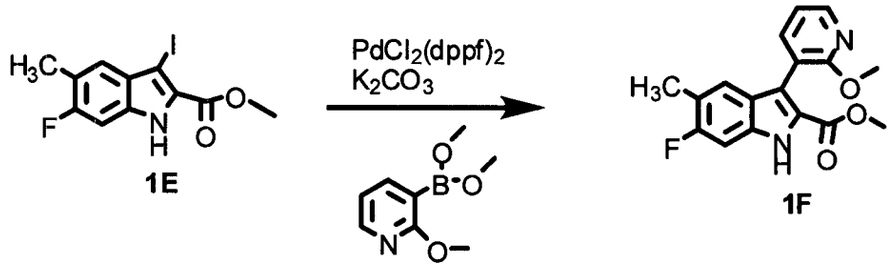
Paso 4:



1D **1E**

A una solución de metil éster del ácido 6—Fluoro—5—Metil—1H—indol—2—carboxílico **1D** (3,53g, 17,03 mmol) en $CHCl_3$/THF (100 ml, 5:1) se agregó NIS (3,83 g, 17,03 mmol) y la mezcla de reacción se dejó agitar a temperatura ambiente hasta la mañana siguiente. La mezcla de reacción se concentró y se disolvió nuevamente Acetato de etilo y se lavó con 1M $Na_2S_2O_3$, $NaHCO_3$ saturado, agua y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró, se concentró y el producto se trituró usando acetato de etilo/hexanos y se filtró para proporcionar el compuesto **1E** (5,34g, 94,1%). ^1H RMN (400 MHz, $CDCl_3$): δ 2,39(s, 3H), 3,97 (s, 3H), 7,07 (d, J = 9,5 Hz, 1H), 7,32 (d, J = 7,3 Hz, 1H), 9,1 (s, 1H).

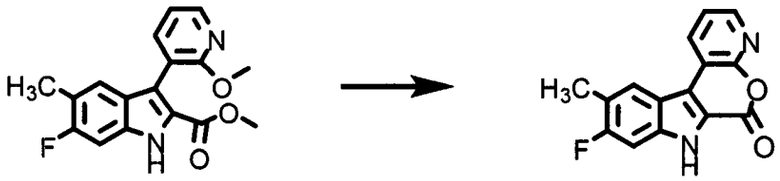
Paso 5:



Se agregó ácido 2–metoxi–3–piridin borónico (2,94 g, 19,23 mmol) a una solución de metil éster del ácido 6–Fluoro–3–iodo–5–metil–1*H*–indol–2–carboxílico **1E** (5,34 g, 16,03 mmol) en 1, 2 dimetoxietano (105 ml). La mezcla se desgasificó y $PdCl_2(dppf)_2$ (1,3g, 1,60 mmol) se agregó a la mezcla de reacción. Luego de dejar la solución naranja resultante agitar a temperatura ambiente durante 30 minutos., se agregó una solución de K_2CO_3 (8,86g en 64ml de H_2O). La solución marrón resultante se dejó agitar a 90°C durante 4h, se enfrió hasta la temperatura ambiente y se diluyó usando acetato de etilo. La fase orgánica se lavó con agua, salmuera y se secó sobre $MgSO_4$. El filtrado concentrado se purificó sobre SiO_2 usando 0 hasta 30% acetato de etilo en hexanos para proporcionar el compuesto **1F** como un sólido blanco (4,14g, 82%). ^1H RMN (400

MHz, d_6–DMSO): δ 2,06 (s, 3H), 3,68 (s, 3H, 3,76 (s, 3H), 7,08 (m, 1H), 7,19 (m, 2H), 7,65 (d, J = 10,0 Hz, 1H), 8,20 (m, 1H).

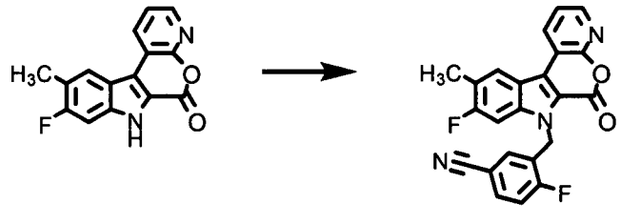
Paso 6:



1F **1G**

A metil éster del ácido 6–Fluoro–3–(2–Metoxi–piridin–3–il)–5–metil–1*H*–2–carboxílico **1F** (4,14g, 13,17 mmol) se agregó HCl 4N en dioxano (40 ml) y la mezcla de reacción se calentó a 80°C durante 12h, se enfrió y se concentró para proporcionar metil éster del ácido 6–Fluoro–3–(2–hidroxi–piridin–3–il)–5–metil–1*H*–2–carboxílico. Al producto en bruto del último paso se agregó LiOH (1,65g, 39,51 mmol) en THF/MeOH/H_2O (75 ml, 2:2:1) y la emulsión se calentó a 65°C durante 12 horas, se enfrió, se lavó con HCl 1 N y agua. El producto se filtró, se lavó con acetato de etilo y se secó al vacío para proporcionar ácido 6–Fluoro–3–(2–hidroxi–piridin–3–il)–5–metil–1*H*–2–carboxílico (3,59g, 95,2% en 2 pasos) y se usó directamente en el paso siguiente. Al hidroxiácido (3,59g, 12,54 mmol) del paso anterior en DMF (70,0 ml) se agregó EDCI.HCl (4,8 g, 25,08 mmol) y Et_3N (8,73 ml, 62,7 mmol) y la mezcla de reacción se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con acetato de etilo, la emulsión se lavó con agua y se filtró. La fase de acetato de etilo se lavó con HCl 1N, salmuera, se secó sobre $MgSO_4$ y se concentró al vacío y el bruto se agregó al filtrado del paso anterior y se secó al vacío para proporcionar 9–Fluoro–10–metil–7H–5–oxa–4,7–diaza–benzo[c]fluoren–6–ona **1G** como un sólido blanco (3,36g, 75%). ^{1}H RMN (400 MHz, d_6–DMSO): δ 2,40 (s, 3H), 7,28 (d, J = 10Hz, 1H), 7,54 (m, 1H), 8,40 (m, 2H), 8,87 (d, J = 7,2 Hz, 1H).

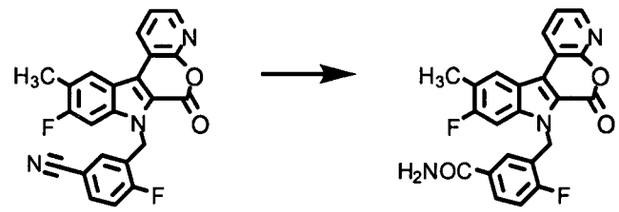
Paso 7:



1G 1H

A una solución de 9–Fluoro–10–metil–7H–5–oxa–4,7–diaza–benzo[c]fluoren–6–ona **1G** (167 mg, 0,622 mmol) en DMF (3,0 ml) se agregó 3–Bromometil–4–fluoro–benzonitrilo (160,0 mg, 0,747 mmol) y $CsCO_3$ (243 mg, 0,747 mmol) a temperatura ambiente y la mezcla de reacción se dejó agitar hasta la mañana siguiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El producto en bruto concentrado se purificó usando cromatografía sobre SiO_2 usando 0 hasta 30% acetato de etilo en hexano para proporcionar 4–Fluoro–3–(9–fluoro–10–metil–6–oxo–6*H*–5–oxa–4,7–diaza–benzo[c]fluoren–7–ilmetil)–benzonitrilo **1H** (200 mg, 80%). E. M. encontrada para C23H13F2N3O2: 402,9 $(M+H)^+$.

Paso 8:

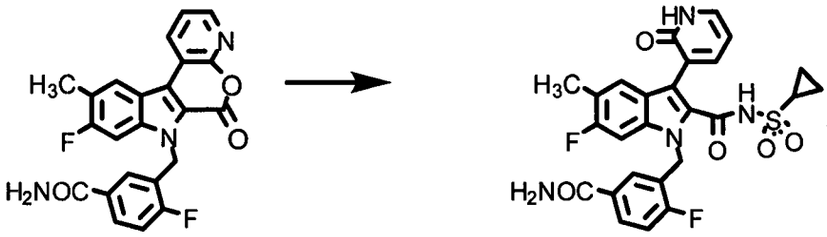


1H 1I

A una solución de 4–Fluoro–3–(9–fluoro–10–metil–6–oxo–6*H*–5–oxa–4,7–diaza–benzo[c]fluoren–7–ilmetil)–benzonitrilo **1H** (126 mg, 0,313 mmol) en AcOH (1,0 ml) se agregó H_2SO_4 (4 gotas). La mezcla de reacción se calentó a 100ºC durante 12h y se concentró al vacío. Los sólidos se lavaron con agua y acetato de etilo y se secaron con alto vacío para proporcionar el compuesto **1I** como un sólido blanco (124,0 mg, 94%). E. M. encontrada para C23H15F2N3O3: 420,1 $(M+H)^+$.

Paso 9 :

610

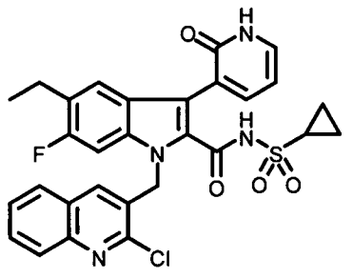


1l **600**

Una emulsión de 9–Fluoro–10–metil–7H–5–oxa–4,7–diaza–benzo[c]fluoren–6—ona **A9** (34 mg, 0,08 mmol) **y** ciclopropil sulfonamida (20,0 mg, 0,165 mmol) en DMF anhidra (3,0 ml) se trató con NaH (16,0 mg, 0,4 mmol, suspensión al 60% en aceite mineral). La mezcla de reacción se calentó hasta la mañana siguiente a 40°C. El pH de la mezcla de reacción enfriada (temperatura ambiente) se ajustó hasta pH=3 con HCl 1N y se extrajo con acetato de etilo. La fase de acetato de etilo se lavó con agua, salmuera y se filtró a través de Na_2SO_4. El producto en bruto concentrado se purificó usando HPLC usando una columna C18 eluyendo con 20 –90% CH_3CN/H_2O como gradiente para proveer el compuesto **600**. E. M. encontrada para C26H22F2N4O5S: 541,3 $(M+H)^+$.

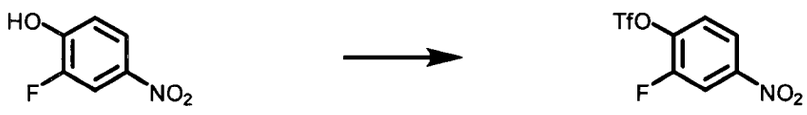
Ejemplo 2

Preparación del compuesto **601**



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Paso 1:



2A **2B**

Una solución de 2–fluoro–4–nitro–fenol (**2A**) (2,53 g; 16,1 mmol) en 60 ml de diclorometano anhidro y 5 ml de THF anhidro se enfrió con hielo y se trató con

piridina (10 ml) y anhídrido tríflico (1,1 eq, 5,0 g, d 1,677). La mezcla se dejó agitar durante 10 min y se trató con una cantidad catalítica de 4–dimetilamino piridina (punta de espátula). Se retiró el baño de frío y la reacción se dejó agitar durante 1 hora. La TLC (10% acetato de etilo en hexanos) mostró que no quedaba material de partida y la mezcla se diluyó con acetato de etilo (300 ml) y se lavó con bicarbonato de sodio saturado ac. (80 ml) y salmuera (80 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó sobre gel de sílice (Columna Biotage 40—M; gradiente: 0 hasta 10% acetato de etilo en hexanos) para proporcionar el compuesto **2B** (4,0 g; 87%) como un aceite incoloro.

Paso 2:

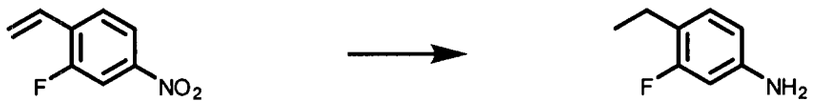


2B **2C**

Una solución de 2–fluoro–4–nitro–fenilo éster del ácido trifluoro–metansulfónico (**2B**) (13,2 g; 45,64 mmol) en 225 ml of THF se trató con cloruro de litio (7,0 eq, 13,5 g) y tributil(vinil)estaño (2,0 eq, 26,6 ml, d 1,085). La mezcla se desgasificó (vacío/enjuague de nitrógeno) y se agregó tetrakis(trifenilfosfin)paladio (10% en moles, 5,26 g). La mezcla de reacción se calentó hasta 80°C y se agitó hasta la mañana siguiente. La TLC (5% acetato de etilo en hexanos) mostró el consumo completo de material de partida. La mezcla se diluyó con agua (100 ml) y se extrajo con 1:1 éter/acetato de etilo (900 ml). La fase orgánica se lavó con hidróxido de amonio acuoso al 10% (100 ml), agua (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre una columna Biotage 40-S (gradiente: 0 hasta 4% acetato de etilo en hexanos) para proporcionar el compuesto **2C** (7,6 g; 99%) como un aceite

levemente amarillo que contiene algunas impurezas de estanano (aproximadamente 1,4 g)

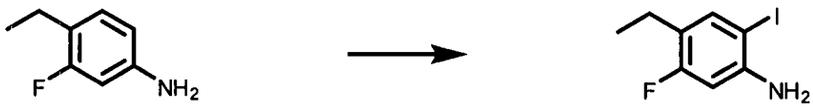
Paso 3:



2C **2D**

Una solución de 2–fluoro–4–nitro–1–vinil-benceno (**2C**) (42,65 mmol) en 140 ml of metanol se trató con una cantidad catalítica de paladio sobre carbón al 10% (aprox 1,0 g). La mezcla se hidrogenó a 35 psi durante 2 horas. La TLC (10% acetato de etilo en hexanos) mostró el consumo completo de material de partida. La mezcla se diluyó con diclorometano (100 ml) y se filtró a través de un paso corto de celite. Los sólidos se lavaron con diclorometano (100 ml). El filtrado, que contiene el producto **2D**, se usó para la siguiente reacción .

Paso 4:



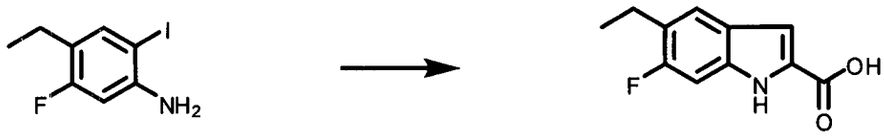
2D **2E**

Una solución de 4–etil–3–fluoro–fenilamina (**2D**) (la solución filtrada del paso anterior) se trató con dicloroyodato de benciltrimetilamonio (1,1 eq, 16,3 g) y carbonato de calcio (2,0 eq, 8,53 g). Se dejó agitar la suspensión a temperatura ambiente durante 1 hora. La TLC (10% acetato de etilo en hexanos) mostró el consumo completo de material de partida. Los sólidos se retiraron por filtración (whatman #1) y el filtrado se concentró *al vacío* . El residuo se repartió entre 800 ml de 1:1 éter/acetato de etilo y sulfato hidrógeno de sodio acuoso al 5% (200 ml). La fase orgánica se lavó con agua (200 ml) y salmuera (200 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se cromatografió sobre una columna Biotage 65-M (gradiente: 0 hasta 10% éter en hexanos) para proporcionar el compuesto **2E** (8,5

613

g; 76%) como un aceite amarillo que contiene algunas impurezas de estanano del paso anterior.

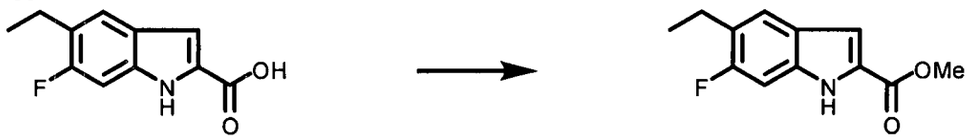
Paso 5:



2E **2F**

Una solución de 4–etil–5–fluoro–2–yodo–fenilamina (**2E**) (7,29 g; 27,50 mmol) en 60 ml de DMF anhidra se trató con ácido pirúvico (3,0 eq, 7,26 g, d 1,267) y DABCO (3,0 eq, 9,24 g). La mezcla se desgasificó (vacío/enjuague de nitrógeno) y se agregó acetato de paladio (II) (0,05 eq, 308 mg). La solución resultante se calentó hasta 105°C durante 3 horas. Los volátiles se retiraron *al vacío* (bomba de alto vacío) y el residuo se repartió entre acetato de etilo (200 ml) y agua (200 ml). La fase acuosa se extrajo nuevamente con acetato de etilo (4 x 100 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y se concentraron al vacío para proporcionar el producto en bruto **2F** como un aceite marrón oscuro. No se llevó a cabo purificación adicional.

Paso 6:

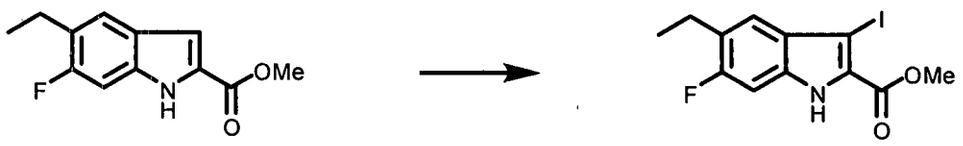


2F **2G**

A una solución enfriada con hielo de ácido 5–etil–6–fluoro–1H–indol–2–carboxílico (**2F**) (27,5 mmol) en 300 ml de 2:1 tolueno/metanol se agregó lentamente una solución de TMS–diazometano en éter (2,0 eq, 27,5 ml de 2,0M). Luego de completar la incorporación se retiró el baño de frío y la mezcla de reacción se dejó agitar durante 1 hora. La mezcla se concentró *al vacío* para proporcionar el producto en bruto como un sólido marrón. La mezcla se adsorbió sobre gel de sílice y se purificó sobre una columna Biotage 65-M (gradiente: 10

hasta 50% diclorometano en hexanos) para proporcionar el compuesto **2G** (3,0 g; 50% para dos pasos) como un sólido blanco.

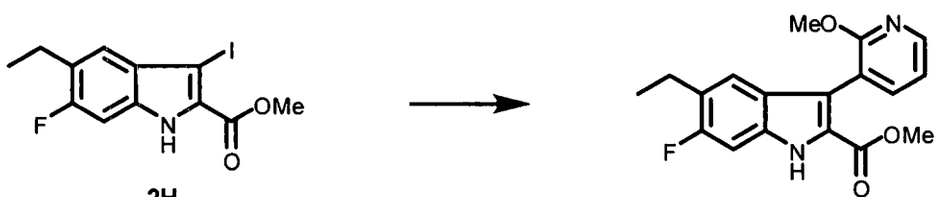
Paso 7:



2G **2H**

Una solución de metil éster del ácido 5–etil–6–fluoro–1H–indol–2–carboxílico (**2G**) (2,6 g; 11,75 mmol) en 60 ml de 1:1 THF–cloroformo se enfrió con hielo y se trató con N–yodosuccinimida (1,15 eq, 3,04 g). Se retiró el baño de frío y la mezcla se dejó agitar durante 2 horas. La TLC (20% acetato de etilo en hexanos) mostró el consumo casi completo de material de partida. La mezcla de reacción se diluyó con acetato de etilo (300 ml) y se lavó con bicarbonato de sodio saturado ac. (2 x 60 ml) y salmuera (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **2H** (4,0 g; 99%) como un sólido levemente amarillo que se usó sin purificación adicional.

Paso 8:

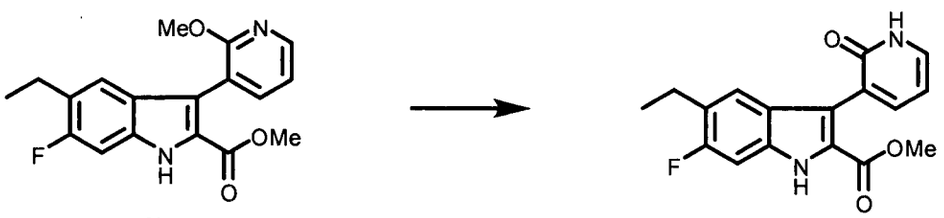


2H **2I**

Se agregó ácido 2–Metoxipiridina–3–borónico (1,5 eq, 2,69 g) a una solución de metil éster del ácido 5–etil–6–fluoro–3–yodo–1H–indol–2–carboxílico (**2H**) (11,75 mmol) en 120 ml de 1,2–dimetoxietano. La mezcla se desgasificó (vacío/enjuague de argón) y se agregó catalizador de paladio (10% en moles, 960 mg de $PdCl_2(dppf)_2$) y la solución naranja resultante se dejó agitar durante 10 min a temperatura ambiente. Se agregó una solución de carbonato de potasio (4,0 eq, 23,5 ml de solución acuosa 2M) y la mezcla marrón resultante se

dejó agitar a 85°C durante 2 h momento en el cual la TLC (20% acetato de etilo en hexanos) mostró el consumo casi completo de material de partida. La mezcla de reacción se enfrió hasta la temperatura ambiente y se diluyó con acetato de etilo (300 ml), se lavó con bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se adsorbió sobre gel de sílice y se purificó sobre una columna Biotage 65-M (gradiente: 0 hasta 15% acetato de etilo en 1:1 hexanos–diclorometano) para proporcionar el compuesto **2I** (3,3 g; 86%) como un sólido blanco.

Paso 9:

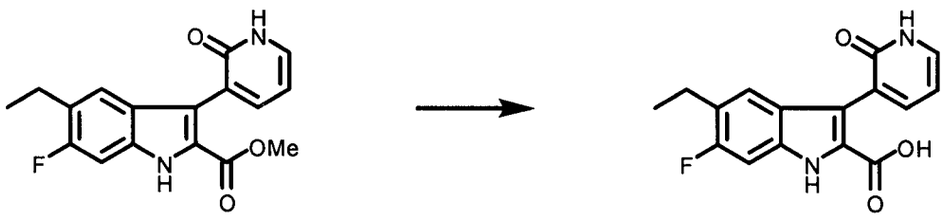


2I **2J**

El metil éster del ácido 5–etil–6–fluoro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico (**2I**) (3,3 g; 10,05 mmol) se disolvió parcialmente en 10 ml de metanol seguido de la incorporación de 40 ml de solución 4 M de HCl en dioxano. La solución resultante se calentó en un tubo sellado a 85°C durante 3 horas. La TLC (40% acetona en 1:1 DCM–hexanos) mostró aproximadamente 40% de conversión. Todos los volátiles se retiraron *al vacío* y el residuo se disolvió nuevamente en solución 4M de HCl en dioxano (40 ml). La mezcla se calentó en un tubo sellado (90°C) durante 3 horas. La TLC mostró restos de algo de material de partida. Todos los volátiles se eliminaron nuevamente *al vacío* y el residuo se adsorbió sobre gel de sílice. La purificación sobre una Columna Biotage 40—M (gradiente: 20 hasta 60% acetona en 1:1 DCM–hexanos) dio el producto **2J** (2,0 g; 63%) como un sólido levemente amarillo.

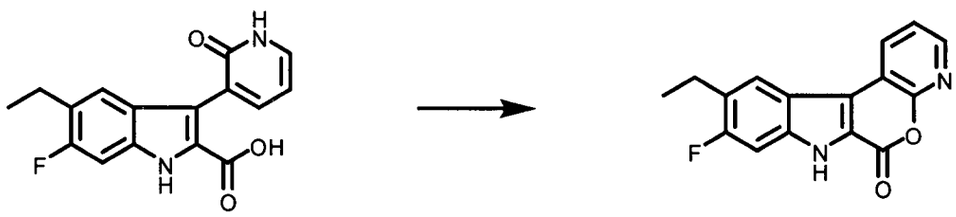
616

Paso 10:



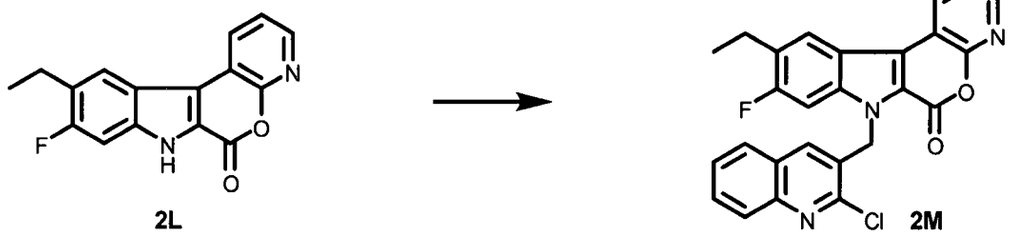
Una solución de metil éster del ácido 5–etil–6–fluoro–3–(2–oxo–1,2–dihidro–piridin–3–il)–1H–indol–2–carboxílico (**2J**) (1,9 g; 6,04 mmol) en 100 ml de 6:1:1 THF/agua/metanol se trató con hidróxido de litio monohidrato (2,5 eq, 634 mg). La mezcla de reacción se dejó agitar a 50ºC y se monitoreó por TLC (50% acetona en 1:1 DCM–hexanos). La totalidad del material de partida se había consumido luego de 3 h (el producto se precipitó en la mezcla de reacción). La mezcla se trató con HCl 1M acuoso (100 ml) y el producto **2K** (1,80 g; 99%) se recuperó por filtración (whatman #1) como un sólido blanco.

Paso 11:



El ácido 5–etil–6–fluoro–3–(2–oxo–1,2–dihidro–piridin–3–il)–1H–indol–2–carboxílico (**2K**) (500 mg; 1,665 mmol) se suspendió en DMF anhidra (40 ml) y se trató con EDCI (2,0 eq, 638 mg) y trietilamina (10,0 eq, 2,33 ml, d 0,72). La mezcla se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla se concentró hasta la sequedad *al vacío* (bomba de alto vacío). El residuo se trató con metanol (10 ml) para producir una suspensión homogénea. El producto se recuperó por filtración (whatman #1) y se lavó con metanol (2 x 5 ml). El producto **2L** (282 mg; 60%) se obtuvo de este modo como un sólido blanco.

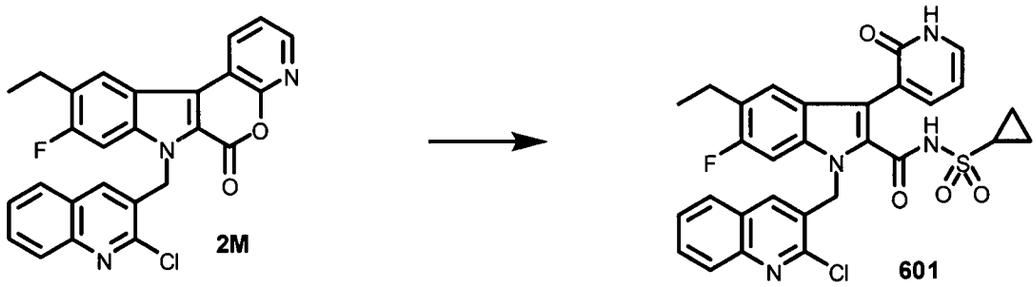
Paso 12:



2L **2M**

La lactona **2L** (40 mg, 0,141 mmol) se suspendió en 2 ml de DMF anhidra y se trató con 2–cloro–3–clorometil–quinolina (1,2 eq, 36 mg) y carbonato de cesio (2,0 eq, 92 mg). Una cantidad catalítica de yoduro de tetrabutilamonio (punta de espátula) se agregó y la mezcla se dejó agitar a temperatura ambiente. La TLC (30% acetato de etilo en hexanos) mostró el consumo completo de material de partida luego de 1 hora. La mezcla se diluyó con 50 ml de 4:1 DCM–THF y se lavó con agua (10 ml). La fase orgánica se concentró *al vacío* para proporcionar el producto en bruto **2M** (65 mg, 99%) que se usó sin purificación adicional.

Paso 13:



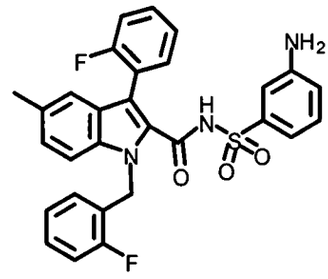
2M **601**

La lactona **2M** (65 mg; 0,141 mmol) se suspendió en 3 ml de DMF anhidra seguido de la incorporación de ciclopropan sulfonamida (1,2 eq, 20 mg) e hidruro de sodio (2,0 eq, 11 mg de suspensión al 60% en aceite mineral). La mezcla se dejó agitar a temperatura ambiente y finalmente se tornó en una solución homogénea (luego de 15 min). La TLC (30% acetato de etilo en hexanos) mostró el consumo completo de material de partida luego de 20 minutos. La reacción se desactivó por la incorporación de 5 gotas de HCl 1M ac. y se diluyó en forma adicional con 5 ml de DMF. La solución se inyectó en un sistema de HPLC semi-

prep. en las siguientes condiciones: Columna Delta Pak, C18, 5 micrómetros, 300A; 300 x 30 mm D. I.; Caudal de flujo: 30 ml/min; Gradiente: 40% acetonitrilo (0,01% TFA) en agua (0,01% TFA) durante 10 min luego aumentar hasta 90% durante 20 min y reposar durante 10 minutos. La fracción que contiene el producto (27 min) de acuerdo con el análisis por EM se concentró *al vacío* para proporcionar el compuesto **601** (42 mg; 52%) como un sólido blanco. Parte del producto (23 mg) se disolvió en THF (3 ml) y se trató con solución acuosa 1M de NaOH (1,2 eq, 0,047 ml de solución ac. 1M). La mezcla se dejó agitar durante 10 min y luego se concentró al vacío para proporcionar la sal de sodio del compuesto **601** (23,8 mg).

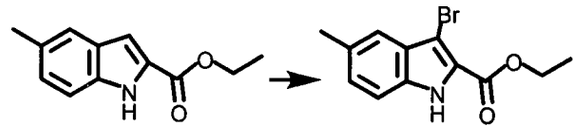
Ejemplo 3

Preparación del Compuesto **271**



271

Paso 1:

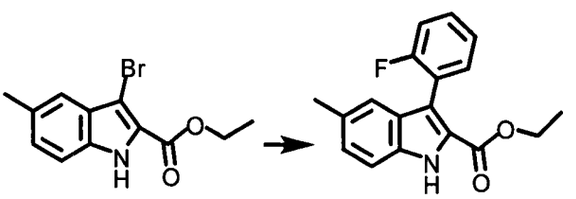


3A **3B**

A una solución de etil éster del ácido 5–metil–1H–indol–2–carboxílico, **3A** (10,17 g, 50,03 mmol) en THF (100 ml) en un baño de agua a temperatura ambiente se agregó lentamente NBS (8,91 g, 50,06 mmol). La solución resultante se dejó agitar a temperatura ambiente durante 3,5 h antes de agregar (800 ml). La mezcla resultante se dejó agitar a temperatura ambiente durante 20 min y luego se filtró. El sólido se lavó con agua (2 x 100 ml), se secó *al vacío* para

proporcionar el producto en bruto **3B** como un polvo (13,8 g, 98% de rendimiento). ^{1}H RMN (500 MHz, CDCl3):δ 8,91 (s, 1H), 7,44 (q, J= 0,95 Hz & 0,63 Hz, 1H), 7,28 (d, J= 8,51 Hz, 1H), 7,21 & 7,19 (dd, J= 1,58 Hz & 8,51 Hz, 1H), 4,46 (q, J= 6,94 Hz & 7,25 Hz, 2H), 2,47 (s, 3H), 1,45 (t, J= 7,25 Hz, 3H).

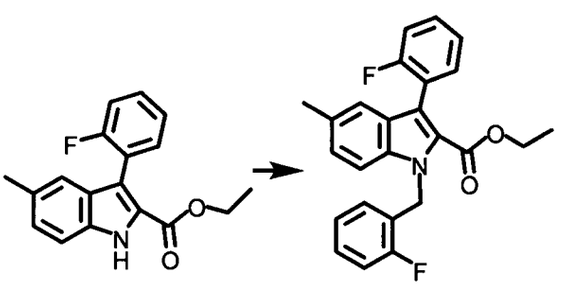
Paso 2:



3B **3C**

A una solución de etil éster del ácido 3–bromo–5–metil–1H–indol–2–carboxílico, **3B** (5,00 g, 17,72 mmol) en DME (80 ml) se agregaron ácido 2–fluorofenilborónico (3,72 g, 26,58 mmol) y complejo [1,1'–bis(difenilfosfin)ferroceno]–dicloropaladio(II) diclorometano (1:1) (1,45 g, 1,77 mmol). Una solución de carbonato de sodio (17 ml de 1,5 M, 25,5 mmol) se agregó a la mezcla anterior a través de una jeringa. La mezcla de reacción se desgasificó, y luego se agitó a reflujo durante 6 horas. La mezcla de reacción luego se enfrió hasta la temperatura ambiente, y se filtró a través de un taco de celite. El filtrado se concentró bajo presión reducida, y el residuo se purificó usando cromatografía flash sobre gel de sílice para proporcionar el compuesto **3C** como un sólido blanco (4,79 g, 90% de rendimiento). E. M. encontrada para $C_{18}H_{16}FNO_2$: 298,3 $(M+H)^+$.

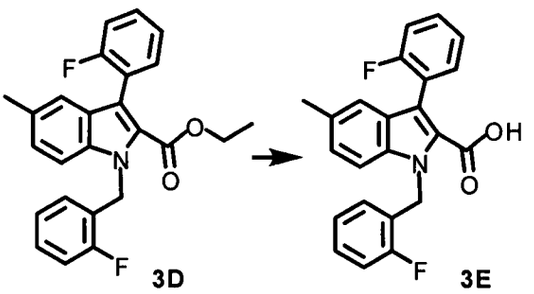
Paso 3:



3C **3D**

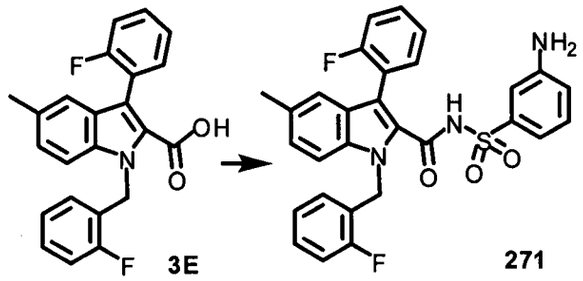
Una suspensión de etil éster del ácido 3–(2–fluoro–phenil)–5–metil–1H–indol–2–carboxílico, **3C** (860 mg, 2,88 mmol), cloruro de 2-fluorobencilo (570 mg, 3,94 mmol), y carbonato de cesio (2,10 g, 6,47 mmol) en DMF (3 ml) se dejó agitar a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con acetato de etilo (300 ml), y se lavó con agua (3 x 80 ml). La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía flash sobre gel de sílice para proporcionar el compuesto **3D** como un aceite incoloro (0,95 g, 81% de rendimiento). E. M. encontrada para $C_{25}H_{21}F2NO_2$: 406,2 $(M+H)^+$.

Paso 4:



A una solución de etil éster del ácido 1–(2–fluoro–bencil)–3–(2–fluoro–fenil)–5–metil–1H–indol–2–carboxílico, **3D** (950 mg, 2,34 mmol) en THF (20 ml) se agregó con una solución acuosa de hidróxido de litio (3,5 ml de 1 M, 3,5 mmol). La solución resultante se mantuvo a reflujo durante 5 días antes de enfriar hasta la temperatura ambiente. Luego de la concentración bajo presión reducida, el residuo se disolvió en metanol (10 ml), se neutralizó con solución acuosa 1,0 M de HCl (8 ml, 8,0 mmol), y luego se concentró nuevamente bajo presión reducida. El residuo se extrajo con acetato de etilo (2 x 50 ml). La fase orgánica combinada se concentró y se secó al vacío para proporcionar el compuesto **3E** (910 mg, ~100% de rendimiento). E. M. encontrada para $C_{23}H_{17}F2NO_2$: 378,2 $(M+H)^+$.

Paso 5:

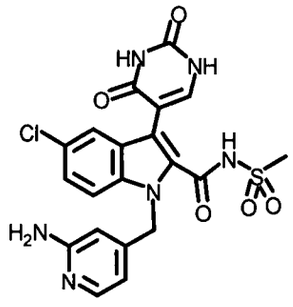


3E 271

A una solución de ácido 1–(2–fluoro–bencil)–3–(2–fluoro–fenil)–5–metil–1H–indol–2–carboxílico, **3E** (135 mg, 0,36 mmol) en THF (3 ml) se agregó 1,1'–carbonildiimidazol (84 mg, 0,52 mmol). La mezcla de reacción se calentó a reflujo bajo nitrógeno durante 1 hora. La mezcla luego se enfrió hasta la temperatura ambiente, y se agregaron 3–aminofenilsulfonamida (100 mg, 0,58 mmol) y DBU (90 mg, 0,58 mmol). La mezcla de reacción se dejó agitar a reflujo durante 2,5 horas. La mezcla se enfrió hasta la temperatura ambiente, y se concentró al vacío. El residuo se purificó usando TLC prep. sobre gel de sílice usando 5% metanol en diclorometano para proporcionar el compuesto **271** (113 mg, 59%). ^{1}H RMN (500 MHz, CD3OD): δ 7,48 (t, J= 6,15 Hz, 1H), 7,43–7,38 (m, 2H), 7,34–7,13 (m, 9H), 7,03 (t, J= 9,30 Hz, 1H), 6,95–6,91 (m, 2H), 6,73 (t, J= 7,09 Hz, 1H), 5,65 (s, 2H), 3,68 (s, 3H), 2,40 (s, 2H). E. M. encontrada para $C_{29}H_{23}F_2N_3O_3S$: 532,3 $(M+H)^+$

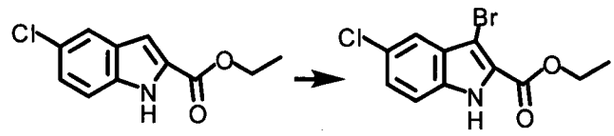
Ejemplo 4

Preparación del compuesto **103**



103

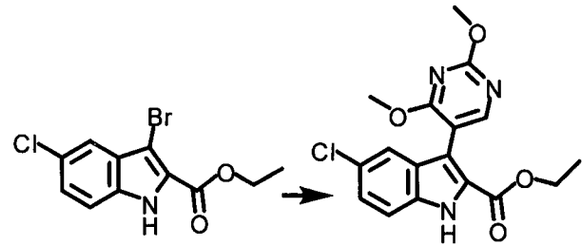
Paso 1:



4A **4B**

A una solución de 5–cloroindol–2–carboxilato de etilo, **4A** (20 g, 89,6 mmol) en THF (200 ml) en un baño de agua enfriada se agregó NBS (16,0 g, 89,9 mmol) lentamente. La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 18 h antes de agregar agua (700 ml). La mezcla continuó con la agitación a temperatura ambiente durante 20 min y luego se filtró. Los sólidos se lavaron con agua (2 x 100 ml), y se secaron para proporcionar el producto en bruto **4B** (25,8 g, 90% de rendimiento). ^{1}H RMN (500 MHz, CDCl3) δ 9,06 (s, 1H), 7,66–7,65 (m, 1H), 7,35–7,31 (m, 2H), 4,47 (q, J= 7,25 Hz, 2H), 1,46 (t, J= 7,09 Hz, 3H).

Paso 2:

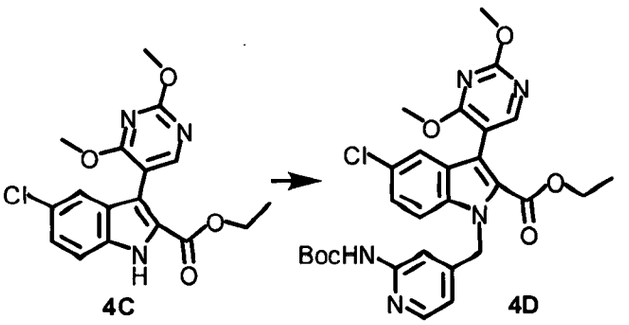


4B **4C**

A una mezcla de etil éster del ácido 3–bromo–5–cloro–1H–indol–2–carboxílico, **4B** (1,00 g, 3,31 mmol), ácido 2,4–dimetoxipirimidin–5–borónico (0,73 g, 3,97 mmol), complejo [1,1'–bis(difenilfosfin)ferroceno]dicloropaladio(II) con diclorometano (1:1) (0,26 g, 0,32 mmol) en DME (15 ml) se agregó una solución de carbonato de sodio (4,5 ml de 1,5 M, 6,75 mmol) a través de una jeringa. La mezcla de reacción se dejó agitar a reflujo durante 6 h antes de bajar la temperatura hasta la temperatura ambiente. La mezcla se diluyó con diclorometano (50 ml), y luego se filtró a través de un taco de celite. El filtrado se concentró bajo presión reducida. El residuo se purificó usando cromatografía flash sobre gel de sílice (20% acetato de etilo en hexanos) para proporcionar el

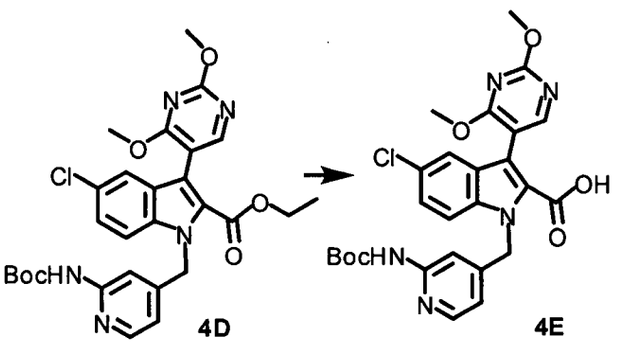
compuesto **4C** como un sólido blanco (0,47 g, 39% de rendimiento). E. M. encontrada para $C_{17}H_{16}ClN_3O_4$: 362,2 $(M+H)^+$.

Paso 3:



A una solución de etil éster del ácido 5–cloro–3–(2,4–dimetoxi–pirimidin–5–il)–1H–indol–2–carboxílico, **4C** (620 mg, 1,71 mmol) en DMF se agregaron ter-butil éster del ácido (4–bromometil–piridin–2–il)–carbámico (490 mg, 1,71 mmol) y carbonato de cesio (1100 mg, 3,39 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 17 horas. Luego se diluyó la mezcla con acetato de etilo (80 ml), y se lavó con agua (3 x 50 ml). La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía sobre gel de sílice usando 30% acetato de etilo en hexanos para proporcionar el compuesto **4D** (705 mg, 73% de rendimiento). E. M. encontrada para $C_{28}H_{30}ClN_5O_6$: 568,3 $(M+H)^+$.

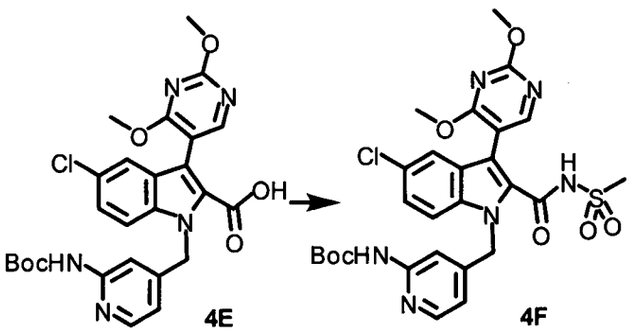
Paso 4:



A una solución de etil éster del ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–5–cloro–3–(2,4–dimetoxi–pirimidin–5–il)–1H–indol–2–carboxílico, **4D** (500 mg, 0,88 mmol) en THF (10 ml) se agregó una solución

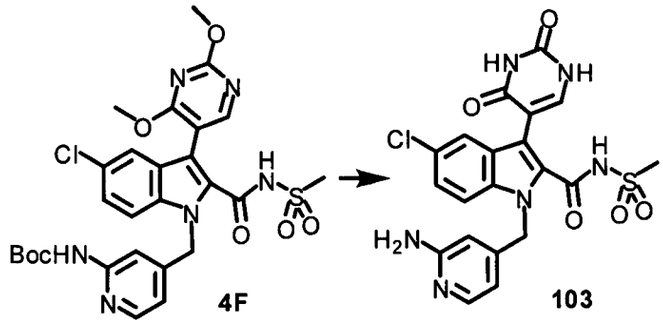
acuosa de hidróxido de litio (2,0 ml de 1 M, 2,9 mmol). La mezcla de reacción resultante se dejó agitar a reflujo durante 16 horas. La reacción luego se enfrió y se concentró al vacío. El residuo se disolvió en metanol (80 ml), se neutralizó con solución acuosa 1,0 M de HCl (2,5 ml, 2,5 mmol) y luego se concentró nuevamente bajo presión reducida. El residuo se extrajo con diclorometano (3 x 30 ml). La fase orgánica combinada se concentró bajo presión reducida, y se secó al vacío para proporcionar el compuesto **4E** (440 mg, 92%). E. M. encontrada para $C_{26}H_{26}ClN_5O_6$: 540,3 $(M+H)^+$.

Paso 5:



Una solución de ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–5–cloro–3–(2,4–dimetoxi–pirimidin–5–il)–1H–indol–2–carboxílico, **4E** (38 mg, 0,070 mmol) y 1,1'–carbonildiimidazol (13 mg, 0,080 mmol) en THF (4 ml) se dejó agitar a reflujo durante 1 h antes de bajar la temperatura hasta la temperatura ambiente. Luego se agregaron metilsulfonamida (10 mg, 0,11 mmol) y DBU (13 mg, 0,086 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 20 h antes de concentrarse bajo presión reducida. El residuo se diluyó con acetato de etilo (100 ml), se lavó con solución acuosa 1,0 M de HCl (2 ml) y luego agua (5 ml). La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando TLC preparativa sobre gel de sílice usando 5% metanol en diclorometano como solvente de desarrollo para proporcionar el compuesto **4F** (5 mg, 12%). E. M. encontrada para $C_{27}H_{29}ClN_6O_7S$: 617,3 $(M+H)^+$.

Paso 6:

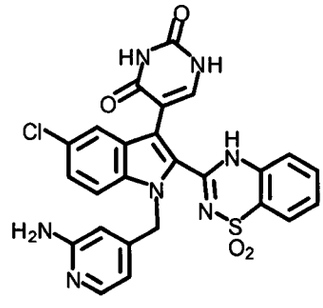


Se disolvió ter-butil éster del ácido {4–[5–Cloro–3–(2,4–dimetoxi–pirimidin–5–il)–2–metanosulfonilaminocarbonil-indol–1–ilmetil]–piridin–2–il}–carbámico, **4F** (5 mg, 0,0082 mmol) en HCl 4,0 M en 1,4–dioxano (0,6 ml, 2,4 mmol). La mezcla de reacción resultante se dejó agitar a 80°C en un tubo sellado durante 15 horas. La mezcla luego se enfrió y se concentró al vacío. El residuo se lavó con tolueno (3 x 1 ml), y se secó bajo vacío para proporcionar el compuesto **103** (3 mg, 75% de rendimiento). ^{1}H RMN (500 MHz, CD3OD): δ 7,80 (d, J= 6,31 Hz, 1H), 7,74 (s, 2H), 7,51 (d, J= 8,83 Hz, 1H), 7,41 (d, J= 8,20 Hz, 1H), 7,25–7,12 (m, 1H), 6,72 (d, J= 6,31 Hz, 1H), 6,47 (s, 1H), 5,72 (s, 2H), 3,32 (s, 3H).

E. M. encontrada para $C_{20}H_{17}ClN_6O_5S$: 489,3 $(M+H)^+$.

Ejemplo 5

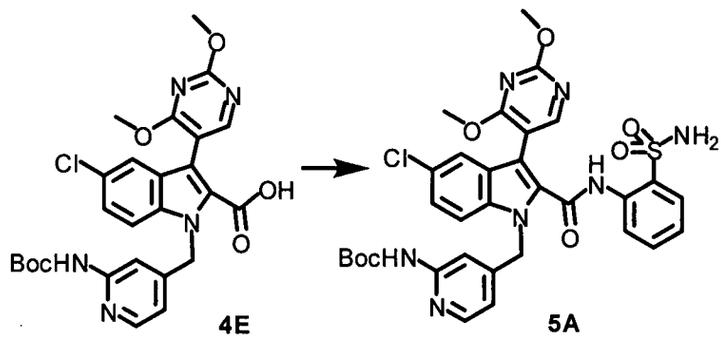
Preparación del compuesto **599**



599

Paso 1:

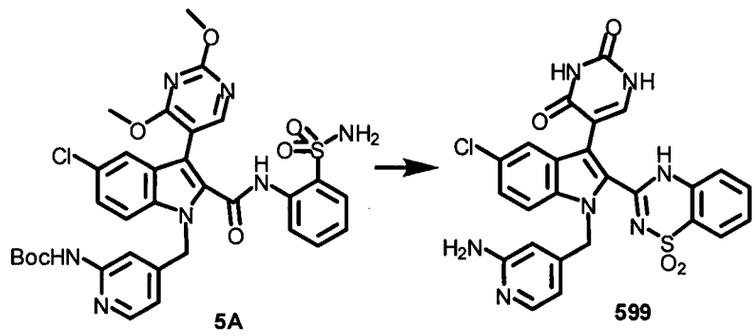
626



4E 5A

A una solución de ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–5–cloro–3–(2,4–dimetoxi–pirimidin–5–il)–1H–indol–2–carboxílico, **4E** (120 mg, 0,22 mmol) en diclorometano (4 ml) en un baño de agua helada se agregó cloruro de oxalilo (0,2 ml, ~2,3 mmol) a través de una jeringa. La mezcla se dejó agitar a temperatura ambiente durante 30 min y luego a temperatura ambiente durante 5 min antes de concentrarse bajo presión reducida. El residuo se disolvió en diclorometano (4 ml), y se agregaron 2–aminofenilsulfonamida (180 mg, 1,05 mmol) y trietilamina (0,3 ml). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 20 h antes de concentrarse bajo presión reducida. El residuo se purificó usando TLC preparativa sobre gel de sílice usando 10% metanol en diclorometano como solvente de desarrollo para proporcionar el compuesto **5A** (30 mg, 19% de rendimiento). E. M. encontrada para $C_{32}H_{32}ClN_7O_7S$: 694,4 $(M+H)^+$.

Paso 2:



5A 599

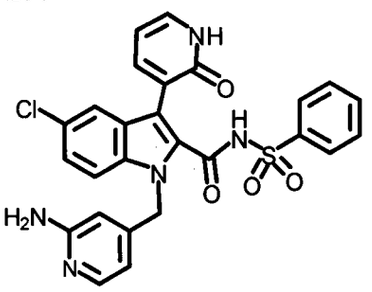
Se disolvió ter-butil éster del ácido {4–[5–Cloro–3–(2,4–dimetoxi–pirimidin–5–il)–2–(2–sulfamoil-fenilcarbamoil)–indol–1–ilmetil]–piridin–2–il}–carbámico, **5A** (30 mg, 0,043 mmol) en HCl 4,0 M en 1,4–dioxano (1,0 ml, 4,0

mmol). La solución resultante se dejó agitar a 90°C en un tubo sellado durante 17 h antes de bajar la temperatura hasta la temperatura ambiente. La mezcla se concentró bajo presión reducida. El residuo se purificó usando TLC prep. sobre gel de sílice con 10% metanol en diclorometano como solvente de desarrollo para proporcionar el compuesto **599** (18 mg, 76% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO): δ 12,35 (s, 1H), 11,28 (s, 1H), 11,13 (s, 1H), 7,84 (d, J= 7,88 Hz, 1H), 7,72–7,69 (m, 3H), 7,57 (d, J= 4,73 Hz, 1H), 7,50 (t, J= 8,04 Hz, 1H), 7,39 (d, J= 9,14 Hz, 1H), 7,32 (d, J= 7,88 Hz, 1H), 6,15 (s, 1H), 6,11–6,08 (m, 1H), 5,76 (s, 1H), 5,67 (s, 2H), 4,04 (s, 2H).

E. M. encontrada para $C_{25}H_{18}ClN_7O_4S$: 548,3 $(M+H)^+$.

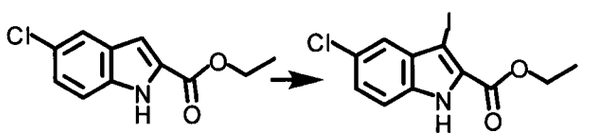
Ejemplo 6

Preparación del compuesto **277**



277

Paso 1:

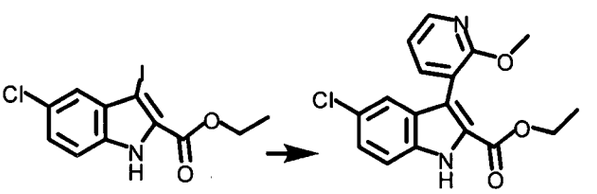


6A **6B**

A una solución de etil éster del ácido 5–cloro–1H–indol–2–carboxílico, **6A** (5,0 g, 22 mmol) en cloroformo (25 ml) a temperatura ambiente se agregó N–yodosuccinimida (5,0 g, 22 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 24 horas. La mezcla luego se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (300 ml). La mezcla se lavó con agua (100 ml) y salmuera respectivamente. La fase orgánica

separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el producto en bruto **6B** (7,0 g, 91% de rendimiento). E. M. encontrada para C11H9ClINO2: 350,2 $(M+H)^+$.

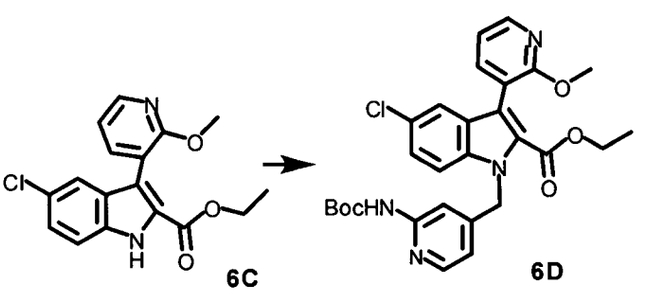
Paso 2:



6B **6C**

Se disolvió etil éster del ácido 5–Cloro–3–yodo–1H–indol–2–carboxílico, **6B** (3,0 g, 8,6 mmol) en 1,2–dimetoxietano (40 ml) y $PdCl_2(dppf)_2$ (0,7 g, 0,86 mmol) se agregó. La mezcla resultante se reflujó a 90°C durante 0,5 horas. A la mezcla anterior se agregó lentamente una solución de ácido 2–metoxi–3–piridin borónico (2,9 g, 18,8 mmol) y carbonato de potasio (2,4 g, 17,3 mmol) en agua (10 ml). La mezcla bifásica resultante se agitó vigorosamente a 90°C durante 1 h antes de dejar enfriar hasta la temperatura ambiente. La mezcla de reacción se filtró y se concentró al vacío. El residuo se diluyó con acetato de etilo (150 ml), y se lavó con una solución de sulfito de sodio (5 g) en agua (50 ml). La fase acuosa se extrajo con acetato de etilo (2 x 100 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía flash para proporcionar el compuesto **6C** (1,87 g, 66% de rendimiento). E. M. encontrada para C17H15ClN2O3: 331,20 $(M+H)^+$.

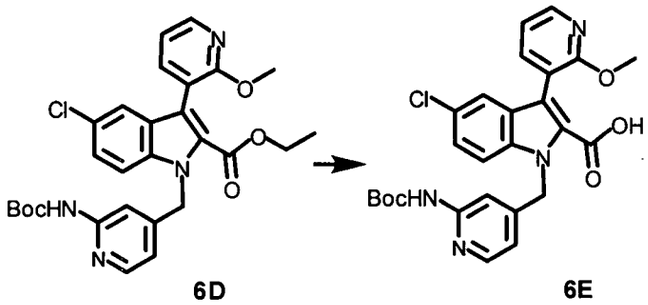
Paso 3:



6C **6D**

Se disolvió etil éster del ácido 5–Cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **6C** (1,0 g, 3,0 mmol) en DMF (15 ml) a temperatura ambiente. Se agregaron ter-butil éster del ácido (4–bromometil–piridin–2–il)–carbámico (1,0 g, 3,6 mmol) y carbonato de cesio (0,9 g, 4,5 mmol) en forma consecutiva y la suspensión resultante se agitó a temperatura ambiente durante 20 horas. Se agregaron acetato de etilo (200 ml) y agua (100 ml) a la mezcla de reacción, y se separaron las fases. La fase orgánica se lavó con salmuera, y se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **6D** (1,49 g, 93% de rendimiento). E. M. encontrada para C29H30ClN3O5: 537,27 $(M+H)^+$; 437,17 $(M–Boc+H)^+$.

Paso 4:

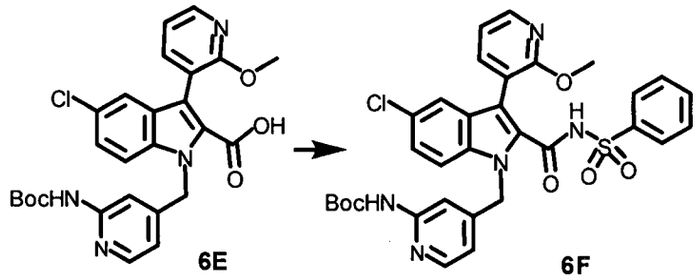


6D **6E**

A una solución de etil éster del ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–5–cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **6D** (1,5 g, 2,79 mmol) en THF (20 ml) se agregó la solución de hidróxido de litio (0,3 g, 8,37 mmol) en agua (5 ml). La suspensión resultante se dejó agitar a 60°C durante 20 horas. La mezcla se concentró bajo presión reducida. Se agregaron acetato de etilo (150 ml) y agua (100 ml) al residuo. La fase acuosa se acidificó hasta pH=1~2 por la incorporación de solución acuosa 1N de HCl, y se saturó con sales de NaCl. Se separaron las fases, y la fase acuosa se extrajo en forma adicional con acetato de etilo (2 X 100 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el

producto en bruto **6E** (100% de rendimiento). ^{1}H RMN (500 MHz, CDCl3) δ 9,36 (s, 1H), 8,22 & 8,21 (dd, J= 1,89 Hz & 5,04 Hz, 1H), 8,07 (s, 1H), 7,81 (d, J= 5,68 Hz, 1H), 7,70 & 7,68 (dd, J= 1,89 Hz & 7,25 Hz, 1H), 7,45 (d, J= 1,89 Hz, 1H), 7,31 & 7,29 (dd, J= 1,89 Hz & 8,83 Hz, 1H), 7,23 (d, J= 8,83 Hz, 1H), 7,01 (q, J= 5,04 Hz & 2,21 Hz, 1H), 6,36 (d, J= 5,04 Hz, 1H), 5,85 (s, 2H), 3,80 (s, 3H), 1,46 (s, 9H).

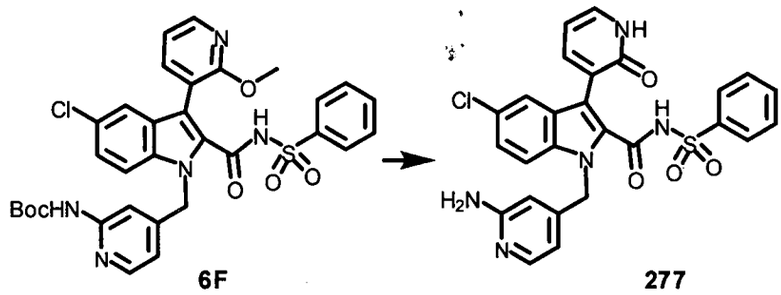
Paso 5:



Se disolvió ácido 1–(2–ter-Butoxicarbonilamino–piridin–4–ilmetil)–5–cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **6E** (400 mg, 0,79 mmol) en tetrahidrofurano (30 ml) a temperatura ambiente. A la mezcla se agregó carbonilo diimidazol (140 mg, 0,87 mmol). La suspensión resultante se reflujó a 75°C durante 1 hora, y luego se enfrió hasta la temperatura ambiente para proveer intermediario acilimidazol no caracterizado en solución de THF (30 ml). A la solución de THF del intermediario anterior (5 ml) se agregaron bencensulfonamida (30 mg, 0,19 mmol) y 1,8–diazabiciclo(5,4,0)undec–7–eno (30 µl). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 20 horas. Se agregaron acetato de etilo (50 ml), tetrahidrofurano (10 ml) y ácido fosfórico acuoso al 1% (15 ml) a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo con acetato de etilo/THF (3:1) (2 x 40 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía flash para proporcionar el compuesto **6F** (60 mg, 57% de rendimiento). E. M. encontrada para C32H30ClN5O6S: 648,27 $(M+H)^+$.

631

Paso 6:

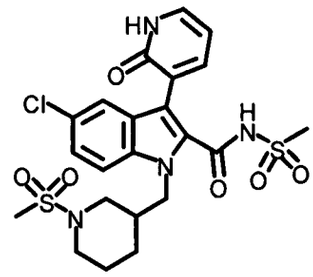


6F **277**

A una solución de ter-butil éster del ácido {4–[2–bencensulfonilaminocarbonil-5–cloro–3–(2–metoxi–piridin–3–il)–indol–1–ilmetil]–piridin–2–il}–carbámico, **6F** (60 mg, 0,09 mmol) en metanol (3 ml) se agregó HCl 4 N en 1,4–dioxano (3 ml). La mezcla de reacción resultante se dejó agitar a 90ºC en un tubo sellado durante 2 horas. La mezcla se concentró bajo presión reducida, y el residuo se purificó usando cromatografía flash para proporcionar el compuesto **277**. ^{1}H RMN (500 MHz, d_6–DMSO) δ 7,88 (d, J= 7,25 Hz, 2H), 7,84–7,79 (m, 2H), 7,66 (t, J= 6,62 Hz, 2H), 7,54–7,48 (m, 4H), 7,37 (d, J= 8,51 Hz, 1H), 6,76 (s, 1H), 6,56 (s, 1H), 6,19 (s, 1H), 5,64 (s, 2H). E. M. encontrada para $C_{26}H_{20}ClN_5O_4S$: 534,17 $(M+H)^+$.

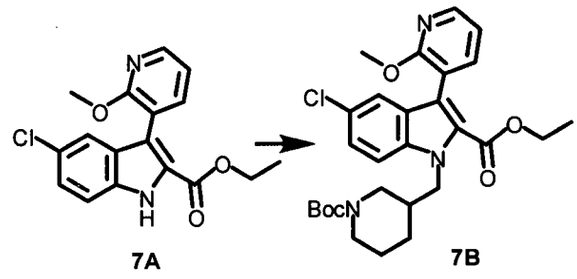
Ejemplo 7

Preparación del compuesto **310**



310

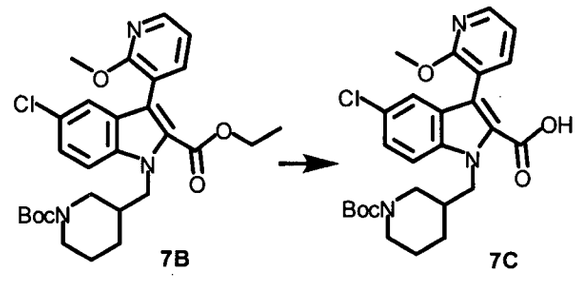
Paso 1:



7A 7B

A una solución de etil éster del ácido 5–cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **7A** (500 mg, 1,51 mmol) en DMF (3 ml) se agregaron 1–N–boc–3–bromometilpiperidina (500 mg, 1,78 mmol) y carbonato de cesio. La suspensión resultante se dejó agitar a 50°C durante 20 horas. La mezcla se enfrió hasta la temperatura ambiente, se diluyó con acetato de etilo (100 ml), y se lavó con agua (3 x 20 ml). La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–10% acetato de etilo en hexanos para proporcionar el compuesto **7B** (780 mg, 97% de rendimiento). ^{1}H RMN (500 MHz, CDCl3) δ 8,21 & 8,20 (dd, J= 1,89 Hz & 5,04 Hz, 1H), 7,61 & 7,60 (dd, J= 1,58 Hz & 7,25 Hz, 1H), 7,41 (d, J= 1,58 Hz, 1H), 7,33 (d, J= 8,51 Hz, 1H), 7,31 & 7,29 (dd, J= 1,89 Hz & 8,83 Hz, 1H), 7,01 (q, J= 5,04 Hz & 2,21 Hz, 1H), 4,48 (s, 2H), 4,14 (q, J= 6,94 Hz & 7,25 Hz, 2H), 3,94 (d, J= 13,24 Hz, 1H), 3,86 (s, 3H), 2,78–2,72 (m, 1H), 2,63 (t, J= 11,67 Hz, 1H), 1,58 (s, 6H), 1,38 (s, 9H), 1,00 (t, J= 7,09 Hz, 3H).

Paso 2:

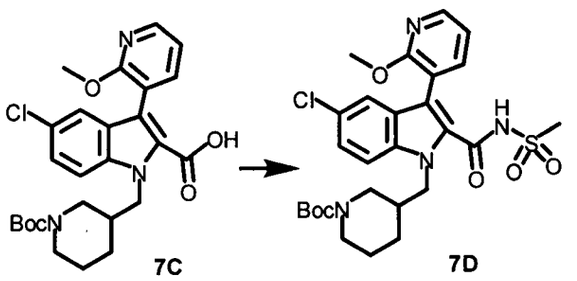


7B 7C

A una solución de etil éster del ácido 1–(1–ter-butoxicarbonil-piperidin–3–ilmetil)–5–cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **7B** (370 mg, 0,70 mmol) en THF (50 ml) se agregó una solución acuosa de hidróxido de litio (2,0 ml de 1 M, 2,0 mmol). La mezcla resultante se dejó agitar a reflujo

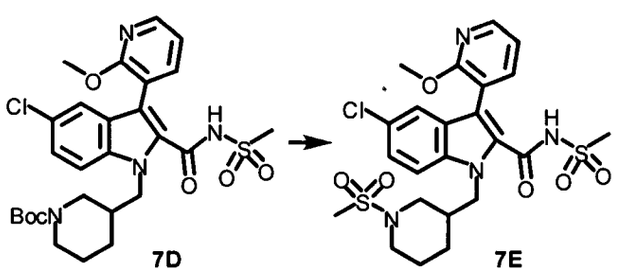
durante 2 días antes de bajar la temperatura hasta la temperatura ambiente. La mezcla se concentró bajo presión reducida. El residuo se disolvió en metanol (5 ml), se neutralizó con solución acuosa 1,0 M de HCl (2,0 ml, 2,0 mmol) y luego se concentró nuevamente bajo presión reducida. El residuo se trituró con acetato de etilo (3 x 30 ml), y la fase orgánica combinada se concentró y se secó al vacío para proporcionar el compuesto **7C** (290 mg, 83% de rendimiento).

Paso 3:



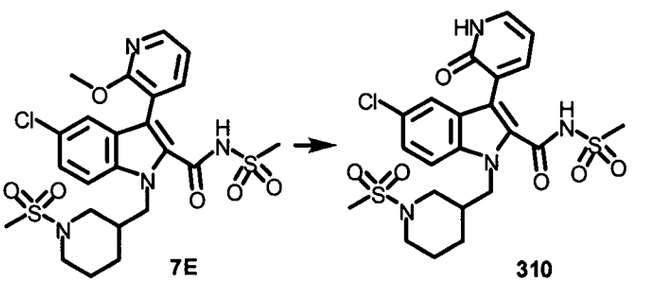
A una solución de ácido 1–(1–ter-butoxicarbonil-piperidin–3–ilmetil)–5–cloro–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **7C** (290 mg, 0,58 mmol) en THF (5 ml) se agregó 1,1'–carbonildiimidazol (150 mg, 0,92 mmol). La mezcla se reflujó durante 1,5 horas, se enfrió hasta la temperatura ambiente y luego se agregaron metilsulfonamida (120 mg, 1,26 mmol) y DBU (190 mg, 1,25 mmol). La mezcla de reacción resultante se dejó agitar a reflujo durante 3 h antes de enfriar hasta la temperatura ambiente. La mezcla se concentró bajo presión reducida. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–5% metanol en diclorometano para proporcionar el compuesto **7D** (280 mg, 84% de rendimiento). E. M. encontrada para $C_{27}H_{33}ClN_4O_6S$: 577,3 $(M+H)^+$.

Paso 4:



Una solución de ter-butil éster del ácido 3–[5–Cloro–2–metanosulfonilaminocarbonil-3–(2–metoxi–piridin–3–il)–indol–1–ilmetil]–piperidin—1–carboxílico, **7D** (85 mg, 0,15 mmol) en ácido trifluoroacético (2 ml) y diclorometano (2 ml) se dejó agitar a temperatura ambiente durante 4 horas. La mezcla luego se concentró bajo presión reducida, se disolvió en diclorometano (3 ml) y se trató con trietilamina (0,5 ml) y metilsulfonil-cloruro (50 mg, 0,44 mmol). La mezcla resultante se dejó agitar a temperatura ambiente durante un adicional de 18 horas. La mezcla luego se concentró bajo presión reducida, y el residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–5% metanol en diclorometano para proporcionar el compuesto **7E** (40 mg, 49% de rendimiento). E. M. encontrada para $C_{23}H_{27}ClN_4O_6S_2$: 555,3 $(M+H)^+$.

Paso 5:

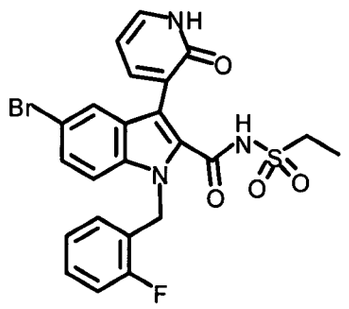


N–[5–Cloro–1–(1–metanosulfonil-piperidin–3–ilmetil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carbonil]– metansulfonamida, **7E** (40 mg, 0,072 mmol) se disolvió en HCl 4,0 N en 1,4–dioxano (2,0 ml, 8,0 mmol). La mezcla se dejó agitar a 90°C en un tubo sellado durante 1 hora, se enfrió hasta la temperatura ambiente, y luego se concentró bajo presión reducida. El residuo se lavó con metanol (2 x 3 ml), y se secó *al vacío* para proporcionar el compuesto **310** como un sólido blanco (26 mg, 67% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO); δ 12,78 (s, 1H), 12,42 (s, 1H), 7,79–7,75 (m, 2H), 7,59 (s, 1H), 7,46 (s, 1H), 7,38 & 7,37 (dd, J= 1,89 Hz & 8,51 Hz, 1H), 6,52 (t, J= 6,94 Hz, 1H), 4,47–4,37 (m, 2H), 3,41 & 3,38 (dd, J= 3,15 Hz & 11,67 Hz, 2H), 3,34 (s, 3H), 3,33 (s, 3H), 2,70–2,58 (m, 2H), 2,05–1,99 (m, 1H), 1,74–1,70 (m, 1H), 1,52–1,48 (m,1H), 1,40 (q, J=

11,67 Hz & 13,56 Hz, 1H), 1,09 (q, J= 11,67 Hz & 11,03 Hz, 1H). E. M. encontrada para $C_{22}H_{25}ClN_4O_6S_2$: 541,3 $(M+H)^+$.

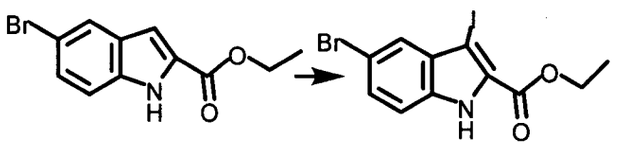
Ejemplo 8

Preparación del compuesto **273**



273

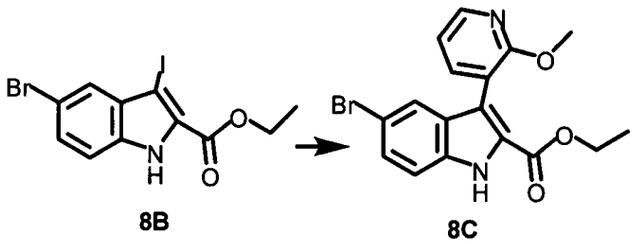
Paso 1:



8A **8B**

Se disolvió 5–bromo 2–indol carboxilato de etilo, **8A** (4,0 g, 14,9 mmol) en acetona (200 ml) a temperatura ambiente. A la mezcla se agregó N–yodosuccinimida (3,65 g, 15,4 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 3 horas. La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (150 ml). La mezcla se lavó con solución acuosa saturada de tiosulfato de sodio (50 ml). Se separaron las fases, y la fase acuosa se extrajo con acetato de etilo (2 X 100 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró y se concentró al vacío para proporcionar el producto en bruto **8B** (100% de rendimiento). ^{1}H RMN (400 MHz, d_6–DMSO): δ 12,48 (s, 1H), 7,55 (s, 1H), 7,45–7,44 (m, 2H), 4,39 (q, J= 6,59 Hz & 7,32 Hz, 2H), 1,38 (t, J= 7,32 Hz, 3H).

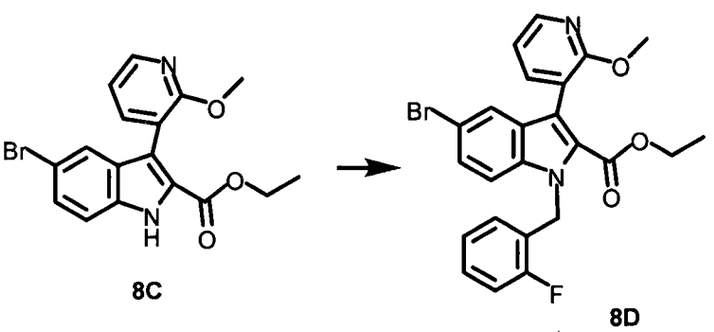
Paso 2:



8B **8C**

Se disolvió etil éster del ácido 5–Bromo–3–yodo–1H–indol–2–carboxílico, **8B** (8,66 g, 21,9 mmol) en 1,2–dimetoxietano (400 ml). y se agregó $PdCl_2(dppf)_2$ (1,80 g, 2,20 mmol). La mezcla resultante se desgasificó con burbujeo de nitrógeno durante 5 min antes de calentarse hasta 90°C y se dejó agitar durante 15 minutos. En un segundo matraz, la mezcla de ácido 2–metoxi–3–piridin borónico (3,72 g, 24,3 mmol) y carbonato de potasio (15,2 g, 110 mmol) en dimetoxietano (100 ml) y agua (100 ml) se desgasificó con burbujeo de nitrógeno durante 5 minutos. La mezcla luego se transfirió en tres porciones al primer matraz. La mezcla bifásica resultante se agitó vigorosamente a 90°C durante 3,5 h antes de dejar enfriar hasta la temperatura ambiente. La reacción se desactivó por la incorporación de una solución de sulfito de sodio (15 g) en agua (200 ml) a temperatura ambiente. Se agregó acetato de etilo (200 ml), y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 300 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró y se concentró al vacío para proporcionar el producto en bruto **8C** (100% de rendimiento). Cálculo de E. M para C17H15BrN2O3: 375,22. Experimental: 377,00.

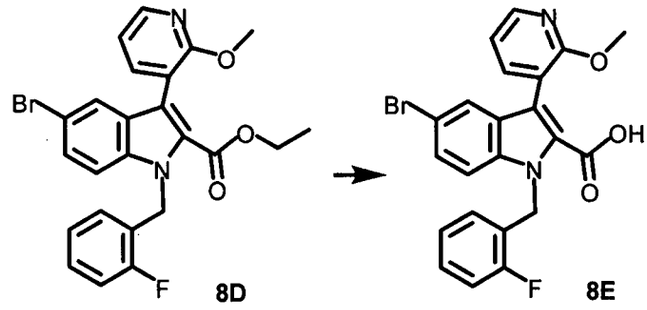
Paso 3:



8C **8D**

Se disolvió etil éster del ácido 5–Bromo–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **8C** (0,66 g, 1,59 mmol) en DMF (50 ml) a temperatura ambiente. A la mezcla se agregaron bromuro de 2—fluorobencilo (0,42 g, 2,23 mmol) y carbonato de cesio (0,84 g, 2,40 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 se separaron las fases. 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 filtró y se concentró al vacío para proporcionar el producto en bruto. El producto en bruto se purificó usando cromatografía flash para proporcionar producto **8D** (0,32 g, 42% de rendimiento). Cálculo de E. M para C24H20N2O3BrF: 483,33. Experimental: 485,3.

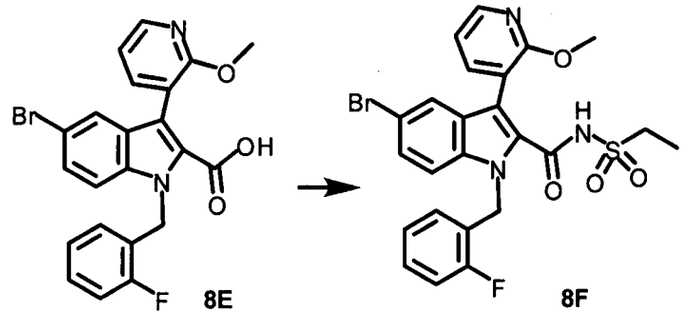
Paso 4:



A una solución de etil éster del ácido 5–bromo–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **8D** (0,32 g, 0,66 mmol) en metanol (5 ml) se agregó hidróxido de litio monohidrato (110 mg, 2,64 mmol). y agua (0,2 ml) se agregó para mejorar la solubilidad. La suspensión resultante se dejó agitar a temperatura ambiente durante 5 min antes de colocarse en un reactor de microondas durante 20 min (120ºC, alta potencia). La mezcla se concentró bajo presión reducida. Se agregaron al residuo acetato de etilo (50 ml) y agua (50 ml). La fase acuosa se acidificó hasta pH=2 por la incorporación de solución acuosa 1N de HCl, y se saturó con sales de NaCl. Las fases se

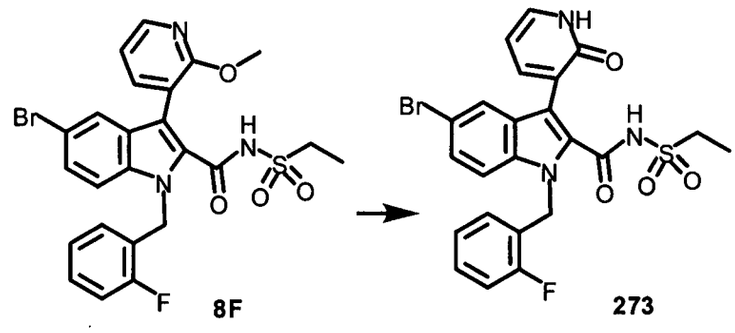
separaron, y la fase acuosa se extrajo en forma adicional con acetato de etilo (2 X 50 ml). La fase orgánica combinada se secó (sulfato de magnesio) y se filtró y se concentró al vacío para proporcionar el producto en bruto **8E** (93% de rendimiento). Cálculo de E. M para C22H16N2O3BrF: 455,28. Experimental: 456,01 $(M+H)^+$.

Paso 5:



Se disolvió ácido 5–Bromo–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **8E** (0,11 g, 0,24 mmol) en tetrahidrofurano (5 ml) a temperatura ambiente. A la mezcla se agregó carbonilo diimidazol (60 mg, 0,36 mmol). La suspensión resultante se reflujó a 75°C durante 1,5 horas, y luego se enfrió hasta la temperatura ambiente antes de agregar etan sulfonamida (77 mg, 0,75 mmol) y 1,8–diazabiciclo(5,4,0)undec–7–eno (0,12 ml, 0,75 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 48 horas. Se agregaron acetato de etilo (80 ml), tetrahidrofurano (16 ml) y ácido fosfórico acuoso al 1% (25 ml) a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo dos veces con acetato de etilo/THF (3:1) (60 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar **8F** (80 mg, 60% de rendimiento). Cálculo de E. M para C24H21N3O4FSBr: 546,41. Experimental: 547,93 $(M+H)^+$.

Paso 6:



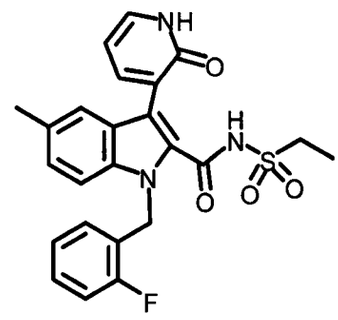
8F 273

Se disolvió [5–bromo–1–(2–fluoro–bencil)–3–(2–oxo–1,2–dihidro–piridin–3–il)–1H–indol–2–carbonil]–amida del ácido etansulfónico, **8F** (80 mg, 0,15 mmol) en HCl 4N en 1,4–dioxano (4 ml) en un tubo. La mezcla de reacción se dejó agitar a 90°C el tubo sellado durante 1,5 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente antes de concentrarse bajo presión reducida. El producto en bruto se purificó usando HPLC de fase inversa para proporcionar el compuesto **273** (55 mg, 71% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO): δ 12,72 (bs, 2H), 7,82 & 7,80 (dd, J= 1,89 Hz & 6,94 Hz, 1H), 7,66 (d, J= 8,83 Hz, 2H), 7,57 (d, J= 1,89 Hz, 1H), 7,49 & 7,48 (dd, J= 1,58 Hz & 8,83 Hz, 1H), 7,33 (q, J= 7,25 Hz & 7,88 Hz, 1H), 7,21 (t, J= 9,14 Hz, 1H), 7,08 (t, J= 7,57 Hz, 1H), 6,82 (t, J= 7,72 Hz, 1H), 6,59 (t, J= 6,62 Hz, 1H), 5,76 (s, 2H), 3,36 – 3,32 (m, 2H), 1,02 (t, J= 7,25 Hz, 3H); ^{13}C RMN (125 MHz, d_6–DMSO) δ163,04, 162,22, 160,79, 160,63, 158,66, 129,57, 129,51, 128,54, 128,51, 127,70, 127,56, 124,57, 124,44, 124,32, 122,69, 115,41, 115,24, 113,62, 113,27, 107,20, 54,84, 46,72, 7,36.

Cálculo de E. M para C23H19BrFN3O4S: 532,38. Experimental: 534,3.

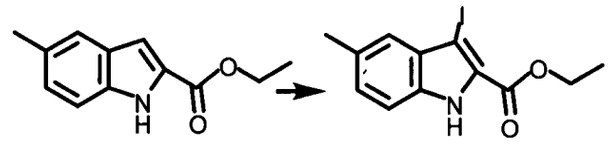
Ejemplo 9

Preparación del compuesto **34**



34

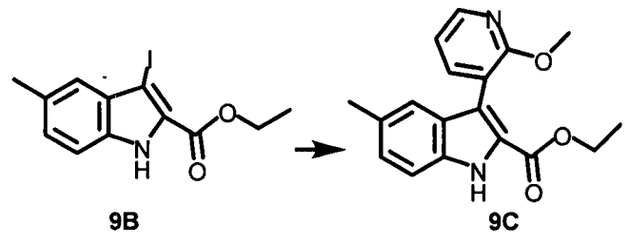
Paso 1:



9A **9B**

A una solución de 5–metilo indol carboxilato de etilo, **9A** (5,0 g, 24,6 mmol) en acetona (200 ml) se agregó N–yodosuccinimida (3,65 g, 15,4 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 4 horas. La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (200 ml). La mezcla se lavó con solución acuosa saturada de tiosulfato de sodio (100 ml). Se separaron las fases, y la fase acuosa se extrajo con acetato de etilo (2 X 100 ml). La fase orgánica combinada se lavó con agua (200 ml), y luego se secó (sulfato de magnesio), se filtró y se concentró al vacío para proporcionar el producto en bruto **9B** (7,62 g, 94% de rendimiento).

Paso 2:

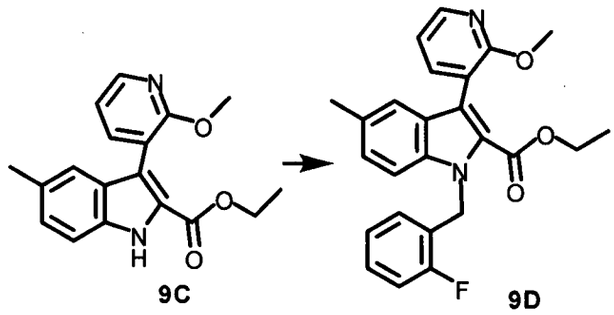


9B **9C**

Se disolvió etil éster del ácido 3–Yodo–5–metil–1H–indol–2–carboxílico, **9B** (7,62 g, 23,2 mmol) en 1,2–dimetoxietano (100 ml) y se agregó $PdCl_2(dppf)_2$ (1,89 g, 2,32 mmol). La mezcla resultante se desgasificó con burbujeo de

nitrógeno durante 10 minutos. En un segundo matraz, la mezcla de ácido 2–metoxi–3–piridin borónico (4,26 g, 27,8 mmol) y carbonato de potasio (16,0 g, 115,8 mmol) en dimetoxietano (50 ml) y agua (50 ml) se desgasificó con burbujeo de nitrógeno durante 5 minutos. La mezcla luego se transfirió lentamente al primer matraz. La mezcla bifásica resultante se dejó agitar a temperatura ambiente durante 15 minutos, y luego se agitó vigorosamente a 90°C durante 4 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, y se desactivó por la incorporación de una solución de sulfito de sodio (5 g) en agua (100 ml) a temperatura ambiente. Se agregó acetato de etilo (200 ml), y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 300 ml). La fase orgánica combinada luego se filtró a través de un taco de celite, se secó sobre sulfato de magnesio, y se concentró al vacío para proporcionar el producto en bruto **9C** (4,12 g, 57% de rendimiento). Cálculo de E. M para C18H18N2O3: 310,35. Experimental: 311,15 $(M+H)^+$.

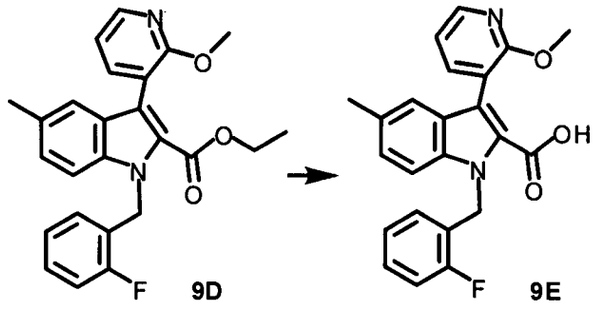
Paso 3:



Se disolvió etil éster del ácido 3–(2–Metoxi–piridin–3–il)–5–metil–1H–indol–2–carboxílico, **9C** (0,70 g, 2,25 mmol) en DMF (25 ml) a temperatura ambiente. A la mezcla se agregaron bromuro de 2—fluorobencilo (0,68 g, 3,60 mmol) y carbonato de cesio (1,60 g, 4,50 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas. 300 ml de THF/acetato de etilo (1:3) y 50 ml de agua se agregaron a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo con 100 ml de THF/acetato de etilo (1:3). La fase

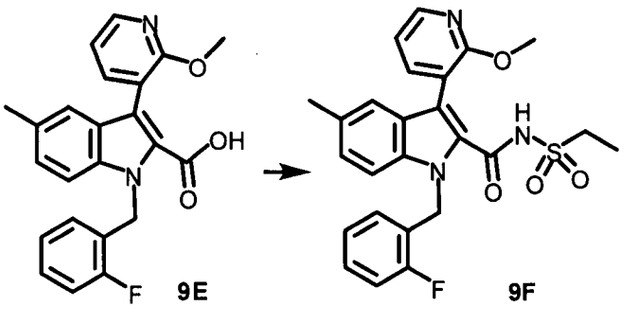
orgánica combinada se lavó con agua (3 X 100 ml). La fase orgánica separada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto obtenido se purificó usando cromatografía flash para proporcionar el compuesto **9D** (0,75 g, 79% de rendimiento). Cálculo de E. M para C25H23FN2O3: 418,46. Experimental: 419,27 $(M+H)^+$.

Paso 4:



A una solución de etil éster del ácido 1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–metil–1H–indol–2–carboxílico, **9D** (0,75 g, 1,79 mmol) en metanol (20 ml) se agregó hidróxido de litio monohidrato (220 mg, 5,24 mmol). Se agregó agua (0,2 ml) para mejorar la solubilidad. La suspensión resultante se dejó agitar a temperatura ambiente durante 5 min antes de colocarse en un reactor de microondas durante 20 min (120°C, alta potencia). La mezcla se concentró bajo presión reducida, y se agregó 30 ml de agua. La fase acuosa se acidificó hasta pH=2 por la incorporación de solución acuosa 1N de HCl, y la mezcla se extrajo tres veces con 100 ml de THF/acetato de etilo (3:1). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **9E** (0,70 g, 99% de rendimiento). Cálculo de E. M para C23H19FN2O3: 390,41. Experimental: 391,2 $(M+H)^+$.

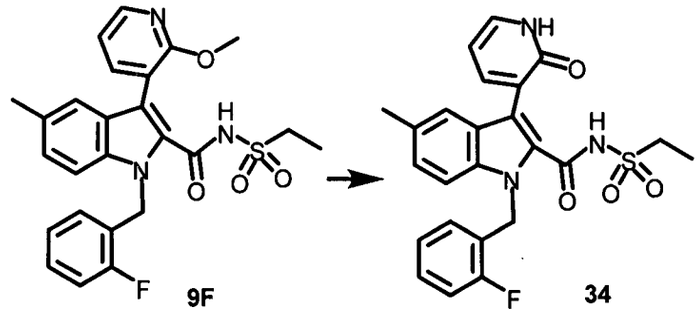
Paso 5:



9E 9F

Se disolvió ácido 1–(2–Fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–metil–1H–indol–2–carboxílico, **9E** (140 mg, 0,36 mmol) en tetrahidrofurano (4 ml) a temperatura ambiente. A la mezcla se agregó carbonilo diimidazol (87 mg, 0,54 mmol). La suspensión resultante se reflujó a 75°C durante 1,5 horas, y luego se enfrió hasta la temperatura ambiente antes de agregar etan sulfonamida (114 mg, 1,07 mmol) y 1,8–diazabiciclo(5,4,0)undec–7–eno (0,16 ml, 1,07 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 48 horas. Se agregaron acetato de etilo (100 ml), tetrahidrofurano (20 ml) y ácido fosfórico acuoso al 1% (25 ml) a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo dos veces con acetato de etilo/THF (3:1) (60 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **9F** (120 mg, 70% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO) δ 11,57 (s, 1H), 8,20 & 8,19 (dd, J= 1,89 Hz & 5,04 Hz, 1H), 7,85 &7,84 (dd,, J= 1,89 Hz & 7,25 Hz, 1H), 7,55 (d, J= 8,51 Hz, 1H), 7,31–7,25 (m, 2H), 7,25–7,15 (m, 3H), 6,72 (t, J= 6,94 Hz, 2H), 5,72 (s, 2H), 3,76 (s, 3H), 3,25 (q, J= 7,25 Hz & 7,57 Hz, 2H), 2,36 (s, 3H), 0,88 (t, J= 7,41 Hz, 3H). ^{13}C RMN (125 MHz, d_6–DMSO) δ161,51, 160,45, 160,24, 151,47, 145,48, 140,09, 135,79, 130,14, 129,40, 128,29, 126,61, 125,56, 124,61, 119,47, 116,61, 115,91, 115,22, 115,06, 114,23, 110,74, 54,84, 52,89, 48,63, 20,97, 7,17. Cálculo de E. M para C25H24FN3O4S: 481,54. Experimental: 482,3 $(M+H)^+$.

Paso 6:

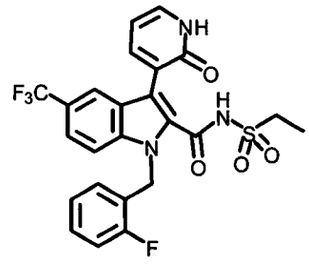


9F **34**

Se disolvió [1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–metil–1H–indol–2–carbonil]–amida del ácido etansulfónico, **9F** (120 mg, 0,25 mmol) en HCl 4N en 1,4-dioxano (5 ml) en un tubo. Luego se agregó agua (0,2 ml). La mezcla de reacción se dejó agitar a 90°C el tubo sellado durante 1,5 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente antes de concentrarse bajo presión reducida. El producto en bruto se purificó usando HPLC de fase inversa para proporcionar el compuesto **34** (53 mg, 46% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO): δ 12,75 (d, J= 7,88 Hz, 2H),7,80 . d, J= 4,41 Hz, 1H), 7,69 (s, 1H), 7,54–7,52 (m, 1H), 7,33–7,27 (m, 1H), 7,23–7,19 (m, 3H), 7,08–7,04 (m, 1H), 6,78 (s, 1H), 6,64 (s, 1H), 5,74 (s, 2H), 3,34–3,32 (m, 2H), 2,36 (s, 3H), 1,03–0,99 (m, 3H). ^{13}C RMN (125 MHz, d_6–DMSO). δ 162,59, 161,12, 160,55, 158,61, 144,16, 136,15, 135,57, 130,18, 129,28, 128,40, 127,14, 126,20, 124,88, 124,47, 119,62, 115,32, 115,15, 114,66, 110,74, 107,47, 66,92, 41,46, 20,94, 7,38. Cálculo de E. M para C24H22FN3O4S: 467,51. Experimental: 468,3 $(M+H)^+$.

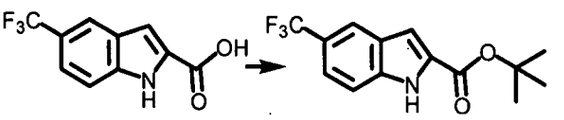
Ejemplo 10

Preparación del compuesto **228**



228

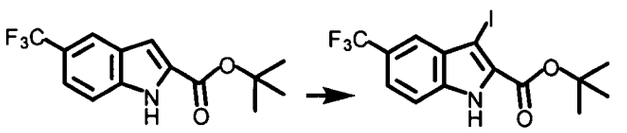
Paso 1:



10A **10B**

A una solución de ácido 5–(trifluorometil)indol–2–carboxílico, **10A** (1,6 g, 6,9 mmol) en tolueno (5,0 ml) a temperatura ambiente se agregó N,N–dimetilformamida di–*ter*-butil acetal (5,0 ml). La mezcla se dejó agitar a 90°C durante 12 horas, y luego se enfrió hasta la temperatura ambiente. Se agregó otra alícuota de *N,N*–dimetilformamida di–ter butil acetal (5 ml). La mezcla de reacción se calentó hasta 90°C durante otras 12 horas, se enfrió hasta la temperatura ambiente, y se diluyó con acetato de etilo (10 ml). La mezcla se lavó con agua (2 X 10 ml), y salmuera respectivamente. La fase orgánica separada se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el compuesto **10B** (1,2 g, 60% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$): δ9,17 (s, 1H), 7,97 (s, 1H), 7,51 (s, 2H), 7,21 (s, 1H), 1,63 (s, 9H).

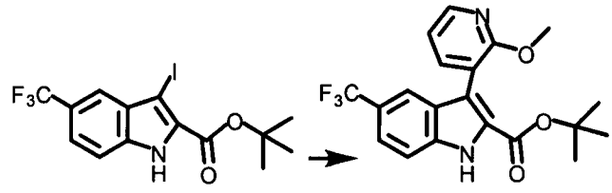
Paso 2:



10B **10C**

A una solución de ter-butil éster del ácido 5–trifluorometil–1H–indol–2–carboxílico, **10B** (1,2 g, 4,2 mmol) en $CHCl_3$ (25 ml) se agregó *N*–yodosuccinimida (946 mg, 4,2 mmol). La mezcla de reacción se dejó agitar a temperatura ambiente durante 12 horas, antes de concentrarse bajo presión reducida. El residuo se diluyó en agua (100 ml), y se extrajo con EtOAc (200 ml). La fase orgánica separada se secó sobre $MgSO_4$, se filtró, y se concentró al vacío. El residuo marrón se absorbió en una cantidad mínima de CH_2Cl_2 y se trituró con hexanos. El producto **10C** se separó como un sólido marrón luego de la filtración, y se secó al vacío (1,23 g, 72% de rendimiento). ^{1}H RMN (400 MHz, CDCl3): δ 9,34 (s, 1H), 7,87 (s, 1H), 7,57 (d, J= 8,06 Hz, 1H), 7,49 (d, J= 8,79 Hz, 1H), 1,68 (s, 9H).

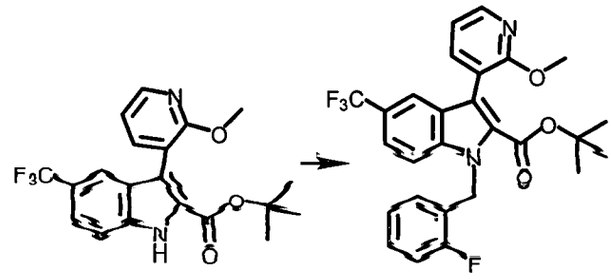
Paso 3:



10C **10D**

A una solución de ter-butil éster del ácido 3–yodo–5–trifluorometil–1H–indol–2–carboxílico, **10C** (1,23 g, 3,0 mmol) en DME (30 ml) bajo atmósfera de nitrógeno se agregó ácido 2–metoxi–3–piridil borónico (0,48 g, 3,15 mmol) y Pd $(dppf)_2Cl_2$ (245 mg, 0,3 mmol). 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 (1,6 g, 12 mmol) en agua (12 ml), y la solución resultante se dejó agitar a 90°C durante 1 hora. La mezcla de reacción luego se diluyó con EtOAc (200 ml), y la solución resultante se concentró bajo presión reducida. El residuo se purificó usando cromatografía flash en columna para proporcionar el compuesto **10D**(820 mg, 70% de rendimiento). E. M. encontrada para C20H19F3N2O3: 393,2 $(M+H)^+$.

Paso 4:

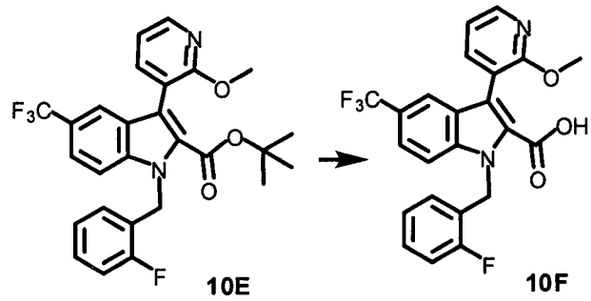


10D **10E**

A una solución de ter-butil éster del ácido 3–(2–metoxi–piridin–3–il)–5–trifluorometil–1H–indol–2–carboxílico, **10D** (400 mg, 1,02 mmol) en DMF (8 ml) se agregaron bromuro de 2—fluorobencilo (0,14 ml, 1,12 mmol) y carbonato de cesio (365 mg, 1,12 mmol). La mezcla 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 se separaron las fases. La fase orgánica se lavó

con agua (2 x 100 ml) y salmuera (50 ml). La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el producto cristalizado **10E** (100% de rendimiento). E. M. encontrada para C27H24F4N2O3: 501,11 $(M+H)^+$.

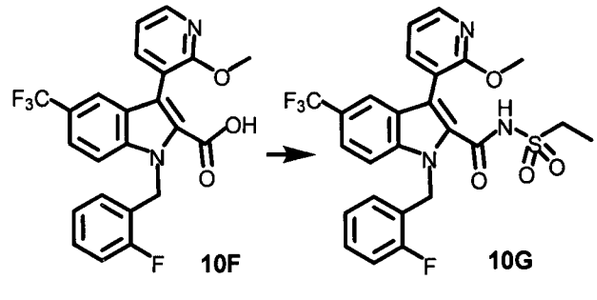
Paso 5:



10E **10F**

A una solución de ter-butil éster del ácido 1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trifluorometil–1H–indol–2–carboxílico, **10E** (510 mg, 1,02 mmol) en CH_2Cl_2 se agregó ácido trifluoroacético (3 ml). La mezcla de reacción se dejó agitar a temperatura ambiente durante 18 horas. El solvente se eliminó bajo presión reducida. El residuo se disolvió en acetato de etilo (200 ml). La solución de acetato de etilo se lavó con agua (4 x 50 ml) y salmuera. La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el compuesto **10F** (100% de rendimiento). E. M. encontrada para C23H16F4N2O3: 445,06 $(M+H)^+$.

Paso 6:

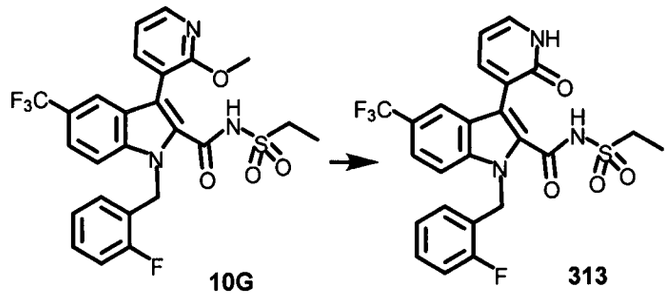


10F **10G**

A una solución de ácido 1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trifluorometil–1H–indol–2–carboxílico, **10F** (100 mg, 0,23 mmol) en tetrahidrofurano (2 ml) se agregó carbonilo diimidazol (44 mg, 0,27 mmol). La

suspensión resultante se reflujó a 70°C bajo argón durante 1,5 horas, y luego se enfrió hasta la temperatura ambiente. A la mezcla se agregaron etan sulfonamida (37 mg, 0,34 mmol) y 1,8–diazabiciclo(5,4,0)undec–7—eno (67 uL, 0,45 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 48 horas. Se agregaron acetato de etilo (100 ml) y ácido fosfórico acuoso al 2% (30 ml) a la mezcla de reacción, y se separaron las fases. La fase orgánica se lavó en forma adicional con ácido fosfórico acuoso al 2% (2 x 30 ml), agua (30 ml) y salmuera respectivamente. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **10G** (76 mg, 63% de rendimiento). E. M. encontrada para C25H21F4N3O4S: 535,91 $(M+H)^+$; 557,89 $(M+Na)^+$.

Paso 7:

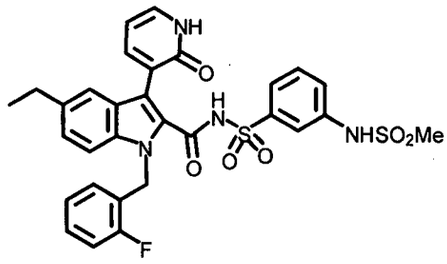


10G **313**

La solución de [1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trifluorometil–1H–indol–2–carbonil]–amida del ácido etansulfónico, **10G** (76 mg, 0,14 mmol) en HCl 4N en 1,4-dioxano (4 ml) y 5 gotas de agua se dejó agitar a 90°C en un tubo sellado durante 1,5 horas. La mezcla se concentró bajo presión reducida, y el residuo se purificó usando cromatografía flash para proporcionar el compuesto **228** (37 mg, 51% de rendimiento). ^{1}H RMN (400 MHz, d_6–DMSO): δ 7,92–7,76 (m, 4H), 7,64 (s, 2H), 7,33 (q, J= 7,32 Hz, 1H), 7,21 (t, J= 9,52 Hz, 1H), 7,08 (t, J= 7,32 Hz, 1H), 6,87 (t, J= 7,69 Hz, 1H), 6,57 (s, 1H), 5,83 (s, 2H), 3,51–3,22 (m, 2H), 1,02 (t, J= 7,32 Hz, 3H). E. M. encontrada para C24H19F4N3O4S: 522,22 $(M+H)^+$.

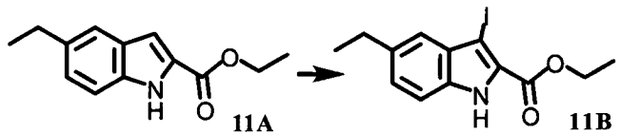
Ejemplo 11

Preparación del compuesto **505**



505

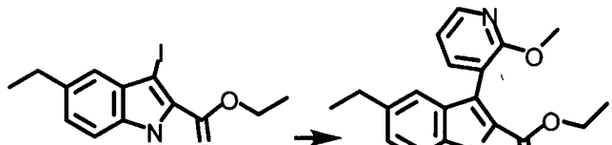
Paso 1:



11A **11B**

A una solución de etil éster del ácido 5–etilindol–2– carboxílico, **11A** (5,0 g, 23 mmol) en cloroformo (100 ml) a temperatura ambiente se agregó N–yodosuccinimida (5,20 g, 23 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 24 horas. La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (200 ml). La mezcla se lavó con agua (100 ml) y salmuera (60 ml). La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el producto en bruto, **11B** (7,35 g, 93% de rendimiento). E. M. encontrada para C13H14INO2: 343,94 $(M+H)^+$.

Paso 2:

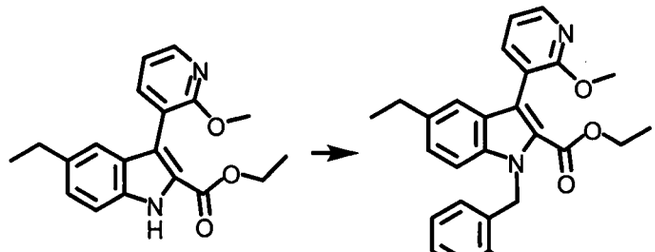


11B **11C**

Se disolvió etil éster del ácido 5–Etil–3–yodo–1H–indol–2–carboxílico, **11B** (7,35 g, 21,4 mmol) en 1,2–dimetoxietano (150 ml) se agregó y $PdCl_2(dppf)_2$ (1,72 g, 0,21 mmol). La mezcla resultante se reflujó a 95°C durante 0,5 horas. A

la mezcla se agregó lentamente la solución de ácido 2–metoxi–3–piridin borónico (9,60 g, 63 mmol) y carbonato de potasio (8,7 g, 63 mmol) en agua (50 ml). La mezcla bifásica resultante se agitó vigorosamente a 95°C durante 1 h antes de dejar enfriar hasta la temperatura ambiente. La mezcla de reacción se filtró y se concentró al vacío. El residuo se diluyó con acetato de etilo (300 ml), y se lavó con una solución de sulfito de sodio (15 g) en agua (200 ml). La fase acuosa se extrajo con acetato de etilo (2 x 300 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía flash para proporcionar el compuesto **11C** (5,0 g, 74% de rendimiento). E. M. encontrada para C19H20N2O3: 325,06 $(M+H)^+$.

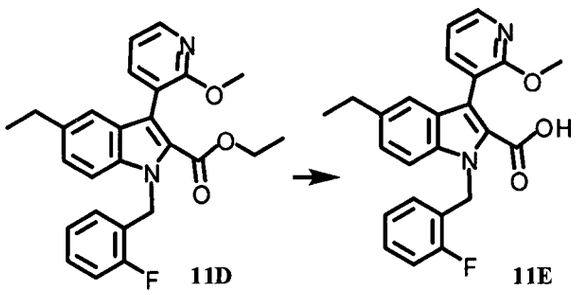
Paso 3:



11C **11D**

Se disolvió etil éster del ácido 5–Etil–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **11C** (500 mg, 1,54 mmol) en DMF (20 ml) a temperatura ambiente. A la mezcla se agregaron cloruro de 2–fluorobencilo (224 mg, 1,54 mmol) y carbonato de cesio (502 mg, 1,54 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 24 horas. Se agregaron acetato de etilo (100 ml) y agua (50 ml) a la mezcla de reacción, y se separaron las fases. 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). La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **11D** (665 mg, 100% de rendimiento).

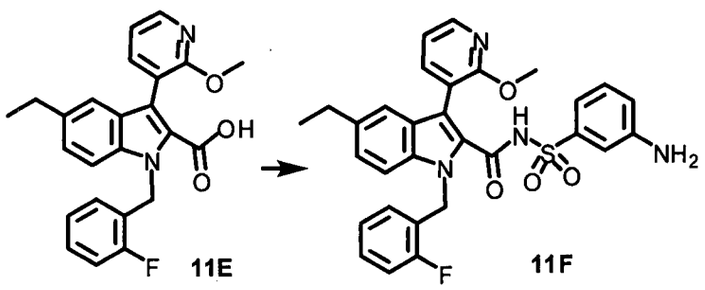
Paso 4:



11D 11E

A una solución de etil éster del ácido 5–etil–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **11D** (665 mg, 1,54 mmol) en THF (50 ml) se agregó la solución de hidróxido de litio (220 mg, 9,24 mmol) en agua (15 ml). La suspensión resultante se dejó agitar a temperatura ambiente hasta que el material de partida se había consumido totalmente. La mezcla se concentró bajo presión reducida. Se agregaron acetato de etilo (50 ml) y agua (50 ml) al residuo. La fase acuosa se acidificó hasta pH=2 por la incorporación de solución acuosa 1N de HCl, y se saturó con sales de NaCl. Se separaron las fases, y la fase acuosa se extrajo en forma adicional con acetato de etilo (2 X 50 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío para proporcionar el producto en bruto **11E** (620 mg, 100% de rendimiento). E. M. encontrada para C24H21N2O3F: 405,28 $(M+H)^+$.

Paso 5:

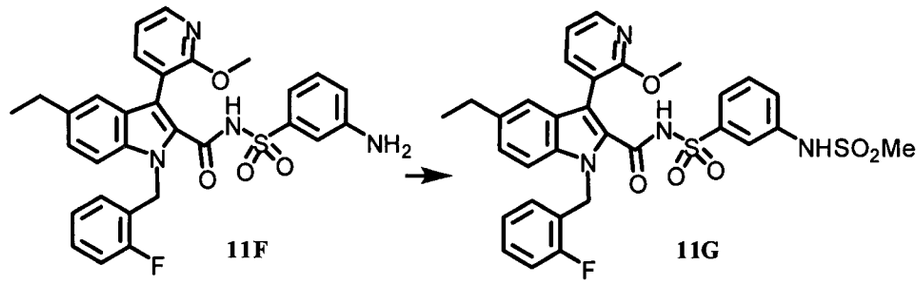


11E 11F

Se disolvió ácido 5–Etil–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **11E** (100 mg, 0,25 mmol) en tetrahidrofurano (10 ml) a temperatura ambiente. A la mezcla se agregó carbonilo diimidazol (49 mg, 0,30 mmol). La suspensión resultante se reflujó a 75°C durante 1 hora, y luego se enfrió hasta la temperatura ambiente antes de la incorporación de 3–

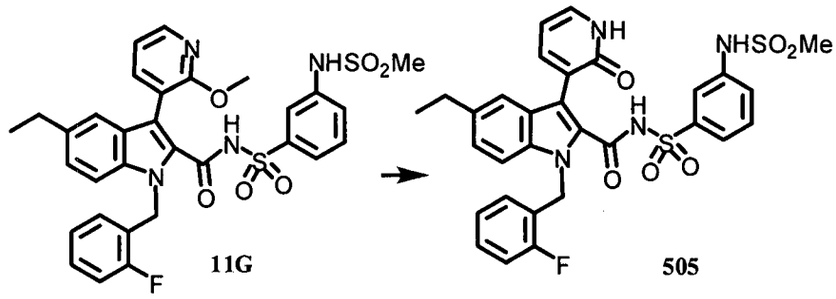
aminobencensulfonamida (52 mg, 0,30 mmol) y 1,8–diazabiciclo(5,4,0)undec–7–eno (46 mg, 0,30 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 24 horas. El solvente luego se evaporó bajo presión reducida. Se agregaron acetato de etilo (80 ml) y ácido fosfórico acuoso al 1% (25 ml) a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 60 ml). La fase orgánica combinada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **11F** (30 mg, 21% de rendimiento).

Paso 7:



A una solución de 3–amino–N–[5–etil–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carbonil]–bencensulfonamida, **11F** (30 mg, 0,05 mmol) en THF (5 ml) y piridina (1 ml) se agregó lentamente $ClSO_2Me$. La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 24 horas, y luego se diluyó con acetato de etilo (50 ml). La mezcla se lavó con solución acuosa 1N de HCl (20 ml) y salmuera (20 ml) respectivamente. La fase orgánica separada se secó sobre sulfato de sodio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **11G** (30 mg, 94% de rendimiento).

Paso 8:

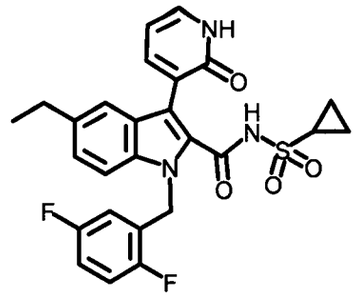


11G 505

A una solución de N–[5–etil–1–(2–fluoro–bencil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carbonil]–3–metanosulfonilamino–bencensulfonamida, **11G** (30 mg, 0,05 mmol) en dioxano (3 ml) se agregó HCl (1 ml). La mezcla de reacción resultante se dejó agitar a 90°C en un tubo sellado durante 2 horas. La mezcla se concentró bajo presión reducida, y el residuo se purificó usando cromatografía flash para proporcionar el compuesto **505** (10 mg, 34% de rendimiento). ^{1}H RMN (500 MHz, CD3OD): δ 7,87 (s, 1H), 7,77 (s, 1H), 7,67 (d, J= 7,88 Hz, 1H), 7,59 (d, J= 7,88 Hz, 1H), 7,54 (t, J= 8,35 Hz, 1H), 7,47–7,35 (m, 3H), 7,27 (s, 1H), 7,22 (q, J= 6,94 Hz & 6,62 Hz, 2H), 7,02 (t, J= 9,46 Hz, 1H), 6,90 (t, J= 7,57 Hz, 1H), 6,67 (s, 2H), 5,69 (s, 2H), 2,98 (s, 3H), 2,72 (q, J= 7,25 Hz & 7,57 Hz, 2H), 1,24 (t, J= 7,57 Hz, 3H). E. M. encontrada para $C_{30}H_{27}FN_4O_6S_2$: 623,3 $(M+H)^+$

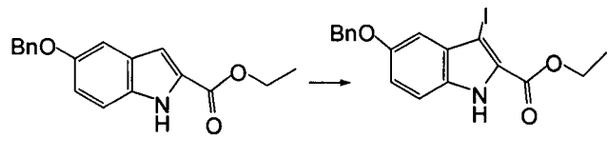
Ejemplo 12

Preparación del compuesto **195**



195

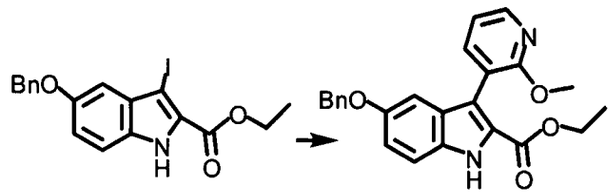
Paso 1:



12A 12B

A una solución de etilo 5–OBn indol carboxilato (**12A**, 10,0 g, 33,9 mmol) en acetona (300 ml) se agregó N–yodosuccinimida (8,0 g, 33,8 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 4 horas. La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (300 ml). La mezcla se lavó con solución acuosa saturada de tiosulfato de sodio (200 ml). Se separaron las fases, y la fase acuosa se extrajo con acetato de etilo (2 X 200 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **12B** (100% de rendimiento). E. M. encontrada para C18H16INO3: 421,89 $(M+H)^+$.

Paso 2:

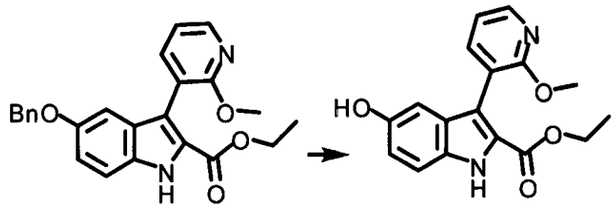


12B **12C**

Se disolvió etil éster del ácido 5–Benciloxi–3–yodo–1H–indol–2–carboxílico, **12B** (10,8 g, 24,1 mmol) en 1,2–dimetoxietano (300 ml). y $PdCl_2(dppf)_2$ (2,0 g, 2,45 mmol) se agregó. La mezcla resultante se desgasificó con burbujeo de nitrógeno durante 5 min antes de calentarse hasta 90°C y se dejó agitar durante 15 minutos. En un segundo matraz, la mezcla de ácido 2–metoxi–3–piridin borónico (4,3 g, 28,1 mmol) y carbonato de potasio (16,7 g, 121 mmol) en dimetoxietano (100 ml) y agua (100 ml) se desgasificó con burbujeo de nitrógeno durante 5 minutos. La mezcla luego se transfirió en tres porciones al primer matraz. La mezcla bifásica resultante se agitó vigorosamente a 90°C durante 3,5 h antes de dejar enfriar hasta la temperatura ambiente. La reacción se desactivó por la incorporación de una solución de sulfito de sodio (15 g) en agua (200 ml) a temperatura ambiente. Se agregó acetato de etilo (300 ml), y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 300 ml). La fase orgánica combinada se secó (sulfato de magnesio), se filtró y se

concentró al vacío para proporcionar el producto en bruto **12C** (7,37 g, 76% de rendimiento). E. M. encontrada para C24H22N2O4: 403,1 $(M+H)^+$.

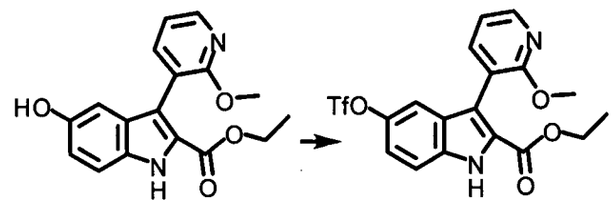
Paso 3:



12C **12D**

A una solución de etil éster del ácido 5–benciloxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **12C** (4,2 g, 10,4 mmol) en EtOH absoluto se agregó Pd-C al 5% (2,0 g). Se vació el matraz, y luego se cargó con H_2 gaseoso. La mezcla de reacción se dejó agitar a temperatura ambiente durante 3 horas. El catalizador de paladio se filtró a través de un taco de celite, y se lavó con 100 ml de MeOH/THF (1:1). El filtrado recolectado se concentró bajo presión reducida para proporcionar el producto en bruto **12D** (3,25 g, 100% de rendimiento). E. M. encontrada para C17H16N2O4: 313,2 $(M+H)^+$.

Paso 4:

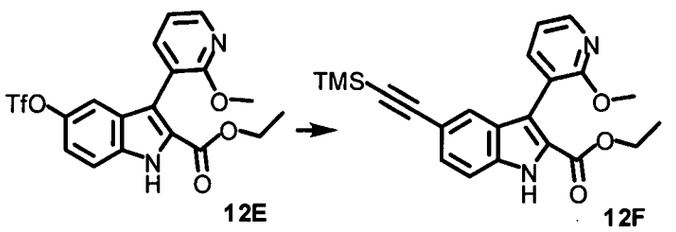


12D **12E**

A la mezcla de etil éster del ácido 5–hidroxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **12D** (3,2 g, 10,4 mmol) y trietil amina (4,0 ml, 28,7 mmol) en diclorometano (100 ml) se agregó $PhN(SO_2CF_3)_2$ (5,4 g, 15,1 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 4 horas. Luego se diluyó la mezcla con diclorometano (100 ml), y se lavó con solución acuosa 1N de carbonato de sodio (2 x 100 ml). La solución acuosa separada se extrajo nuevamente con diclorometano (100 ml). La fase orgánica combinada se

secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **12E** (4,12 g, 88% de rendimiento). E. M. encontrada para C18H15F3N2O6S: 445,2 $(M+H)^+$.

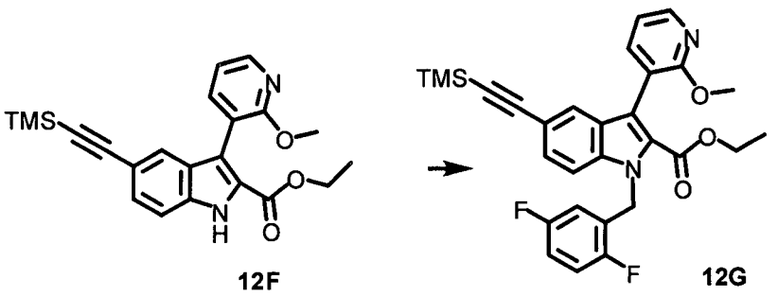
Paso 5:



12E **12F**

A una solución de etil éster del ácido 3–(2–metoxi–piridin–3–il)–5–trifluorometanosulfoniloxi–1H–indol–2–carboxílico, **12E** (1,0 g, 2,25 mmol), TMS acetileno (2,0 ml, 14,4 mmol) y $nBu_4N^+I^-$ (0,92 g, 2,49 mmol) en DMF (48 ml) se agregaron $PdCl_2(PPh_3)_2$ (160 mg, 0,23 mmol), CuI (130 mg, 0,68 mmol) y trietilamina (2,1 ml, 15,1 mmol). La mezcla de reacción resultante se agitó en un tubo sellado a 65ºC durante 18 horas. La mezcla se enfrió hasta la temperatura ambiente, y se diluyó con agua (50 ml) y EtOAc (100 ml). Se separaron las fases, y la fase acuosa se extrajo con EtOAc (2 x 50 ml). La fase orgánica combinada se lavó con agua (2 x 100 ml) antes de secarse sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **12F** (100% de rendimiento). E. M. encontrada para C22H24N2O3Si: 393,3 $(M+H)^+$.

Paso 6:

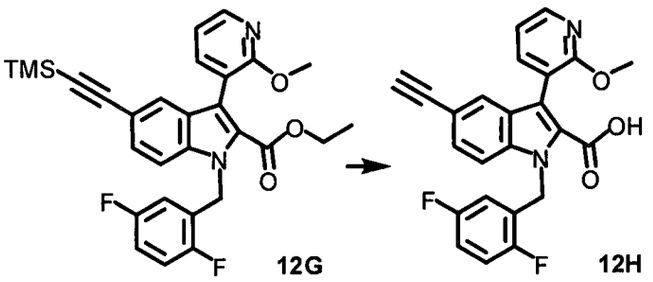


12F **12G**

Se disolvió etil éster del ácido 3–(2–Metoxi–piridin–3–il)–5–trimetilsilaniletinil-1H–indol–2–carboxílico, **12F** (0,76 g, 1,94 mmol) en DMF (40

ml) a temperatura ambiente. A la mezcla se agregaron 2,5–difluorobencil bromuro (0,60 g, 2,9 mmol) y carbonato de cesio (1,1 g, 3,38 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas. 300 ml de THF/acetato de etilo (1:3) y 50 ml de agua se agregaron a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 50 ml). La fase orgánica combinada se lavó con agua (2 X 100 ml). La fase orgánica separada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **12G** (0,65 g, 81% de rendimiento). E. M. encontrada para C29H28F2N2O3Si: 519,3 $(M+H)^+$.

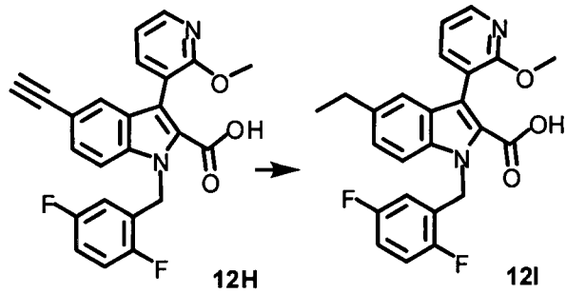
Paso 7:



A una solución de etil éster del ácido 1–(2,5–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trimetilsilaniletinil-1H–indol–2–carboxílico, **12G** (0,65 g, 1,25 mmol) en metanol (12 ml) y THF (5 ml) se agregó hidróxido de litio monohidrato (220 mg, 5,24 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 5 min antes de colocarse en un reactor de microondas durante 20 min (120°C, alta potencia). La mezcla se concentró bajo presión reducida, y 30 ml de agua se agregó. La fase acuosa se acidificó hasta pH=2 por la incorporación de solución acuosa 1N de HCl, y la mezcla se extrajo tres veces con 100 ml de THF/acetato de etilo (3:1). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **12H** (100% de rendimiento). ^{1}H RMN (400 MHz, CDCl3) δ 8,32 & 8,30 (dd, J= 2,20 Hz & 5,13 Hz, 1H), 7,75 & 7,73 (dd, J= 2,20 Hz

& 7,32 Hz, 1H), 7,68 (s, 1H), 7,45 (d, J= 9,52 Hz, 1H), 7,33 (d, J= 8,79 Hz, 1H), 7,09–6,88 (m, 4H), 6,47–6,42 (m, 1H), 5,87 (s, 2H), 3,74 (s, 3H), 3,01 (s, 1H).

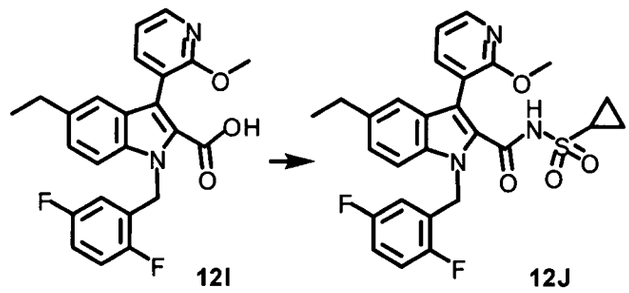
Paso 8::



12H **12I**

A una solución de ácido 1–(2,5–difluoro–bencil)–5–etinil-3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **12H** (0,57 g, 1,25 mmol) en EtOH absoluto y THF se agregó Pd-C al 5% (200 mg). Se vació el matraz, y luego se cargó con H_2 gaseoso. La mezcla de reacción se dejó agitar a temperatura ambiente durante 3 horas. El catalizador de paladio se filtró a través de un taco de celite, y se lavó con 100 ml de MeOH/THF (1:1). El filtrado recolectado se concentró bajo presión reducida para proporcionar el producto en bruto **12I** (100% de rendimiento). E. M. encontrada para C24H20F2N2O3: 423,05 $(M+H)^+$.

Paso 9:

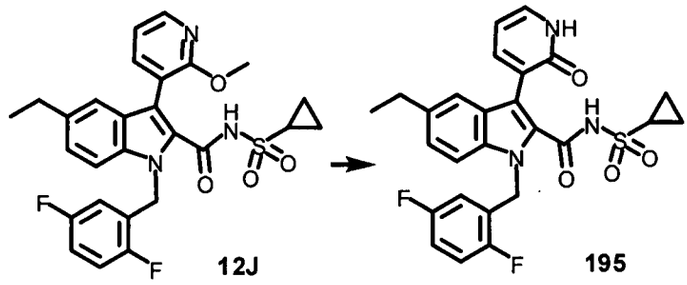


12I **12J**

Se disolvió ácido 1–(2,5–Difluoro–bencil)–5–etil–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **12I** (140 mg, 0,36 mmol) en tetrahidrofurano (5 ml) a temperatura ambiente. A la mezcla se agregó carbonilo diimidazol (78 mg, 0,48 mmol). La suspensión resultante se reflujó a 75°C durante 1 hora, y luego se enfrió hasta la temperatura ambiente antes de agregarse ciclopropilo sulfonamida (89 mg, 0,74 mmol) y 1,8–diazabiciclo(5,4,0)undec–7—eno (0,12 ml, 0,80 mmol).

La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 18 horas. Se agregaron acetato de etilo (150 ml) y ácido fosfórico acuoso al 5% (100 ml), y las fases se separaron. La fase acuosa se extrajo dos veces con acetato de etilo (2 x 60 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **12J** (155 mg, 80% de rendimiento). E. M. encontrada para C27H25F2N3O4S: 526,06 $(M+H)^+$.

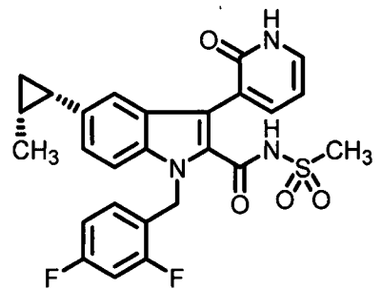
Paso 10:



Se disolvió [1–(2,5–difluoro–bencil)–5–etil–3–(2–metoxi–piridin–3–il)–1H–indol–2–carbonil]–amida del ácido ciclopropansulfónico, **12J** (155 mg, 0,30 mmol) en HCl 4N en 1,4-dioxano (6 ml) en un tubo. La mezcla de reacción se dejó agitar a 90°C el tubo sellado durante 2,5 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente antes de concentrarse bajo presión reducida. El producto en bruto se purificó usando HPLC de fase inversa para proporcionar el compuesto **195** (57 mg, 38% de rendimiento). ^{1}H RMN (500 MHz, d_6–DMSO): δ 12,79 (s, 1H), 12,73 (s, 1H), 7,82 (d, J= 6,62 Hz, 1H), 7,69 (d, J= 5,04 Hz, 1H), 7,57 (d, J= 8,51 Hz, 1H), 7,33–7,15 (m, 4H), 6,64–6,60 (m, 2H), 5,73 (s, 2H), 2,96–2,91 (m, 1H), 2,66 (q, J= 7,25 Hz & 7,57 Hz, 2H), 1,17 (t, J= 7,57 Hz, 3H), 0,98 (d, J= 5,99 Hz, 4H). E. M. encontrada para C26H23F2N3O4S: 512,18 $(M+H)^+$.

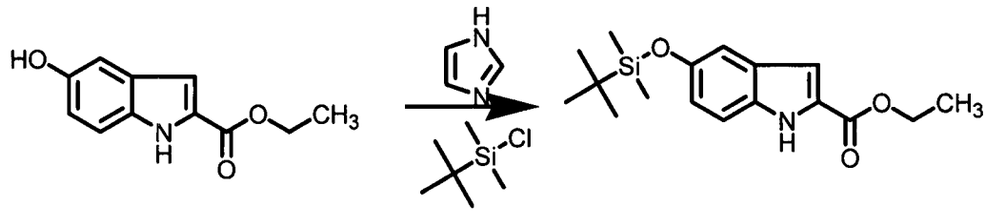
Ejemplo 13

Preparación del compuesto **192**



192

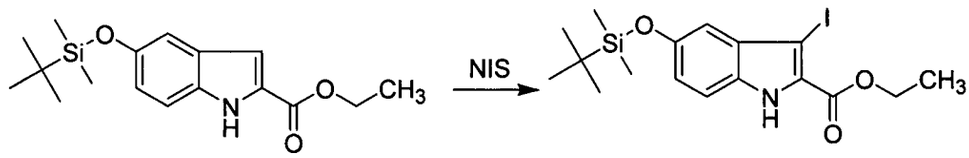
Paso 1:



13A **13B**

Una solución de 5–hidroxi–1H–indol–2–carboxilato de etilo (**13A,** 6,0 g; 29,24 mmol) en 300 ml de diclorometano se trató con imidazol (4,0 eq, 7,96 g) y cloruro de ter-butildimetilsililo (2,0 eq, 8,82 g). La reacción se dejó agitar a temperatura ambiente durante 3 horas. Una pequeña muestra (1 ml) se tomó de la mezcla de reacción, se diluyó con diclorometano (10 ml) y se lavó con agua. La evaporación del solvente y el análisis por RMN mostró que la totalidad del material de partida se había consumido. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con agua (2 x 100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **13B** (9,20 g; 98%) como un sólido blanco.

Paso 2:

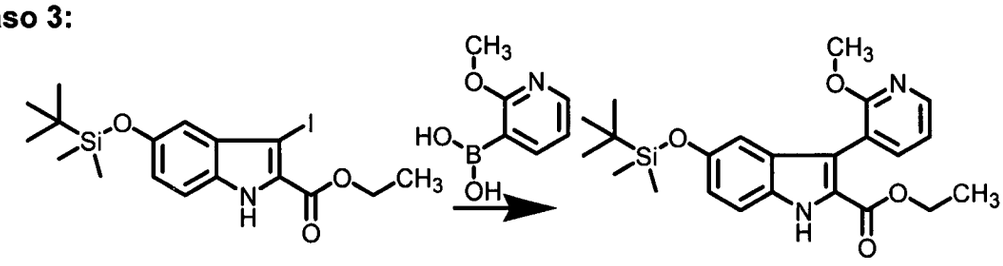


13B **13C**

661

Una solución de 5–ter-butildimetilsililoxi–1H–indol–2–carboxilato de etilo **13B** (9,0 g) en 300 ml de cloroformo se enfrió con hielo y se trató con N–yodosuccinimida (1,1 eq, 6,97 g). La mezcla se dejó agitar a 0°C durante 10 min y luego a temperatura ambiente durante 2 horas. El análisis por RMN de una pequeña alícuota mostró la conversión completa del material de partida. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con tiosulfato de sodio ac. saturado (150 ml), bicarbonato de sodio saturado ac. (150 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **13C** (11,58 g; 92%) como un sólido blanco. E. M. encontrada para C17H24INO3Si: 446,36 $(M+H)^+$.

Paso 3:

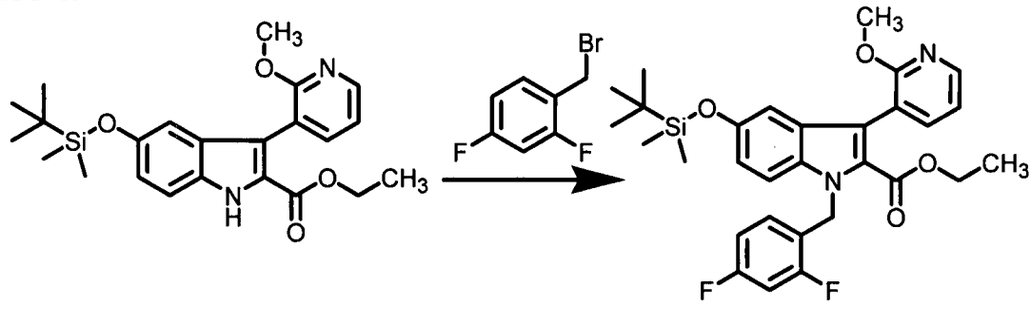


13C **13D**

El ácido 2–metoxi–3–piridin borónico (1,05 eq, 3,27 g) se agregó a una solución de **13C** (9,06 g; 20,345 mmol) en 100 ml de 1,2–dimetoxietano. La mezcla se desgasificó (vacío/enjuague de argón) y $PdCl_2(dppf)_2$ (10% en moles, 1,66 g) se agregó y la solución naranja resultante se dejó agitar durante 30 min a temperatura ambiente. Se agregó una solución de carbonato de potasio (4,0 eq, 81 ml de solución ac. 1M) y la solución marrón resultante se dejó agitar a 90°C durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró. El residuo se diluyó con acetato de etilo (600 ml) y se lavó con bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se dividió en dos porciones iguales y cada una se purificó usando cromatografía con gel de

sílice (Columna Biotage 75—M; gradiente: 0 hasta 30% acetato de etilo en hexanos) para proporcionar el compuesto **13D** como un sólido blanco (6,76 g; 65%). E. M. encontrada para C23H30N2O4Si: 427,56 $(M+H)^+$.

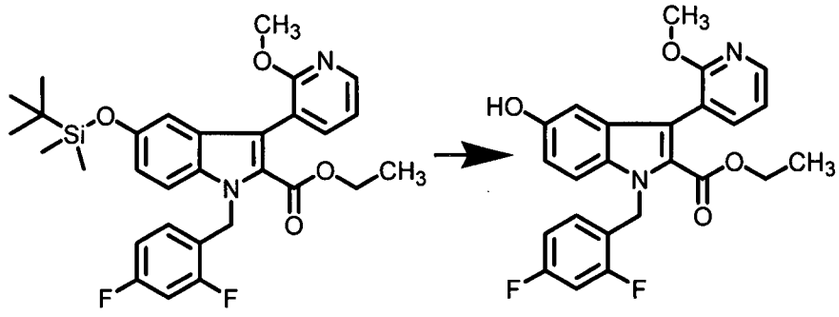
Paso 4:



13D **13E**

Una solución de derivado indólico **13D** (6,5 g, 15,237 mmol) en 50 ml de THF anhidro se agregó a una suspensión enfriada con hielo de yoduro de sodio (1,3 eq, 792 mg de suspensión al 60% en aceite mineral) en 50 ml de THF anhidro. La solución resultante se dejó agitar durante 10 min seguido de la incorporación de 2,4–difluorobencil bromuro (1,3 eq, 2,54 ml, d 1,613). Se agregó una cantidad catalítica de yoduro de tetrabutilamonio (0,2 eq, 1,12 g) a la mezcla de reacción y la agitación se continuó durante 18 h (temperatura desde 0 hasta 25°C). La reacción se desactivó por la incorporación de agua (10 ml) y la mezcla se diluyó con acetato de etilo (500 ml). La fase orgánica se lavó con agua (2 x 100 ml) y salmuera (80 ml), se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el producto en bruto **13E** una espuma incolora contaminada con producto bis-N,O-difluorobencilo no deseado. La mezcla en bruto se usó para la siguiente reacción sin ninguna purificación adicional. E. M. encontrada para C30H34N2O4Si: 553,65 $(M+H)^+$.

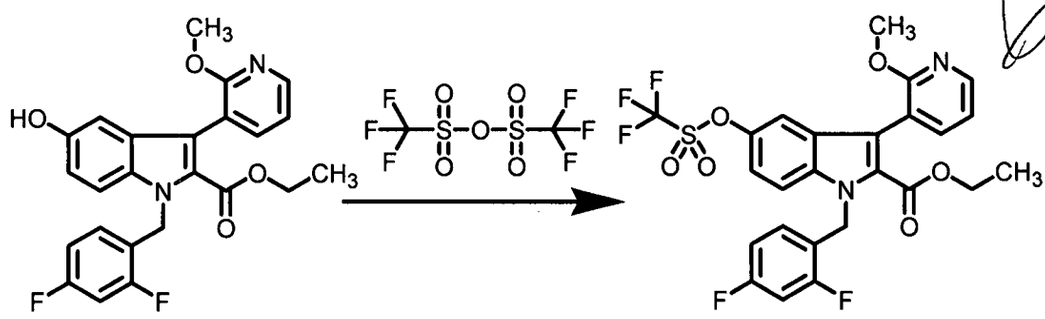
Paso 5:



13E **13F**

Una solución de sililéter en bruto **13E** (15,237 mmol; 8,4 g) en 100 ml de THF (NOTE: **13E** contiene una impureza identificada como el compuesto bis—N,O—difluorobencilo) se enfrió con hielo y se trató con aprox. 1,0 eq de TBAF (15 ml de solución 1,0M en THF). La mezcla inmediatamente se tornó color amarillo-verde y la TLC luego de 5 min (30% acetato de etilo en hexanos) mostró que no quedaba material de partida. La mezcla se diluyó con acetato de etilo (500 ml) y se lavó con agua (100 ml), bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 75—M; gradiente: 10 hasta 50% acetato de etilo en hexanos) para proporcionar el compuesto **13F** como un sólido blanco (5,8 g; 88% para dos pasos). ^{1}H RMN (400 MHz, d_6–DMSO): δ 9,09 (s, 1H), 8,17 & 8,16 (dd, J = 2,20 & 5,13 Hz, 1H), 7,71 & 7,69 (dd, J = 1,46 & 7,32 Hz, 1H), 7,45 (d, J = 8,79 Hz, 1H), 7,26 (t, J = 10,98 Hz, 1H), 7,10–7,06 (m, 1H), 6,97 (dt, J = 8,79 & 2,20 Hz, 1H), 6,88 & 6,86 (dd, J = 8,79 & 2,20 Hz, 1H), 6,76–6,71 (m, 1H), 6,67 (d, J = 2,20 Hz, 1H), 5,77 (s, 2H), 3,99 (q, J = 7,32 Hz, 2H), 3,75 (s, 3H), 0,85 (t, J = 7,32 Hz, 3H).

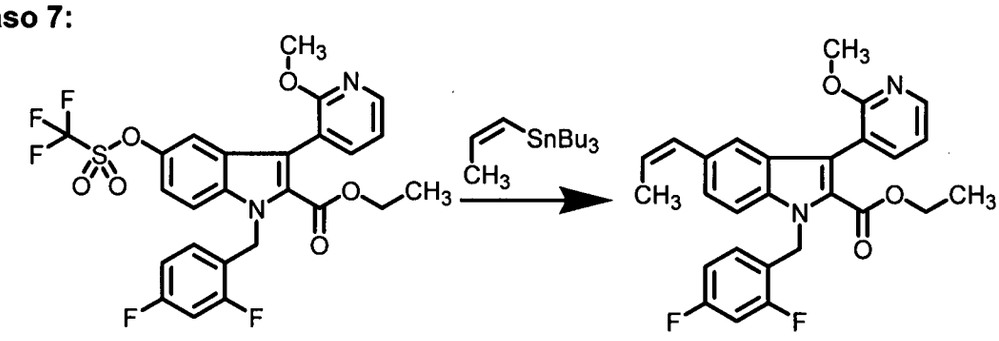
Paso 6:



13F **13G**

Una solución de etil éster del ácido 1–(2,4–Difluoro–bencil)–5–hidroxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico **13F** (2,0 g; 4,56 mmol) en 20 ml de diclorometano anhidro se enfrió con hielo y se trató con piridina (4 ml) y anhídrido tríflico (2,1 eq, 1,61 ml, d 1,677). La mezcla se dejó agitar durante 10 min y se trató con una cantidad catalítica de 4–dimetilamino piridina. Se retiró el baño de frío y la reacción se dejó agitar durante 2 horas. La TLC (10% acetato de etilo en hexanos) mostró que no quedaba material de partida y la mezcla se diluyó con acetato de etilo (200 ml) y se lavó con agua (50 ml) y salmuera (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 40—M; gradiente: 0 hasta 20% acetato de etilo en hexanos) para proporcionar el compuesto **13G** (2,50 g; 96%) como un aceite incoloro. EM encontrada para C25H19F5N2O6S: 571,12 $(M+H)^+$.

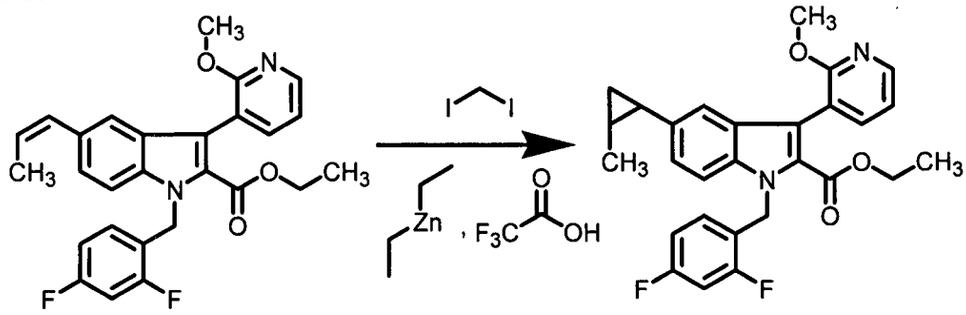
Paso 7:



13G **13H**

Una solución de etil éster del ácido 1–(2,4–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trifluorometanosulfoniloxi–1H–indol–2–carboxílico **13G** (650 mg; 1,13 mmol) en 10 ml de THF se trató con cloruro de litio (7,0 eq, 336 mg) y (Z)–1–propeniltributil estanano (1,5 eq, 0,51 ml, d 1,1). La mezcla se desgasificó (vacío/enjuague de nitrógeno) y se agregó tetrakis(trifenilfosfin)paladio (10% en moles, 130 mg). La mezcla de reacción se calentó hasta 70°C y se agitó hasta la mañana siguiente. La TLC (10% acetato de etilo en hexanos) y los análisis por EM mostraron conversión completa de material de partida. La mezcla se diluyó con acetato de etilo (80 ml) y se lavó sucesivamente con agua (10 ml), hidróxido de amonio ac. al 10% (10 ml), agua (10 ml), y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía con gel de sílice (columna Biotage 25–M; gradiente: 80 ml de hexanos luego 0 hasta 25% acetato de etilo en hexanos) para proporcionar el compuesto **13H** (400 mg; 77%) como un aceite incoloro. EM encontrada para C27H24F2N2O3: 463,30 $(M+H)^+$.

Paso 8:

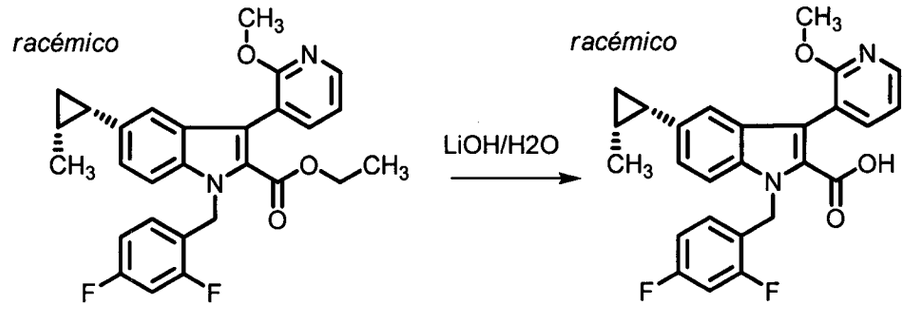


13H **13I**

A una solución agitada vigorosamente de dietilzinc (10,0 eq, 3,9 ml de solución 1M en heptano) en 2 ml de diclorometano anhidro a 0°C (baño de agua hielo) se agregó gota a gota una solución de ácido trifluoroacético (10,0 eq, 0,299 ml, d 1,480) en 0,5 ml de diclorometano. La mezcla resultante se dejó agitar durante 10 min luego de lo cual se agregó una solución de diyodometano (10,0

eq, 0,31 ml, d 3,325) en 0,5 ml de diclorometano gota a gota. La mezcla se dejó agitar durante 10 min seguido de la incorporación de una solución de etil éster del ácido 1–(2,4–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–prop–Z–enil-1H–indol–2–carboxílico **13H** (180 mg; 0,389 mmol) en 1 ml de diclorometano anhidro. La reacción se dejó agitar a 0ºC y se monitoreó por TLC y análisis de EM (NOTA: el Rf de material de partida y producto es el mismo en diferentes sistemas solventes). Luego de 4 h la reacción se desactivó por la incorporación de bicarbonato de sodio saturado ac. (10 ml). La mezcla se extrajo con acetato de etilo (50 ml). La fase orgánica se lavó con HCl 1M ac. (10 ml), bicarbonato de sodio saturado ac. (10 ml), y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 12—S, gradiente: 0 hasta 20% acetato de etilo en hexanos) para proporcionar el compuesto **13I** como un aceite incoloro. E. M. encontrada para C28H26F2N2O3: 477,26 $(M+H)^+$.

Paso 9:

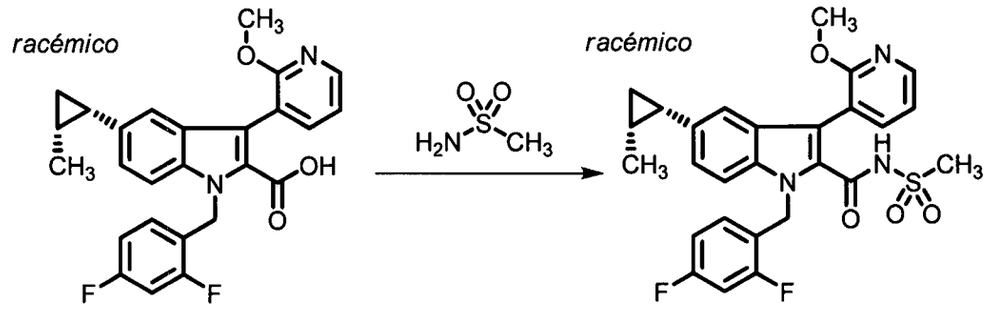


13I **13J**

Una solución de etil éster del ácido 1–(2,4–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–cis–metil–ciclopropil)–1H–indol–2–carboxílico **13I** (230 mg; 0,482 mmol) en 10 ml de una mezcla 5:1:1 de THF/agua/metanol se trató con hidróxido de litio monohidrato (5,0 eq, 101 mg). La mezcla se calentó hasta 50ºC durante 5 horas. La TLC (20% acetato de etilo en hexanos) mostró el consumo completo de the material de partida. La mezcla se diluyó con HCl 1M ac. (40 ml) y

el producto se absorbió en diclorometano (3 x 25 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para proporcionar el compuesto **13J** (205 mg; 95% de rendimiento) como un sólido blanco.

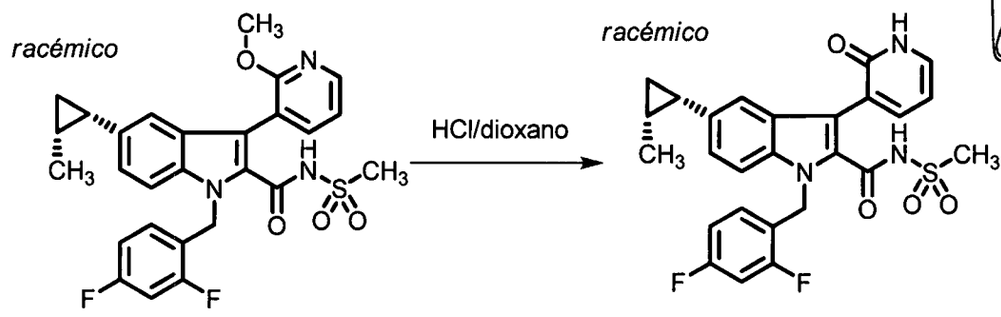
Paso 10:



13J **13K**

Una solución de ácido 1–(2,4–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–cis–metil–ciclopropil)–1H–indol–2–carboxílico **13J** (100 mg; 0,222 mmol) en 5 ml de THF anhidro se trató con carbonil diimidazol (1,25 eq, 45 mg). La mezcla se calentó hasta 70°C durante 2 h y luego se enfrió hasta la temperatura ambiente. Se agregaron metansulfonamida (1,25 eq, 26 mg) y DBU (1,5 eq, 0,049 ml, d 1,018) y la mezcla se calentó hasta 70°C hasta la mañana siguiente. La mezcla se diluyó con acetato de etilo (60 ml) y se lavó con HCl 1M ac. (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía con gel de sílice (columna Biotage 25–S de gel de sílice, gradiente: 0 hasta 20% acetona in diclorometano) para proporcionar el compuesto **13K** (85 mg; 73%) como un sólido blanco. E. M. encontrada para C27H25F2N3O4S: 526,16 $(M+H)^+$.

Paso 11:

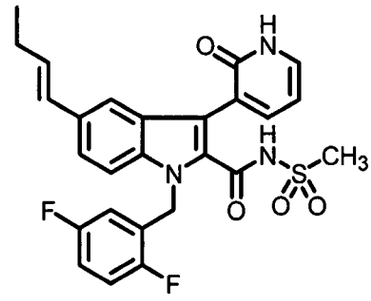


13K **192**

La N–[1–(2,4–Difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–metil–ciclopropil)–1H–indol–2–carbonil]–metansulfonamida **13K** (0,152 mmol) se disolvió en 3 ml de solución 4M de HCl en dioxano. Se agregó metanol (1 ml) y la solución se calentó a 90°C en un tubo sellado durante 2,5 horas. La mezcla de reacción se concentró para proporcionar el producto en bruto como un sólido blanco. Una muestra (1 mg) se disolvió en 0,5 ml de DMF y se analizó sobre HPLC analítica en las siguientes condiciones: Columna: Delta Pak; C18, 5 micrómetros, 300A; 150 x 3,9 mm I.D.; Caudal de flujo: 1 ml/min; Gradiente: 40% acetonitrilo en agua durante 5 min luego aumentar hasta 80% durante 25 minutos. El producto se purificó sobre HPLC semi-prep. en las siguientes condiciones: Columna: Delta Pak, C18, 5 micrómetros, 300A; 300 x 30 mm I.D.; Caudal de flujo: 30 ml/min; Gradiente: 50% acetonitrilo en agua durante 20 min luego aumentar hasta 80% durante 30 min y reposar allí durante 10 minutos. La fracción que contiene el producto de acuerdo con el análisis por EM se concentró para eliminar el acetonitrilo y agua para proporcionar el compuesto **192** (30 mg; 40%) como un sólido blanco. EM encontrada para C26H23F2N3O4S: 512,06 $(M+H)^+$. ^{1}H RMN (400 MHz, d_6–DMSO): δ 7,78 & 7,76 (dd, J = 2,20 & 6,59 Hz, 1H), 7,64 (bs,1H), 7,52 (d, J = 8,06 Hz, 1H), 7,29–7,17 (m, 3H), 7,02–6,94 (m, 2H), 6,62–6,58 (m, 1H), 5,67 (s, 2H), 3,25 (s, 3H), 2,14–2,09 (m, 1H), 1,11–1,10 (m, 1H), 0,94–0,89 (m, 1H), 0,68–0,67 (m, 3H), 0,56–0,52 (m, 1H).

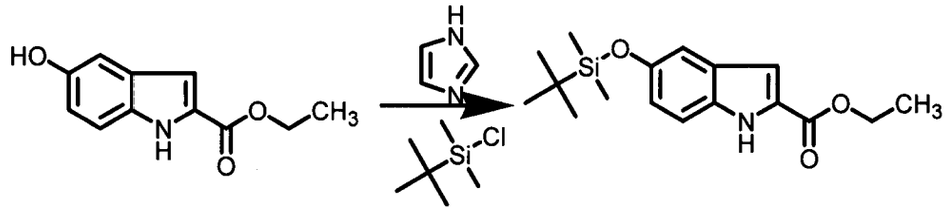
Ejemplo 14

Preparación del compuesto **194**



194

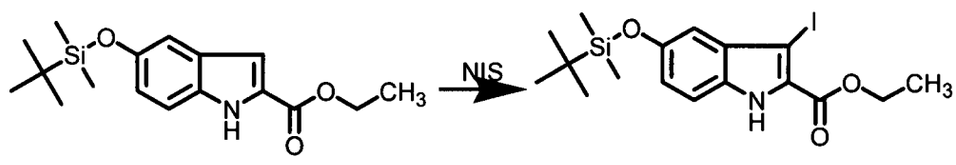
Paso 1:



14A **14B**

Una solución de 5–hidroxi–1H–indol–2–carboxilato de etilo **14A** (6,0 g; 29,24 mmol) en 300 ml de diclorometano se trató con imidazol (4,0 eq, 7,96 g) y cloruro de ter-butildimetilsililo (2,0 eq, 8,82 g). La reacción se dejó agitar a temperatura ambiente durante 3 horas. Se tomó una pequeña muestra (1 ml) de la mezcla de reacción, se diluyó con diclorometano (10 ml) y se lavó con agua. La evaporación del solvente y el análisis por RMN mostró que la totalidad del material de partida se había consumido. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con agua (2 x 100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **14B** (9,20 g; 98%) como un sólido blanco.

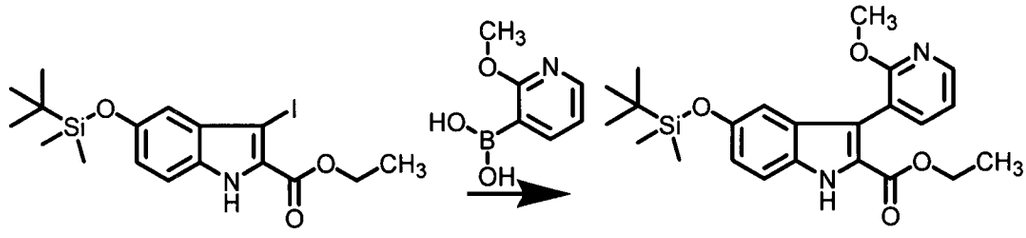
Paso 2:



14B **14C**

Una solución de 5–ter-butildimetilsililoxi–1H–indol–2–carboxilato de etilo **14B** (9,0 g) en 300 ml de cloroformo se enfrió con hielo y se trató con N–yodosuccinimida (1,1 eq, 6,97 g). La mezcla se dejó agitar a 0ºC durante 10 min y luego a temperatura ambiente durante 2 horas. El análisis por RMN de una pequeña alícuota mostró la conversión completa de material de partida. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con tiosulfato de sodio ac. saturado (150 ml), bicarbonato de sodio saturado ac. (150 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **14C** (11,58 g; 92%) como un sólido blanco. E. M. encontrada para C17H24INO3Si: 446,36 $(M+H)^+$.

Paso 3:

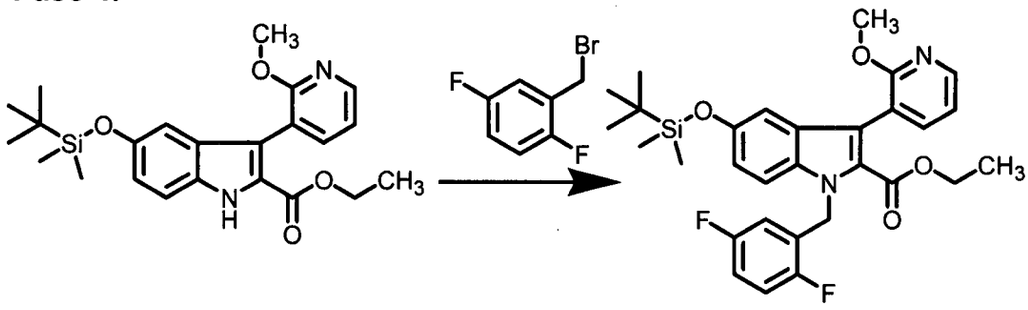


14C **14D**

El ácido 2–metoxi–3–piridin borónico (1,05 eq, 3,27 g) se agregó a una solución de **14C** (9,06 g; 20,345 mmol) en 100 ml de 1,2–dimetoxietano. La mezcla se desgasificó (vacío/enjuague de argón) y se agregó $PdCl_2(dppf)_2$ (10% en moles, 1,66 g) y la solución naranja resultante se dejó agitar durante 30 min a temperatura ambiente. Se agregó una solución de carbonato de potasio (4,0 eq, 81 ml de solución ac. 1M) y la solución marrón resultante se dejó agitar a 90ºC durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró. El residuo se diluyó con acetato de etilo (600 ml) y se lavó con bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se dividió

en dos porciones iguales y cada una se purificó usando cromatografía con gel de sílice (Columna Biotage 75—M; gradiente: 0 hasta 30% acetato de etilo en hexanos) para proporcionar el compuesto **14D** como un sólido blanco (6,76 g; 65%). E. M. encontrada para C23H30N2O4Si: 427,56 $(M+H)^+$.

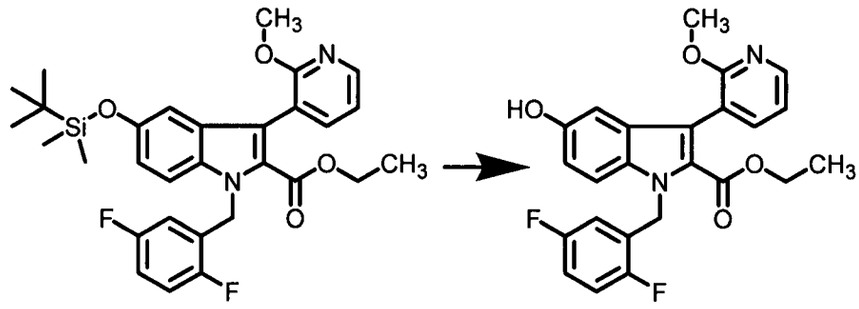
Paso 4:



14D **14E**

Una solución de derivado indólico **14D** (6,5 g, 15,237 mmol) en 50 ml de THF anhidro se agregó a una suspensión enfriada con hielo de yoduro de sodio (1,3 eq, 792 mg de suspensión al 60% en aceite mineral) en 50 ml de THF anhidro. La solución resultante se dejó agitar durante 10 min seguido de la incorporación de 2,5–difluorobencil bromuro (1,3 eq, 2,54 ml, d 1,613). Se agregó una cantidad catalítica de yoduro de tetrabutilamonio (0,2 eq, 1,12 g) a la mezcla de reacción y la agitación se continuó durante 18 h (temperatura desde 0 hasta 25°C). La reacción se desactivó por la incorporación de agua (10 ml) y la mezcla se diluyó con acetato de etilo (500 ml). La fase orgánica se lavó con agua (2 x 100 ml) y salmuera (80 ml), se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el producto en bruto **14E** una espuma incolora contaminada con producto bis-N,O-difluorobencilo no deseado. La mezcla en bruto se usó para la siguiente reacción sin ninguna purificación adicional.

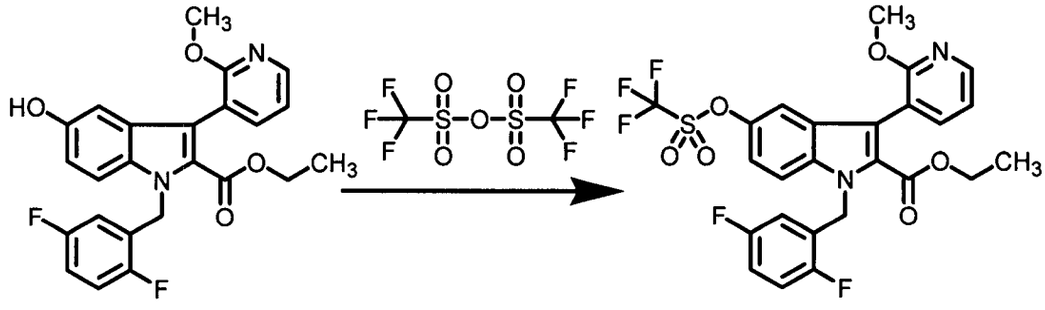
Paso 5:



14E **14F**

Una solución de sililéter en bruto **14E**(15,237 mmol; 8,4 g) en 100 ml de THF (NOTE: **14E** contiene una impureza identificada como el compuesto bis—N,O—difluorobencilo) se enfrió con hielo y se trató con aprox. 1,0 eq de TBAF (15 ml de solución 1,0M en THF). La mezcla inmediatamente se tornó color amarillo-verde y TLC luego de 5 min (30% acetato de etilo en hexanos) mostró que no quedaba material de partida. La mezcla se diluyó con acetato de etilo (500 ml) y se lavó con agua (100 ml), bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 75—M; gradiente: 10 hasta 50% acetato de etilo en hexanos) para proporcionar el compuesto **14F** como un sólido blanco (5,8 g; 88% para dos pasos).

Paso 6:

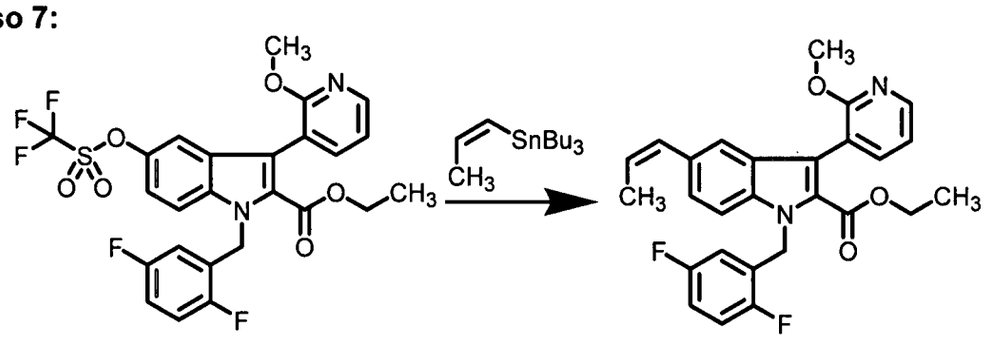


14F **14G**

Una solución de etil éster del ácido 1–(2,5–Difluoro–bencil)–5–hidroxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico **14F** (2,0 g; 4,56 mmol) en 20 ml

de diclorometano anhidro se enfrió con hielo y se trató con piridina (4 ml) y anhídrido tríflico (2,1 eq, 1,61 ml, d 1,677). La mezcla se dejó agitar durante 10 min y se trató con una cantidad catalítica de 4–dimetilamino piridina. Se retiró el baño de frío y la reacción se dejó agitar durante 2 horas. La TLC (10% acetato de etilo en hexanos) mostró que no quedaba material de partida y la mezcla se diluyó con acetato de etilo (200 ml) y se lavó con agua (50 ml) y salmuera (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 40–M; gradiente: 0 hasta 20% acetato de etilo en hexanos) para proporcionar el compuesto **14G** (2,50 g; 96%) como un aceite incoloro.

Paso 7:

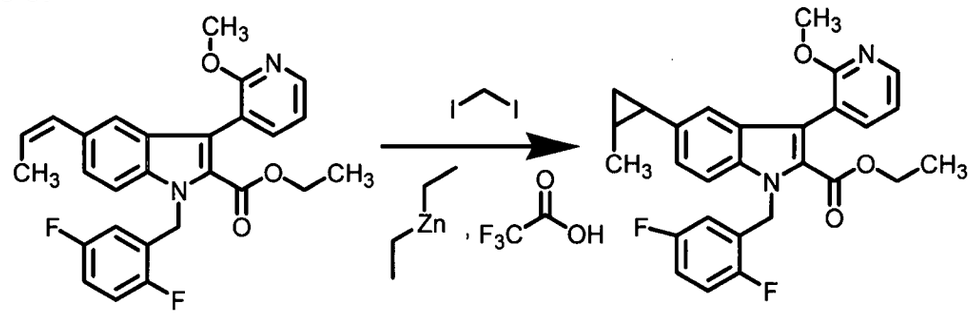


14G **14H**

Una solución de etil éster del ácido 1–(2,5–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–trifluorometanosulfoniloxi–1H–indol–2–carboxílico **14G** (650 mg; 1,13 mmol) en 10 ml de THF se trató con cloruro de litio (7,0 eq, 336 mg) y (Z)–1–propeniltributil estanano (1,5 eq, 0,51 ml, d 1,1). La mezcla se desgasificó (vacío/enjuague de nitrógeno) y se agregó tetrakis(trifenilfosfin)paladio (10% en moles, 130 mg). La mezcla de reacción se calentó hasta 70°C y se agitó hasta la mañana siguiente. La TLC (10% acetato de etilo en hexanos) y los análisis por EM mostraron conversión completa de material de partida. La mezcla se diluyó con acetato de etilo (80 ml) y se lavó sucesivamente con agua (10 ml), hidróxido de amonio ac. al 10% (10 ml), agua (10 ml), y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se

purificó usando cromatografía con gel de sílice (Columna Biotage 25—M; gradiente: 80 ml de hexanos luego 0 hasta 25% acetato de etilo en hexanos) para proporcionar el compuesto **14H** (400 mg; 77%) como un aceite incoloro.

Paso 8:

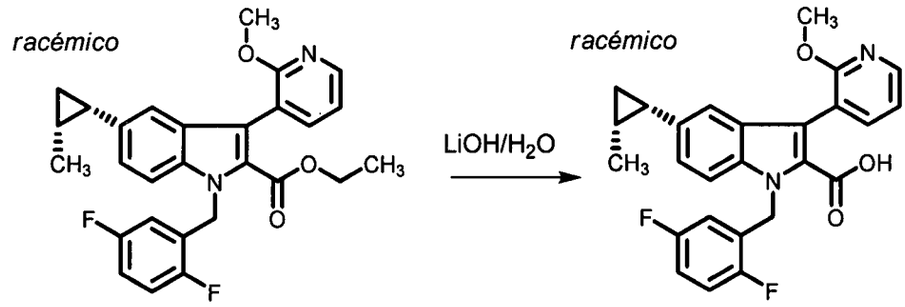


14H **14I**

A una solución agitada vigorosamente de dietilzinc (10,0 eq, 3,9 ml de solución 1M en heptano) en 2 ml de diclorometano anhidro a 0°C (baño de agua-hielo) se agregó gota a gota una solución de ácido trifluoroacético (10,0 eq, 0,299 ml, d 1,480) en 0,5 ml de diclorometano. La mezcla resultante se dejó agitar durante 10 min luego de lo cual una solución de diyodometano (10,0 eq, 0,31 ml, d 3,325) en 0,5 ml de diclorometano se agregó gota a gota. La mezcla se dejó agitar durante 10 min seguido de la incorporación de una solución de etil éster del ácido 1–(2,5–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–prop–Z–enil-1H–indol–2–carboxílico **14H** (180 mg; 0,389 mmol) en 1 ml de diclorometano anhidro. La reacción se dejó agitar a 0°C y se monitoreó por TLC y análisis de EM (NOTA: el Rf de material de partida y producto es el mismo en diferentes sistemas solventes). Luego de 4 h la reacción se desactivó por la incorporación de bicarbonato de sodio saturado ac. (10 ml). La mezcla se extrajo con acetato de etilo (50 ml). La fase orgánica se lavó con HCl 1M ac. (10 ml), bicarbonato de sodio saturado ac. (10 ml), y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 12—S, gradiente: 0 hasta 20%

acetato de etilo en hexanos) para proporcionar el compuesto **14I** como un aceite incoloro.

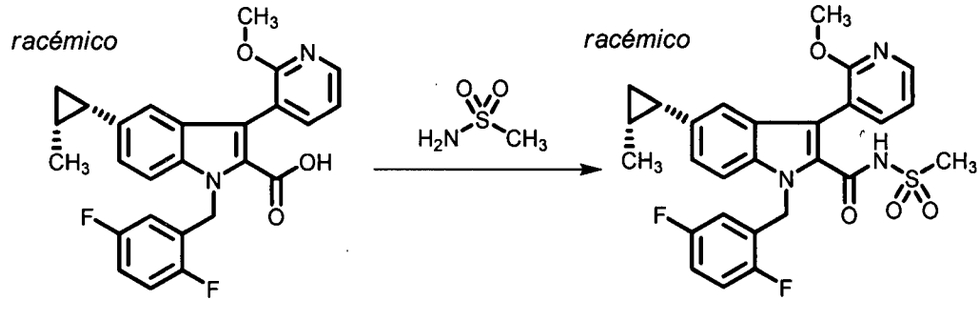
Paso 9:



14I **14J**

Una solución de etil éster del ácido 1–(2,5–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–cis–metil–ciclopropil)–1H–indol–2–carboxílico **14I** (230 mg; 0,482 mmol) en 10 ml de una mezcla 5:1:1 de THF/agua/metanol se trató con hidróxido de litio monohidrato (5,0 eq, 101 mg). La mezcla se calentó hasta 50°C durante 5 horas. La TLC (20% acetato de etilo en hexanos) mostró el consumo completo del material de partida. La mezcla se diluyó con HCl 1M ac. (40 ml) y el producto se absorbió en diclorometano (3 x 25 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para proporcionar el compuesto **14J** (205 mg; 95%) como un sólido blanco.

Paso 10:

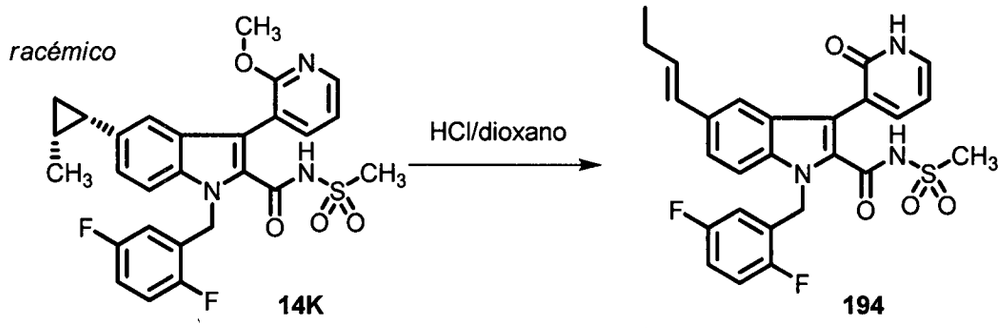


14J **14K**

Una solución de ácido 1–(2,5–difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–cis–metil–ciclopropil)–1H–indol–2–carboxílico **14J** (100 mg; 0,222 mmol) en 5 ml de THF anhidro se trató con carbonilo diimidazol (1,25 eq, 45 mg).

La mezcla se calentó hasta 70ºC durante 2 h y luego se enfrió hasta la temperatura ambiente. Se agregaron metansulfonamida (1,25 eq, 26 mg) y DBU (1,5 eq, 0,049 ml, d 1,018) y la mezcla se calentó hasta 70ºC hasta la mañana siguiente. La mezcla se diluyó con acetato de etilo (60 ml) y se lavó con HCl 1M ac. (10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía con gel de sílice (Columna de gel de sílice Biotage 25—S, gradiente: 0 hasta 20% acetona en diclorometano) para proporcionar el compuesto **14K** (85 mg; 73%) como un sólido blanco. E. M. encontrada para C27H25F2N3O4S: 526,22 $(M+H)^+$.

Paso 11



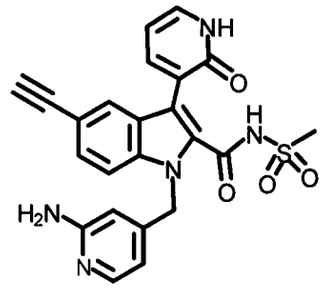
14K **194**

La N–[1–(2,4–Difluoro–bencil)–3–(2–metoxi–piridin–3–il)–5–(2–metil–ciclopropil)–1H–indol–2–carbonil]–metansulfonamida **14K** (0,152 mmol) se disolvió en 3 ml de solución 4M de HCl en dioxano. Se agregó metanol (1 ml) y la solución se calentó a 90ºC en un tubo sellado durante 2,5 horas. La mezcla de reacción se concentró para proporcionar el producto en bruto como un sólido blanco. Se disolvió una muestra (1 mg) en 0,5 ml de DMF y se analizó sobre HPLC analítica en las siguientes condiciones: Columna: Delta Pak; C18, 5 micrómetros, 300A; 150 x 3,9 mm I.D.; Caudal de flujo: 1 ml/min; Gradiente: 40% acetonitrilo en agua durante 5 min luego aumentar hasta 80% durante 25 minutos. El producto se purificó sobre HPLC semi-prep. en las siguientes condiciones: Columna: Delta Pak, C18, 5 micrómetros, 300A; 300 x 30 mm I.D.; Caudal de

flujo: 30 ml/min; Gradiente: 50% acetonitrilo en agua durante 20 min luego aumentar hasta 80% durante 30 min y reposar allí durante 10 minutos. La fracción que contiene el producto de acuerdo con el análisis por EM se concentró para retirar el acetonitrilo y agua para proporcionar un producto mayor como un sólido blanco y un producto menor, que se identificó como Compuesto **194**. ^{1}H RMN (400 MHz, d_6–DMSO): δ 7,84 & 7,82 (dd, J = 2,20 & 7,32 Hz, 1H), 7,65 (bs,1H), 7,55 (d, J = 8,79 Hz, 1H), 7,49 (d, J = 8,79 Hz, 1H), 7,34 (bs, 1H), 7,31–7,25 (m, 1H), 7,19–7,12 (m, 1H), 6,60 (t, J = 6,59 Hz, 2H), 6,46–6,42 (m, 1H), 6,27–6,20 (m, 1H), 5,70 (s, 2H), 3,24 (s, 3H), 2,16 (quinteto, J = 6,59 & 7,32 Hz, 2H), 1,02 (t, J = 7,32 Hz, 3H). E. M. encontrada para C26H23F2N3O4S: 512,16 $(M+H)^+$.

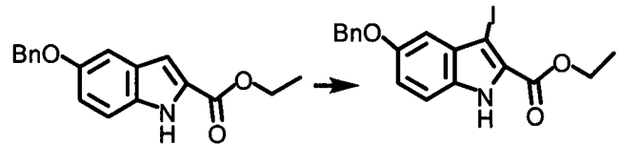
Ejemplo 15

Preparación del compuesto **26**



26

Paso 1:

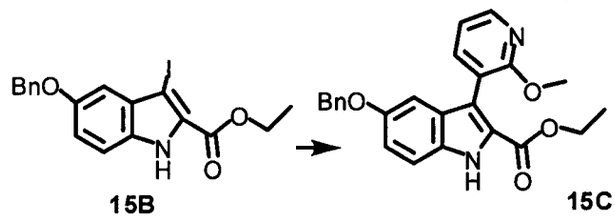


15A **15B**

Se disolvió 5–benciloxiindol–2–carboxilato de etilo, **15A** (5,0 g, 16,9 mmol) en acetona (400 ml) a temperatura ambiente. A la mezcla se agregó N–yodosuccinimida (4,0 g, 16,9 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 3 horas. La mezcla se concentró bajo presión reducida, y el residuo se disolvió en acetato de etilo (300 ml). La mezcla se lavó con solución acuosa saturada de tiosulfato de sodio (100 ml). Se separaron las

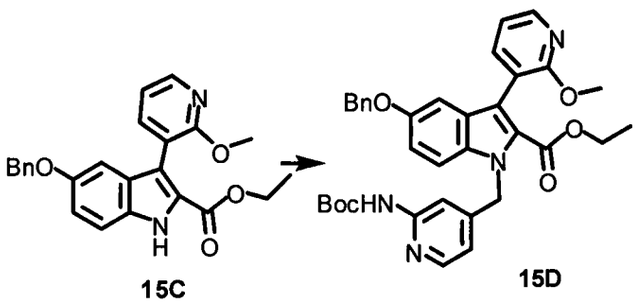
fases, y la fase acuosa se extrajo con acetato de etilo (2 X 150 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **15B** (100% de rendimiento). E. M. encontrada para C18H16INO3: 421,89 $(M+H)^+$.

Paso 2:



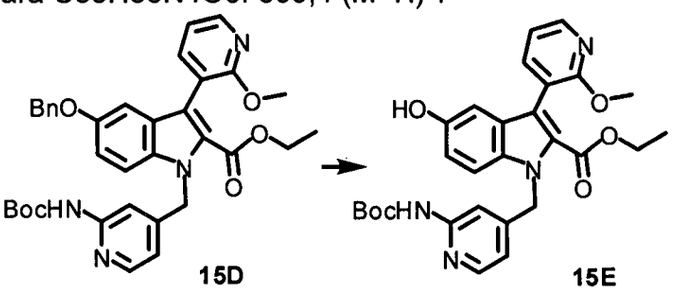
Se disolvió etil éster del ácido 5–Benciloxi–3–yodo–1H–indol–2–carboxílico, **15B** (4,0 g, 9,48 mmol) en 1,2–dimetoxietano (90 ml) y se agregó $PdCl_2(dppf)_2$ (775 mg, 0,95 mmol). La mezcla resultante se desgasificó con burbujeo de argón durante 5 min antes de calentarse hasta 90°C y se dejó agitar durante 30 minutos. En un segundo matraz, la mezcla de ácido 2–metoxi–3–piridin borónico (1,95 g, 11,4 mmol) y carbonato de potasio (6,6 g, 47,8 mmol) en dimetoxietano (30 ml) y agua (30 ml) se desgasificó con burbujeo de argón durante 5 minutos. La mezcla luego se transfirió en tres porciones al primer matraz. La mezcla bifásica resultante se agitó vigorosamente a 90°C durante 4 h antes de dejar enfriar hasta la temperatura ambiente. La reacción se desactivó por la incorporación de una solución de sulfito de sodio (10 g) en agua (400 ml) a temperatura ambiente. Se agregó acetato de etilo (500 ml), y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 500 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **15C** (3,2 g, 84% de rendimiento). E. M. encontrada para C24H22N2O4: 403,2 $(M+H)^+$.

Paso 3:



15C 15D

Se disolvió etil éster del ácido 5–Benciloxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **15C** (2,0 g, 4,96 mmol) en DMF (60 ml) a temperatura ambiente. A la mezcla se agregaron ter-butil éster del ácido (4–bromometil–piridin–2–il)–carbámico (1,4 g, 4,88 mmol) y carbonato de cesio (3,6 g, 11,0 mmol). La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas. Se agregaron acetato de etilo (200 ml) y agua (150 ml), y las fases se separaron. La fase acuosa se extrajo con acetato de etilo (2 x 150 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **15D** (1,95 g, 65% de rendimiento). E. M. encontrada para C35H36N4O6: 609,4 $(M+H)^+$.



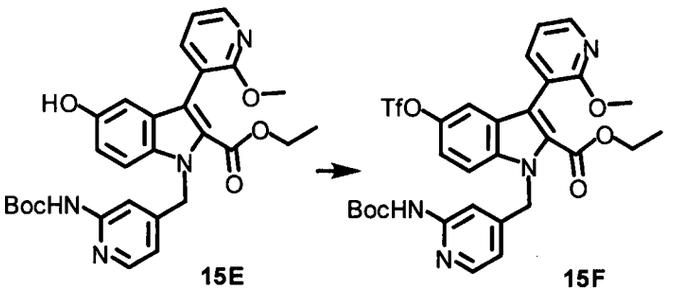
15D 15E

Paso 4:

A una solución de etil éster del ácido 5–benciloxi–1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **15D** (1,90 g, 3,12 mmol) en EtOH se agregó 10% Pd–C (1,0 g). Se vació el matraz, y luego se cargó con H_2 gaseoso. La mezcla de reacción se dejó agitar a temperatura ambiente bajo H_2 gaseoso durante 3 horas. El catalizador de paladio se filtró a través de un taco de celite, y se lavó con 100 ml de MeOH/THF (1:1). El filtrado recolectado se concentró bajo presión reducida para proporcionar

el producto en bruto **15E** (1,54 g, 95% de rendimiento). E. M. encontrada para C28H30N4O6: 519,5 $(M+H)^+$.

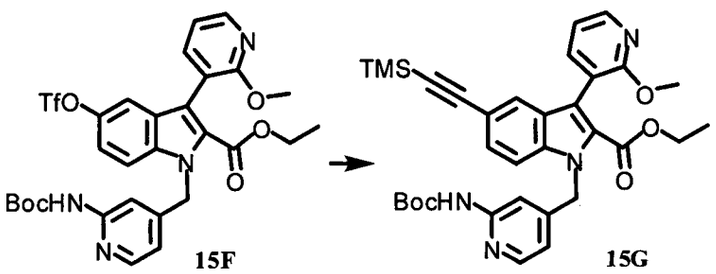
Paso 5:



15E **15F**

A la mezcla de etil éster del ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–5–hidroxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **15E** (1,54 g, 2,97 mmol) y trietilo amina (1,0 ml, 7,17 mmol) en diclorometano (50 ml) se agregó $PhN(SO_2CF_3)_2$ (1,35 g, 3,78 mmol). La mezcla de reacción resultante se dejó agitar a 0°C hasta la temperatura ambiente durante 18 horas. Luego se diluyó la mezcla con diclorometano (100 ml), y se lavó con solución acuosa 1N de carbonato de sodio (2 x 50 ml). La solución acuosa separada se extrajo con diclorometano (100 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **15F** (1,55 g, 80% de rendimiento). E. M. encontrada para C29H29F3N4O8S: 651,5 $(M+H)^+$.

Paso 6:

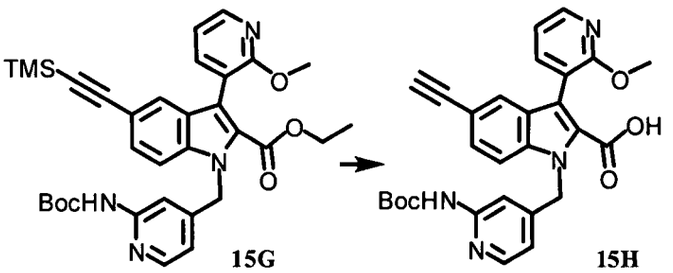


15F **15G**

A una solución de etil éster del ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–3–(2–metoxi–piridin–3–il)–5–trifluorometanosulfoniloxi–1H–indol–2–carboxílico, **15F** (600 mg, 0,92 mmol), se agregaron TMS acetileno (0,65

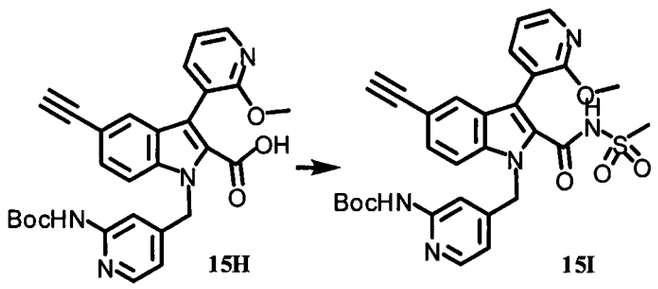
ml, 4,69 mmol) y $nBu_4N^+I^-$ (409 mg, 1,11 mmol) en DMF (20 ml) $PdCl_2(PPh_3)_2$ (65 mg, 0,09 mmol), CuI (53 mg, 0,28 mmol) y trietil amina (0,65 ml, 4,66 mmol). La mezcla de reacción resultante se agitó en un tubo sellado a 65ºC durante 18 horas. La mezcla se enfrió hasta la temperatura ambiente, y se diluyó con agua (90 ml) y EtOAc (150 ml). Se separaron las fases, y la fase acuosa se extrajo con EtOAc (2 x 90 ml). La fase orgánica combinada se lavó con agua (2 x 50 ml) antes de secarse sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **15G** (514 mg, 93% de rendimiento). E. M. encontrada para C33H38N4O5Si: 599,5 $(M+H)^+$.

Paso 7:



A una solución de etil éster del ácido 1–(2–ter-butoxicarbonilamino–piridin–4–ilmetil)–3–(2–metoxi–piridin–3–il)–5–trimetilsilaniletinil-1H–indol–2–carboxílico, **15G** (251 mg, 0,42 mmol) en agua (3 ml) y se agregó THF (3 ml) solución acuosa 1N de hidróxido de litio (1,3 ml). La suspensión resultante se dejó agitar a 70ºC durante 18 horas. La mezcla se enfrió hasta la temperatura ambiente, y la fase acuosa se acidificó hasta pH=2 por la incorporación de solución acuosa 1N de HCl La mezcla se diluyó con acetato de etilo (50 ml) y agua (30 ml), y se separaron las fases. La fase acuosa se extrajo dos veces con 50 ml de THF/acetato de etilo (1:1). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **15H** (191 mg, 91% de rendimiento). E. M. encontrada para C28H26N4O5: 499,4 $(M+H)^+$.

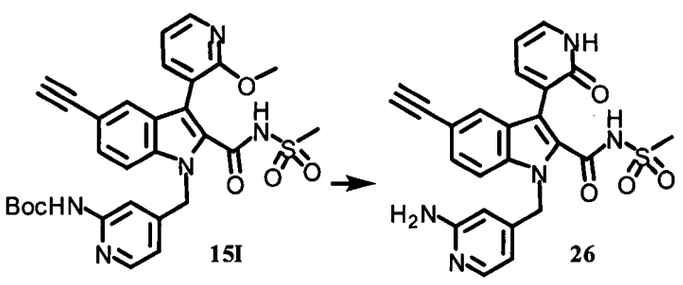
Paso 8:



15H 15I

Se disolvió ácido 1–(2–ter-Butoxicarbonilamino–piridin–4–ilmetil)–5–etinil-3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico, **15H** (128 mg, 0,26 mmol) en tetrahidrofurano (5 ml) a temperatura ambiente. A la mezcla se agregó carbonil diimidazol (50 mg, 0,31 mmol). La suspensión resultante se reflujó a 75°C durante 1 hora, y luego se enfrió hasta la temperatura ambiente antes de agregar metilsulfonamida (49 mg, 0,52 mmol) y 1,8–diazabiciclo(5,4,0)undec–7—eno (0,08 ml, 0,52 mmol). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 24 horas. Se agregaron acetato de etilo (50 ml), tetrahidrofurano (10 ml) y ácido fosfórico acuoso al 1% (15 ml) a la mezcla de reacción, y se separaron las fases. La fase acuosa se extrajo dos veces con acetato de etilo/THF (3:1) (40 ml). La fase orgánica combinada se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash para proporcionar el compuesto **15I** (80 mg, 54% de rendimiento). E. M. encontrada para C29H29N5O6S: 576,20 $(M+H)^+$.

Paso 9:



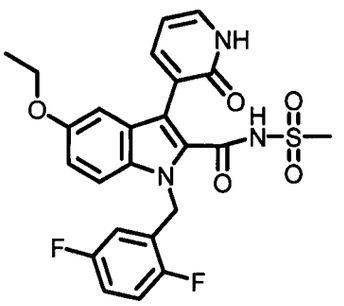
15I 26

La solución de ter-butil éster del ácido {4–[5–etinil-2–metanosulfonilaminocarbonil-3–(2–metoxi–piridin–3–il)–indol–1–ilmetil]–piridin–2–il}–carbámico, **15I** (5 mg, 0,01 mmol) en cloroformo se trató con TMSI (3,5 uL,

0,03 mmol). La mezcla de reacción se dejó agitar a 50°C durante 18 horas. La mezcla luego se enfrió hasta la temperatura ambiente, y se desactivó con MeOH (1 ml). La mezcla se concentró bajo presión reducida para proporcionar el compuesto **26**. E. M. encontrada para C23H19N5O4S: 462,3 $(M+H)^+$.

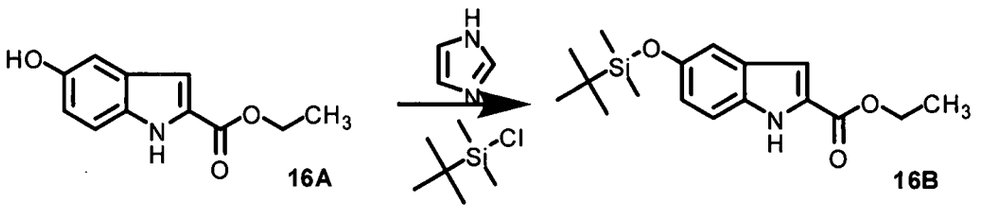
Ejemplo 16

Preparación del compuesto **156**



156

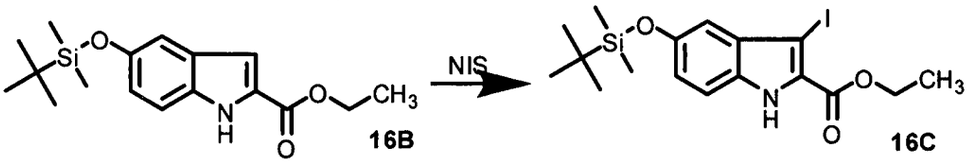
Paso 1:



16A **16B**

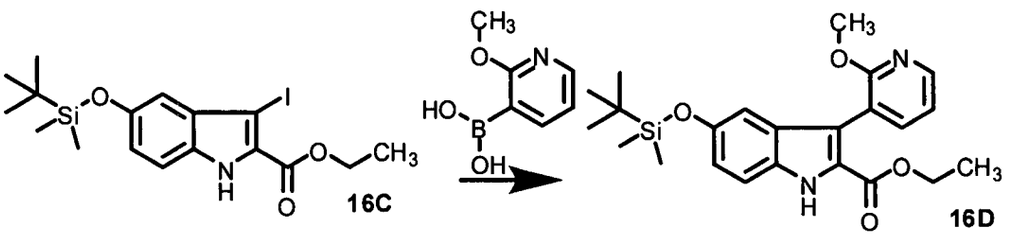
Una solución de 5–hidroxi–1H–indol–2–carboxilato de etilo **16A** (10,0 g; 48,73 mmol) en 300 ml de diclorometano se trató con imidazol (4,0 eq, 13,27 g) y cloruro de ter-butildimetilsililo (2,0 eq, 14,69 g). La reacción se dejó agitar a temperatura ambiente durante 3 horas. Una pequeña muestra (1 ml) se tomó de la mezcla de reacción, se diluyó con diclorometano (10 ml) y se lavó con agua. La evaporación del solvente y el análisis por RMN mostró que la totalidad del material de partida se había consumido. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con agua (2 x 200 ml) y salmuera (200 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **16B** (15,75 g) como un sólido blanco.

Paso 2:



Una solución de 5–ter-butildimetilsililoxi–1H–indol–2–carboxilato de etilo **16B** (15,6 g) en 500 ml de cloroformo se enfrió con hielo y se trató con N–yodosuccinimida (1,1 eq, 12,06 g). La mezcla se dejó agitar a 0°C durante 10 min y luego a temperatura ambiente durante 2 horas. El análisis por RMN de una pequeña alícuota mostró la conversión completa de material de partida. La mezcla de reacción se diluyó con diclorometano (300 ml) y se lavó con tiosulfato de sodio ac. saturado (200 ml), bicarbonato de sodio saturado ac. (200 ml) y salmuera (200 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el compuesto **16C** (19,47 g; 90%) como un sólido blanco. E. M. encontrada para C17H24INO3Si: 446,36 $(M+H)^+$.

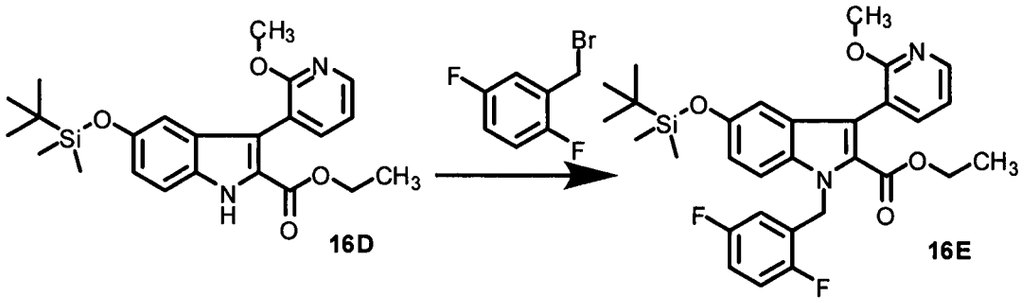
Paso 3:



El ácido 2–metoxi–3–piridin borónico (1,05 eq, 6,99 g) se agregó a una solución de **16C** (19,4 g; 43,55 mmol) en 500 ml de 1,2–dimetoxietano. La mezcla se desgasificó (vacío/enjuague de argón) y $PdCl_2(dppf)_2$ (5% en moles, 1,78 g) se agregó y la solución naranja resultante se dejó agitar durante 30 min a temperatura ambiente. Se agregó una solución de carbonato de potasio (4,0 eq, 174 ml de solución ac. 1M) y la solución marrón resultante se dejó agitar a 90°C durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró. El residuo se diluyó con acetato de etilo (1 L) y se lavó con salmuera (200 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y

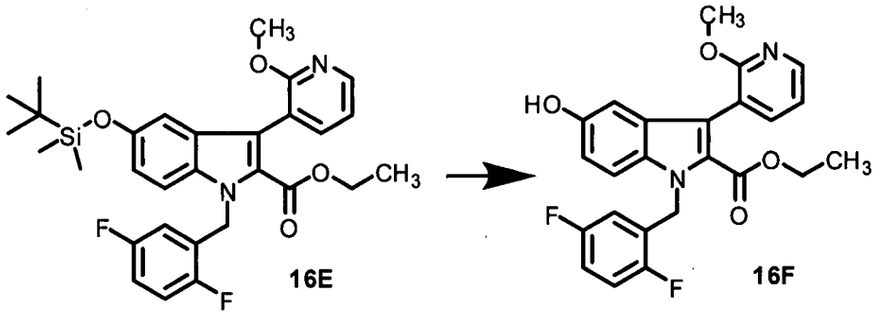
se concentró. El residuo se dividió en dos porciones iguales y cada una se purificó usando cromatografía con gel de sílice (Columna Biotage 75—M; gradiente: 0 hasta 35% acetato de etilo en hexanos) para proporcionar el compuesto **16D** como un sólido blanco (14,5 g; 80%). E. M. encontrada para C23H30N2O4Si: 427,56 $(M+H)^+$.

Paso 4:



Una solución de derivado indólico **16D** (4,0 g, 9,376 mmol) en 90 ml de DMF anhidra se enfrió con hielo y se trató con 2,5–difluorobencil bromuro (1,1 eq, 1,32 ml, d 1,613) y carbonato de cesio (3,0 eq, 9,16 g). La mezcla se tornó de color amarillo y se eliminó el baño de hielo. Se agregó una cantidad catalítica de yoduro de tetrabutilamonio (aprox. 20 mg). La mezcla de reacción se dejó agitar durante 30 min donde se tornó de color verde y la TLC (20% acetato de etilo en hexanos) mostró que no quedaba material de partida. La reacción se desactivó por la incorporación de agua (10 ml) y la mezcla se diluyó con acetato de etilo (400 ml). La fase orgánica se lavó con agua (3 x 80 ml) y salmuera (80 ml), se secó sobre sulfato de magnesio, se filtró y se concentró para proporcionar el producto en bruto **16E**. La mezcla en bruto se usó para la siguiente reacción sin ninguna purificación adicional.

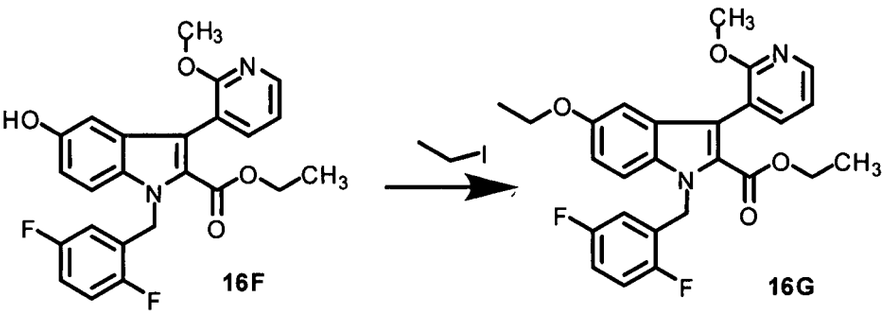
Paso 5:



16E 16F

Una solución de sililéter en bruto **16E** (9,376 mmol) en 100 ml de THF se enfrió con hielo y se trató con aproximadamente 1,0 eq de TBAF (9,3 ml de solución 1,0M en THF). La mezcla inmediatamente se tornó color amarillo-verde y TLC luego de 5 min (20% acetato de etilo en hexanos) mostró que no quedaba material de partida. La mezcla se diluyó con acetato de etilo (400 ml) y se lavó con agua (100 ml), bicarbonato de sodio saturado ac. (100 ml) y salmuera (100 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 75—M; gradiente: 10 hasta 50% acetato de etilo en hexanos) para proporcionar el compuesto **16F** como un sólido blanco (3,81 g; 94%). ^{1}H RMN (400 MHz, d_6–DMSO): δ 9,12 (s, 1H), 8,18 & 8,17 (dd, J = 1,46 & 5,13 Hz, 1H), 7,74 & 7,72 (dd, J = 2,20 & 7,32 Hz, 1H), 7,46 (d, J = 9,52 Hz, 1H), 7,31–7,25 (m, 1H), 7,16–7,07 (m, 1H), 6,87 (d, J = 8,79 Hz, 1H), 6,67 (s, 1H), 6,40–6,35 (m, 1H), 5,80 (s, 2H), 3,99 (q, J = 7,32 Hz, 2H), 3,75 (s, 3H), 0,845 (t, J = 7,32 Hz, 3H).

Paso 6:

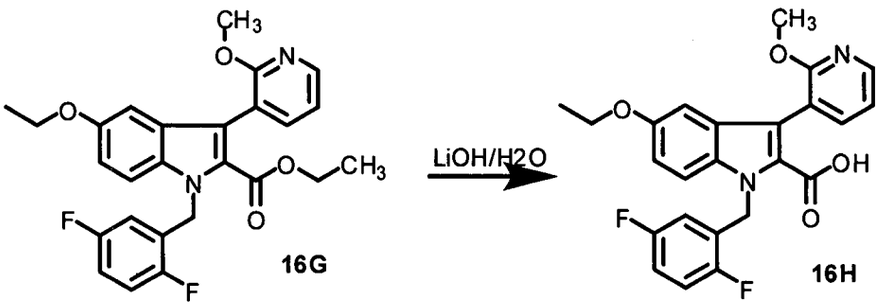


16F 16G

Una solución de etil éster del ácido 1–(2,5–Difluoro–bencil)–5–hidroxi–3–(2–metoxi–piridin–3–il)–1H–indol–2–carboxílico **16F** (600 mg; 1,368 mmol) en

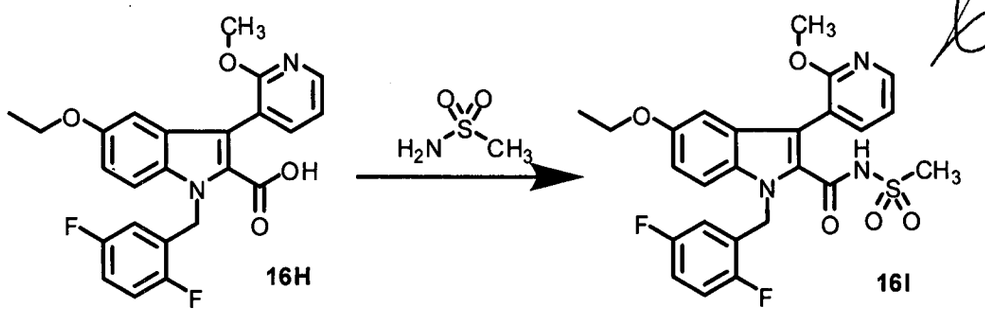
10 ml de DMF anhidra se enfrió con hielo y se trató con yodoetano (3,0 eq, 0,34 ml, d 1,950) y carbonato de cesio (2,5 eq, 1,11 g). La solución amarilla resultante se dejó agitar a 50°C durante 30 min momento en el cual la TLC (20% acetato de etilo en hexanos) mostró que no quedaba material de partida y la mezcla se diluyó con acetato de etilo (100 ml) y se lavó con agua (3 x 20 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó usando cromatografía con gel de sílice (Columna Biotage 25—M; gradiente: 0 hasta 20% acetato de etilo en hexanos) para proporcionar el compuesto **16G** (530 mg; 87%) como un sólido blanco. EM encontrada para C26H24F2N2O4: 467,13 $(M+H)^+$.

Paso 7:



Una solución de **16G** (530 mg; 1,136 mmol) en 12 ml de una mezcla 4:1:1 de THF/agua/metanol se trató con hidróxido de litio monohidrato (5,0 eq, 238 mg). La mezcla se calentó hasta 60°C durante 5 horas. La TLC (20% acetato de etilo en hexanos) mostró el consumo completo de the material de partida. La mezcla se diluyó con HCl 1M ac. (50 ml) y el producto se absorbió en diclorometano (3 x 40 ml). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para proporcionar el compuesto **16H** (0,912 mmol; 80%) como un sólido blanco. EM encontrada para C24H20F2N2O4: 439,02 $(M+H)^+$.

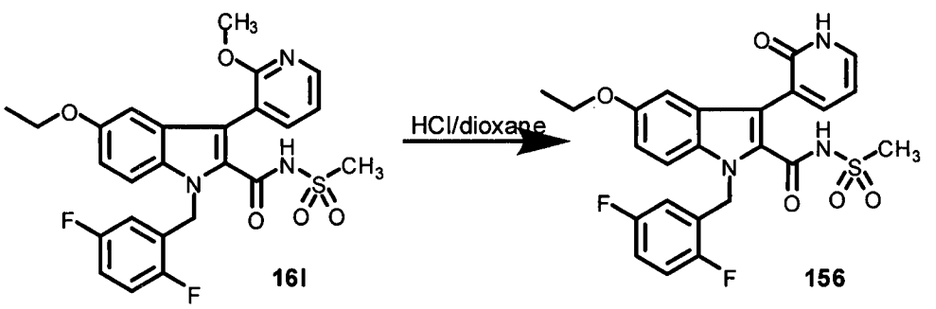
Paso 8:



16H **16I**

Una solución de **16H** (150 mg; 0342 mmol) en 3 ml de THF anhidro se trató con carbonilo dimidazol (1,2 eq, 67 mg). La mezcla se calentó hasta 70°C durante 2 h y luego se enfrió hasta la temperatura ambiente. Se agregaron metansulfonamida (1,3 eq, 43 mg) y DBU (1,3 eq, 0,079 ml, d 1,018) y la mezcla se calentó hasta 70°C hasta la mañana siguiente. La mezcla se diluyó con acetato de etilo (100 ml) y se lavó con HCl 1M ac. (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó usando cromatografía con gel de sílice (Columna de gel de sílice Biotage 25—S, gradiente: 0 hasta 20% acetona en diclorometano) para proporcionar el compuesto **16I** (0,242 mmol; 71%) como un sólido blanco. E. M. encontrada para C25H23F2N3O5S: 516,02 $(M+H)^+$.

Paso 9:



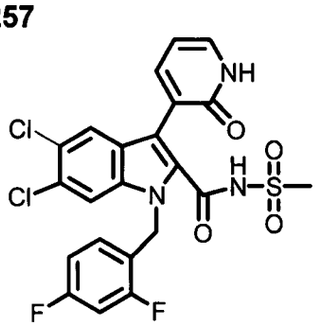
16I **156**

El Compuesto **16I** (115 mg, 0,230 mmol) se disolvió en 4 ml de solución 4M de HCl en dioxano. Se agregó metanol (3 ml) y la solución se calentó a 90°C en un tubo sellado durante 3 horas. La mezcla de reacción se enfrió y se concentró para proporcionar el producto en bruto como un sólido blanco. Se utilizó separación por HPLC para recuperar el producto. La fracción que contiene el producto de acuerdo con el análisis por EM se concentró para proporcionar el

compuesto **156**(0,175 mmol, 76%) como un sólido blanco. ^{1}H RMN (400 MHz, d_6–DMSO): δ 7,82 (d, J = 6,59 Hz, 1H), 7,63 (bs, 1H), 7,51 (d, J = 8,79 Hz, 1H), 7,31–7,25 (m, 1H), 7,17–7,11 (m, 1H), 7,00 (d, J = 8,79 Hz, 1H), 6,82 (s, 1H), 6,60–6,54 (m, 2H), 5,68 (s, 2H), 3,69 (q, J = 6,59 & 7,32 Hz, 2H), 3,24 (s, 3H), 1,29 (t, J = 6,59 Hz, 3H). E. M. encontrada para C24H21F2N3O5S: 502,04 $(M+H)^+$.

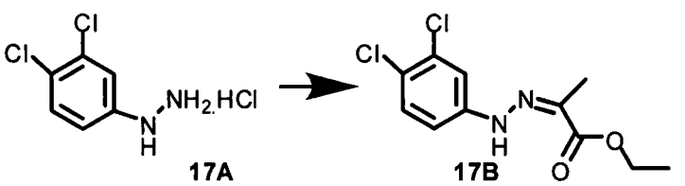
Ejemplo 17

Preparación del compuesto **257**



257

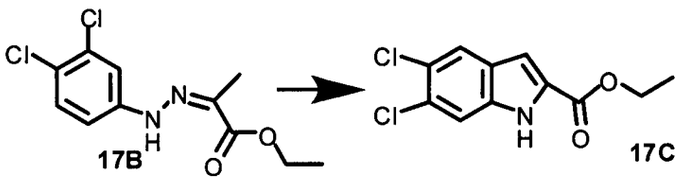
Paso 1:



17A **17B**

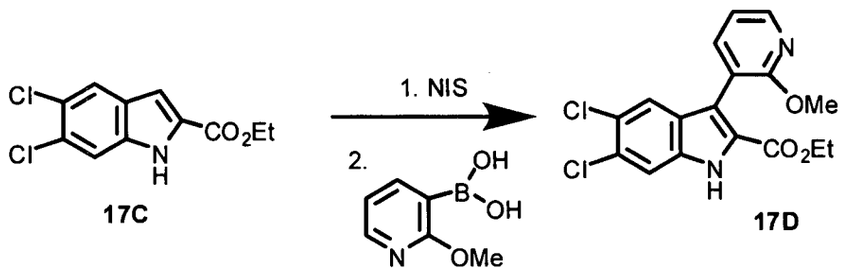
El Compuesto **17A** (15,72g, 90% de pureza, 67 mmol) se disolvió en etanol (100 ml) a temperatura ambiente. A la solución se agregaron piruvato de etilo (11 ml) y ácido acético (1 ml). La mezcla de reacción se reflujó durante 2 horas. Luego de enfriarse hasta la temperatura ambiente, la mezcla se concentró bajo presión reducida. El producto en bruto se purificó usando cromatografía con gel de sílice (EtOAc/Hexano=1/10) para proporcionar producto **17B** como un sólido amarillo (7,43 g). ^{1}H RMN (500 MHz, d_6–DMSO): δ 10,06 (s, 1H), 7,49 (d, J = 8,79 Hz, 1H), 7,41 (d, J = 2,20 Hz, 1H), 7,22 & 7,20 (dd, J = 2,20 & 8,79 Hz, 1H), 4,18 (q, J = 7,32 Hz, 2H), 2,04 (s, 3H), 1,24 (t, J = 7,32 Hz, 3H).

Paso 2:



El Compuesto **17B** (7,22 g) se trituró hasta obtener un polvo antes de mezclarse con ácido polifosfórico (50 g). La mezcla bifásica se agitó vigorosamente a 120ºC durante 2 horas. Luego de enfriar hasta la temperatura ambiente, la mezcla de reacción se repartió entre EtOAc y agua. La fase orgánica combinada se secó (sulfato de magnesio), se filtró y se concentró al vacío. El producto en bruto se purificó usando cromatografía flash (0–50% EtOAc/hexano) para proporcionar una mezcla de 5,6–dicloroindol **17C** y el 4,5–dicloroindol no deseado. ^{1}H RMN (500 MHz, d_6–DMSO): δ12,19 (s, 1H), 7,95 (s, 1H), 7,62 (s, 1H), 7,14 (s, 1H), 4,33 (q, J = 7,32 Hz, 2H), 1,32 (t, J = 7,32 Hz, 3H).

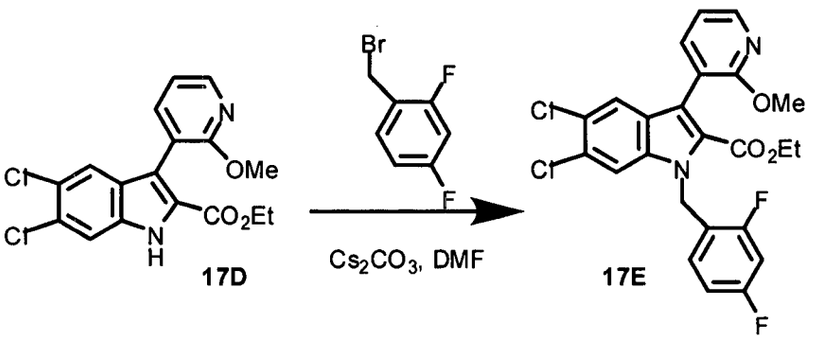
Paso 3:



La N–yodosuccinimida (0,5 g) se agregó a una solución agitada en CH_2Cl_2 (10 ml) del Indol **17C** (0,57 g) a temperatura ambiente hasta la mañana siguiente bajo atmósfera de nitrógeno. La reacción se repartió entre EtOAc y tiosulfato de sodio acuoso diluido. Se separó la fase orgánica, se lavó con bicarbonato de sodio ac. al 10%, agua, se secó ($MgSO_4$) y se concentró para proporcionar el yodoindol en bruto deseado (0,828 g) que se agregó al DME (4 ml). Se agregó $PdCl_2(dPPF)_2$ (176 mg, 0,1 eq) a la mezcla y se calentó hasta 100° C (temperatura del baño de aceite) durante un período de 0,5 hora y una solución del ácido borónico (99 mg, 3 eq) y carbonato de potasio (1,50 g, 5 eq) en H_2O/DME (1,5 ml/1,5ml) se agregó gota a gota. Cuando la incorporación estuvo

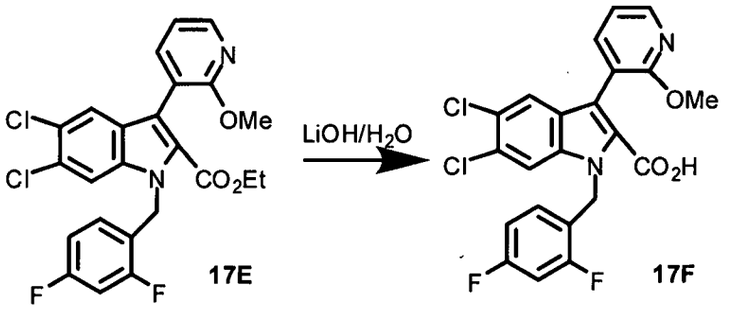
completa la mezcla de reacción se calentó hasta 100° C (baño de aceite) durante 3 horas. Luego de enfriar, se agregó sulfato de sodio acuoso al 3% seguido de EtOAc y se filtró a través de celite. El filtrado se repartió entre agua y CH_2Cl_2. Se separó la fase orgánica y la fase acuosa se extrajo en forma adicional con CH_2Cl_2. La fase orgánica combinada se secó ($MgSO_4$) y se concentró. El residuo se purificó usando cromatografía con gel de sílice (EtOAc:Hexano=3:7) para proporcionar el compuesto **17D** como un sólido amarillo (0,522 g). E. M. encontrada para C17H14Cl2N2O3: 365,10 $(M+H)^+$.

Paso 4:



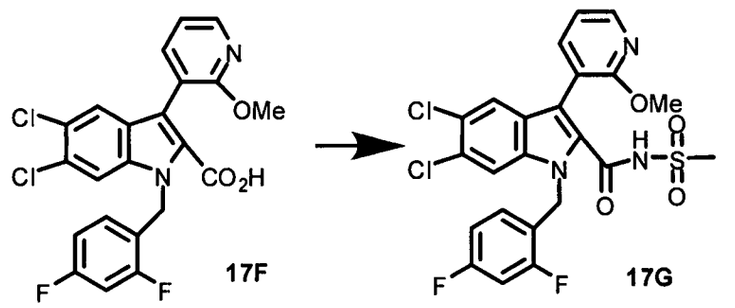
Se agregó 2, 4–difluorobencilbromuro (53 uL, 1,5 eq) gota a gota a una mezcla agitada del indol **17D** (100 mg, 1 eq) y Cs_2CO_3 (134 mg, 1,5 eq) en DMF a temperatura ambiente bajo atmósfera de nitrógeno. Luego de 16 horas, la mezcla de reacción se repartió entre EtOAc y agua. La fase acuosa se separó, se lavó con agua tres veces, se secó ($MgSO_4$) y se concentró. El residuo se purificó usando cromatografía en columna de gel de sílice (EtOAc:Hexano=1:10) para proporcionar el compuesto **17E** (0,105 g) como un sólido blanco. E. M. encontrada para C24H18Cl2F2N2O3: 490,98 $(M+H)^+$.

Paso 5:



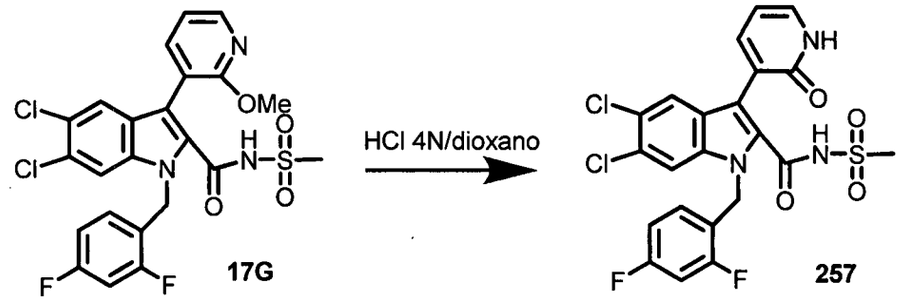
Se agregó hidróxido de litio (26 mg, 3 eq) a una solución agitada del etil éster **17E** (100 mg, 1 eq) en THF/H_2O (7 ml / 3 ml) bajo atmósfera de nitrógeno. La mezcla de reacción resultante se calentó hasta reflujo hasta la mañana siguiente. Luego de enfriar, la reacción se repartió entre EtOAc y HCl 1N acuoso diluido. Las fases orgánicas se separaron. La fase orgánica se secó ($MgSO_4$) y se concentró para proporcionar el producto en bruto **17F** (100 mg). E. M. encontrada para C22H14Cl2F2N2O3: 462,97 $(M+H)^+$.

Paso 6:



Una solución de ácido **17F** (58 mg, 1 eq) en THF (3 ml) se trató con carbonildiimidazol (22 mg, 1,1 eq) y se calentó a reflujo durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se trató con metilsulfonamida (18 mg, 1,5 eq), y DBU (23 mg, 1,2 eq) y se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla se concentró y se agregó EtOAc y se lavó con HCl 1N y agua. El solvente se eliminó bajo presión reducida y el bruto material se purificó usando cromatografía con gel de sílice (MeOH/CH_2Cl_2=5%) para proporcionar un producto puro incoloro **17G** (9 mg). E. M. encontrada para C23H17Cl2F2N3O4S: 540,24 $(M)^+$.

Paso 7:

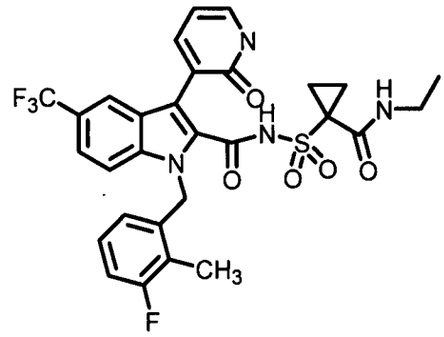


17G 257

Se agregó HCl (4N en dioxano, 2 ml) a **17G** (9 mg) en un tubo sellado y la suspensión resultante se calentó hasta 105° C (baño de aceite) durante 3 horas. Luego de enfriar, el solvente se eliminó bajo presión reducida. Se agregó éter y el sólido se recolectó para proporcionar el compuesto **257** (8 mg). E. M. encontrada para C22H15Cl2F2N3O4S: 527,96 $(M+H)^+$.

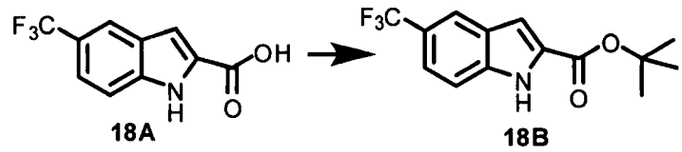
Ejemplo 18

Preparación del compuesto **498**



498

Paso 1:

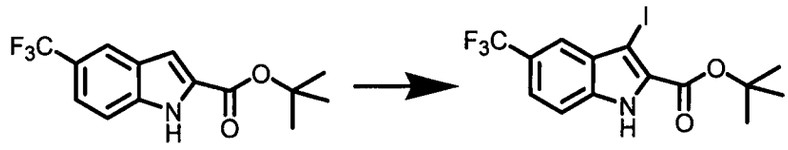


18A 18B

A una solución del indol **18A** (1,6 g, 6,9 mmol) en tolueno (5,0 ml) se agregó *N,N*–dimetilformamida di–ter-butil acetal (5 ml), y se calentó hasta 90°C durante 12h, se enfrió hasta la temperatura ambiente, se agregó otra alícuota de *N,N*–dimetilformamida di–ter-butil acetal (5 ml) y la mezcla de reacción se calentó hasta 90°C durante 12h, se enfrió hasta la temperatura ambiente, se diluyó con

acetato de etilo (10,0 ml), se lavó con agua (2 X 10,0 ml), salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el compuesto **18B** (1,2 g, 60%) como un sólido blanco. ^1H RMN (400 MHz, CDCl3): δ 9,17 (s, 1H), 7,97 (s, 1H), 7,51 (s, 2H), 7,21 (s, 1H), 1,63 (s, 9H).

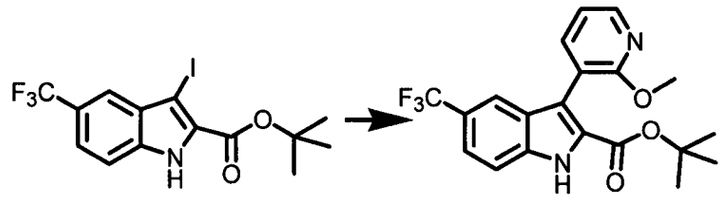
Paso 2:



18B **18C**

A una solución de **18B** (1,2 g, 4,2 mmol) en $CHCl_3$ (25 ml) se agregó *N*–yodosuccinimida (946 mg, 4,2 mmol) y la reacción se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró al vacío, se diluyó con agua y se extrajo en EtOAc (200 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, y se concentró al vacío. El residuo marrón se absorbió en cantidad mínima de CH_2Cl_2 y se trituró con hexanos. El Compuesto **18C** se separó como un sólido marrón que se filtró, y se secó al vacío. (1,23 g, 72% de rendimiento). ^1H RMN (400 MHz, CDCl3): δ 9,34 (s, 1H), 7,87 (s, 1H), 7,57 (d, J= 8,06 Hz, 1H), 7,49 (d, J= 8,79 Hz, 1H), 1,68 (s, 9H).

Paso 3:

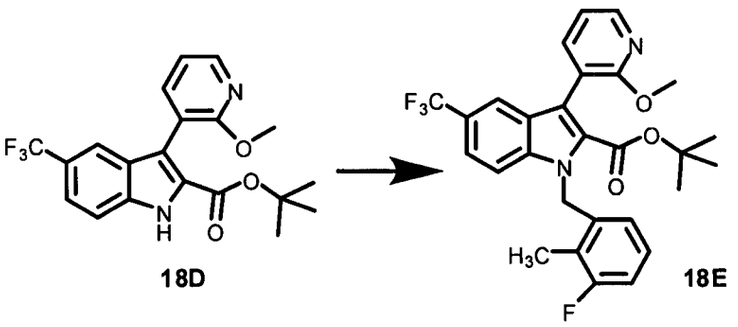


18C **18D**

A una solución del compuesto **18C** (1,23 g, 3,0 mmol) en DME (30 ml) bajo atmósfera de nitrógeno se agregó con ácido 2–metoxi–3–piridilo borónico (0,482 g, 3,15 mmol) y $Pd(dppf)_2Cl_2$ (245 mg, 0,3 mmol) 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 (1,6 g, 12 mmol)

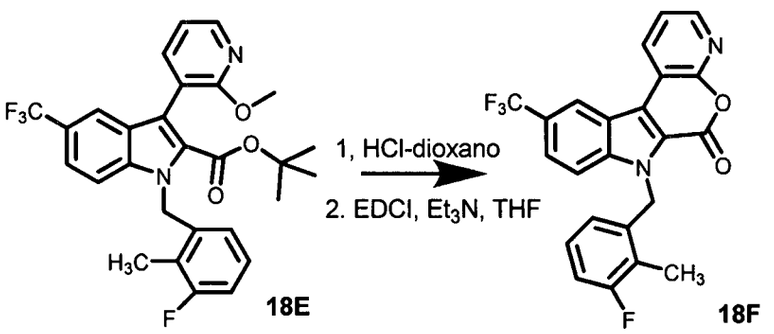
en agua (12 ml) y la solución resultante se calentó hasta 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción luego se diluyó con EtOAc (200 ml) y la solución resultante se concentró *al vacío* para proporcionar un residuo en bruto que se purificó usando cromatografía flash en columna (EtOAc/Hexanos, 0 hasta 30% EtOAc) para proporcionar el compuesto **18D** como un sólido (820,0 mg). E. M. encontrada para C20H19F3N2O3: 393,2 $(M+H)^+$.

Paso 4:



A una solución de indol **18D** (10,0 g, 25,4 mmol) en DMF (100 ml) se agregó carbonato de cesio (9,93g, 30,5 mmol) y 3–fluoro–3–metilbencil bromuro (3,57 ml, 30,5 mmol) y se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con EtOAc (500 ml), se lavó con agua (3x100 ml) y con salmuera (2x100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, y se concentró al vacío y se purificó usando cromatografía flash en columna sobre gel de sílice para proporcionar el compuesto **18E** un sólido incoloro.

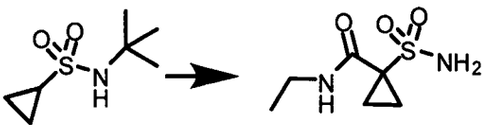
Paso 5:



646

Una solución del compuesto **18E** (1,0 g, 1,94 mmol) se disolvió en HCl 4N en dioxano (20 ml) y se calentó a 80 ^{0}C hasta la mañana siguiente. Luego de enfriar los volátiles se retiraron bajo presión reducida para proporcionar el producto en bruto, que se usó directamente en el paso siguiente. El residuo del primer paso se disolvió en THF anhidro (10,0 ml) y se agregaron a este EDCI (3,8 mmol, 746 mg) y Et_3N (2,55 ml, 19,0 mmol). La mezcla de reacción se dejó agitar a temperatura ambiente durante 12 horas, se lavó con HCl 1N y se extrajo con CH_2Cl_2 (3 x 20 ml). La fase orgánica combinada se lavó con salmuera y se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el compuesto **18F** (724 mg). E. M. encontrada para C23H14F4N2O2: 427,2 $(M+H)^+$.

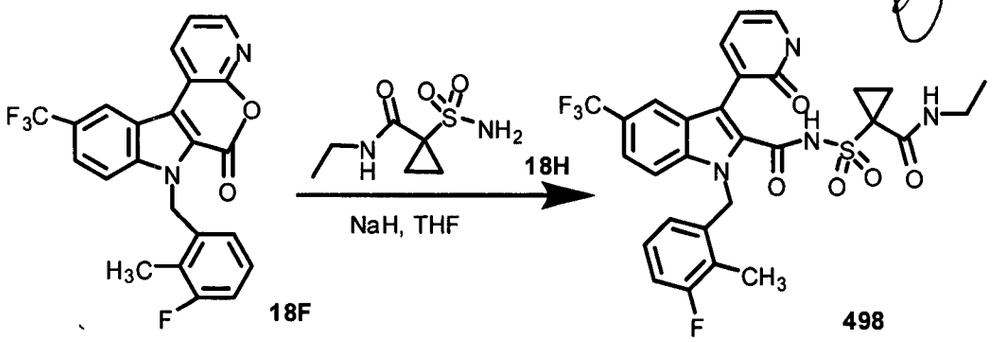
Paso 6:



18G **18H**

A una solución enfriada de **18G** (Preparada como se describe en la Publicación Internacional No. WO 2004/043339) en THF (7,0 ml) se agregó BuLi (1,6 M en hexanos) gota a gota. La mezcla de reacción se dejó agitar durante 1 hora, a esta se agregó isocianato de etilo y luego se dejó entibiar hasta la temperatura ambiente hasta la mañana siguiente. La mezcla de reacción se acidificó usando HCl 1N y se extrajo con acetato de etilo (3 x 20 ml). La fase orgánica se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna sobre gel de sílice 10% EtOAc/Hexano (0 hasta 60%) para proporcionar el intermediario como un residuo oleoso (110,0 mg). El residuo oleoso se agitó hasta la mañana siguiente en HCl 4N en dioxano, y luego se concentró para proporcionar el compuesto **18H** (46,0 mg).

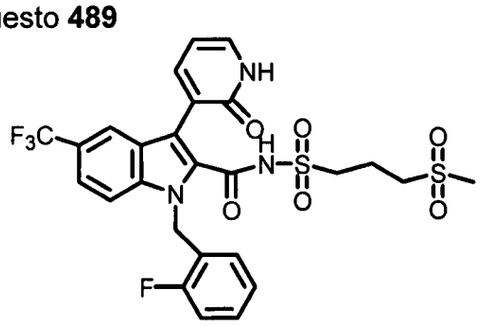
Paso 7:



A una solución del compuesto **18F** (25,0 mg, 0,06 mmol) en THF (2,0 ml) se agregó sulfonamida **18H** y NaH (11,5 mg, 0,48 mg). La mezcla de reacción resultante se dejó agitar a temperatura ambiente durante 30 minutos., luego se diluyó con EtOAc (10 ml) y la solución resultante se lavó con agua y HCl acuoso (1N). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, y se concentró al vacío y el residuo resultante se purificó usando cromatografía flash en columna sobre gel de sílice 10% $MeOH/CH_2Cl_2$ (0 hasta 90%) para proporcionar el compuesto **498** (20 mg). ^1H RMN (400 MHz, d_6–DMSO) δ 8,30 (bs, 1H), 7,70 (s, 1H), 7,63–7,54 (m, 2H), 7,50–7,43 (m, 2H), 7,15 (t, J = 7,56 Hz, 1H), 6,91 (t, J = 7,56 Hz, 1H), 6,65 (t, J = 7,56 Hz, 1H), 6,28 (s, 1H), 5,86 (s, 2H), 3,00 (t, J = 6,94 Hz, 2H), 2,25 (s, 3H), 1,37–1,24 (m, 2H), 1,17–1,07 (m, 2H), 0,90 (t, J = 6,94 Hz, 3H).

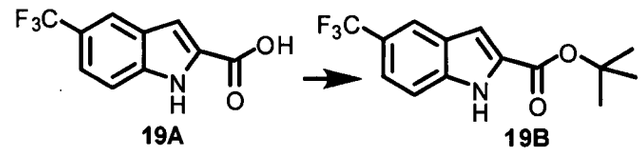
Ejemplo 19

Preparación del compuesto **489**



489

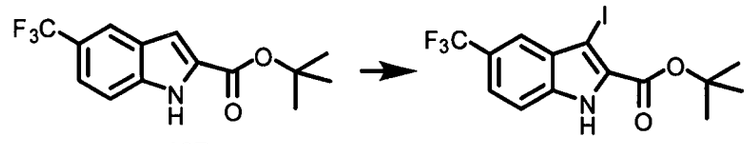
Paso 1:



19A **19B**

A una solución de the indol **19A** (1,6 g, 6,9 mmol) en tolueno (5,0 ml) se agregó *N,N*–dimetilformamida di–ter-butil acetal (5 ml), y se calentó hasta 90°C durante 12h, se enfrió hasta la temperatura ambiente, se agregó otra alícuota de *N,N*–dimetilformamida di–ter-butil acetal (5 ml) y la mezcla de reacción se calentó hasta 90°C durante 12h, se enfrió hasta la temperatura ambiente, se diluyó con acetato de etilo (10,0 ml), se lavó con agua (2 X 10,0 ml), salmuera, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el compuesto **19B** (1,2 g, 60%) como un sólido blanco.

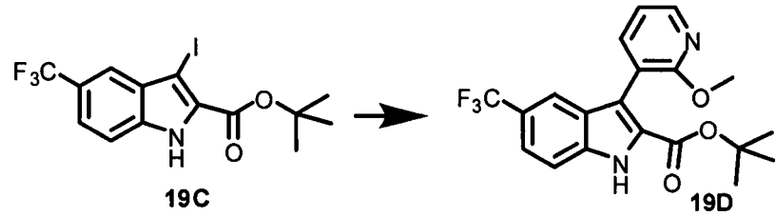
Paso 2:



19B **19C**

A una solución del compuesto **19B** (1,2 g, 4,2 mmol) en $CHCl_3$ (25 ml) se agregó *N*–yodosuccinimida (946 mg, 4,2 mmol) y la reacción se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se concentró al vacío, se diluyó con agua y se extrajo en EtOAc (200 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, y se concentró al vacío. El residuo marrón se absorbió en cantidad mínima de CH_2Cl_2 y se trituró con hexanos. El producto **19C** se separó como un sólido marrón que se filtró, y se secó al vacío. (1,23 g, 72% de rendimiento)

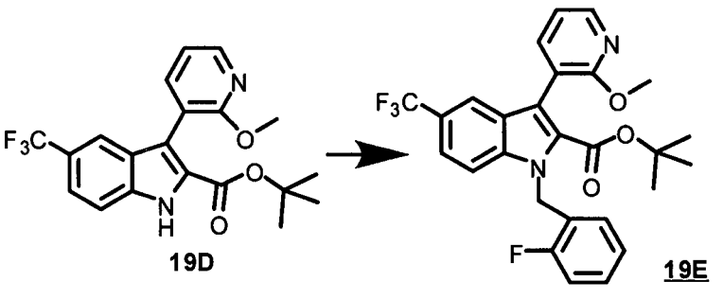
Paso 3:



19C **19D**

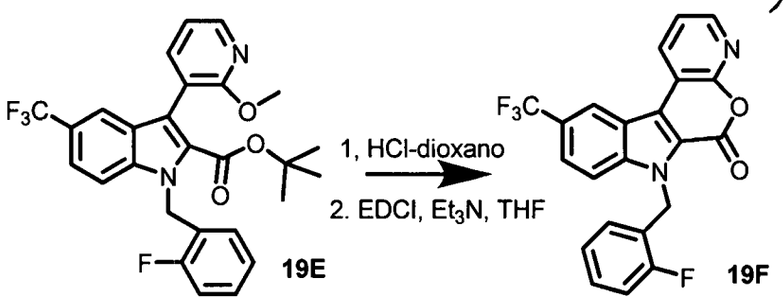
A una solución del compuesto **19C** (1,23 g, 3,0 mmol) en DME (30 ml) bajo atmósfera de nitrógeno se agregó con ácido 2–metoxi–3–piridilo borónico (0,482 g, 3,15 mmol) y Pd $(dppf)_2Cl_2$ (245 mg, 0,3 mmol) y la reacción resultante se dejó agitar a temperatura ambiente bajo nitrógeno durante 0,5 horas. La mezcla de reacción luego se trató con una solución de carbonato de potasio (1,6 g, 12 mmol) en agua (12 ml) y la solución resultante se calentó hasta 90°C y se dejó agitar a esta temperatura durante 1 hora. La mezcla de reacción luego se diluyó con EtOAc (200 ml) y la solución resultante se concentró *al vacío* para proporcionar un residuo en bruto que se purificó usando cromatografía flash en columna (EtOAc/Hexanos, 0 hasta 30% EtOAc) para proporcionar el compuesto **19D** como un sólido incoloro (820,0 mg).

Paso 4:



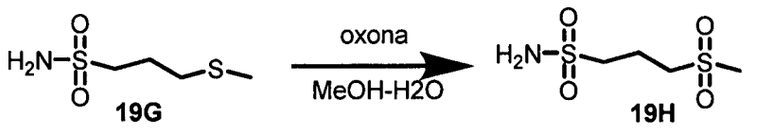
A una solución de indol **19D** (10,0 g, 25,4 mmol) en DMF (100 ml) se agregó carbonato de cesio (9,93g, 30,5 mmol) y bromuro de 2—fluorobencilo (3,57 ml, 30,5 mmol) y se dejó agitar a temperatura ambiente durante 12 horas. La mezcla de reacción se diluyó con EtOAc (500 ml), se lavó con agua (3x100 ml) y con salmuera (2x100 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtró, y se concentró al vacío y se purificó usando cromatografía flash en columna sobre gel de sílice para proporcionar el compuesto **19E** un sólido incoloro.

Paso 5:



Se agregó HCl 4N en dioxano (20 ml) al compuesto **19E** (1,30 g) en un tubo sellado y se calentó hasta 80° C (baño de aceite) hasta la mañana siguiente. Luego de enfriar hasta la temperatura ambiente, los solventes se retiraron bajo presión reducida para proporcionar un producto en bruto que se disolvió en THF anhidro (20 ml) y se agregaron EDCI (1,15 g) seguido de Et3N (4,10 ml) y la mezcla de reacción resultante se agitó hasta la mañana siguiente a temperatura ambiente. La mezcla de reacción se repartió entre HCl ac. diluido (~10%) y CH_2Cl_2. Se separó la fase orgánica, se extrajo con CH_2Cl_2 dos veces. Las fases orgánicas combinadas se lavaron con agua, se secaron ($MgSO_4$) y se concentró para proporcionar la lactona **19F** un sólido marrón claro (0,991 g). ^{1}H RMN (400 MHz, d_6–DMSO) δ 9,13 & 9,11 (dd, J = 1,46 & 8,06 Hz, 1H), 8,94 (s, 1H), 8,48 & 8,46 (dd, J = 1,46 & 5,13 Hz, 1H), 7,99 (d, J = 8,79 Hz, 1H), 7,89 (d, J = 8,79 Hz, 1H), 7,57 (dd, J = 4,39 & 8,06 Hz, 1H), 7,33–7,21 (m, 2H), 7,01 (t, J = 7,32 Hz, 1H), 6,77 (t, J = 7,32 Hz, 1H), 6,12 (s, 2H). E. M. encontrada para C22H12F4N2O2: 412,93 $(M+H)^+$.

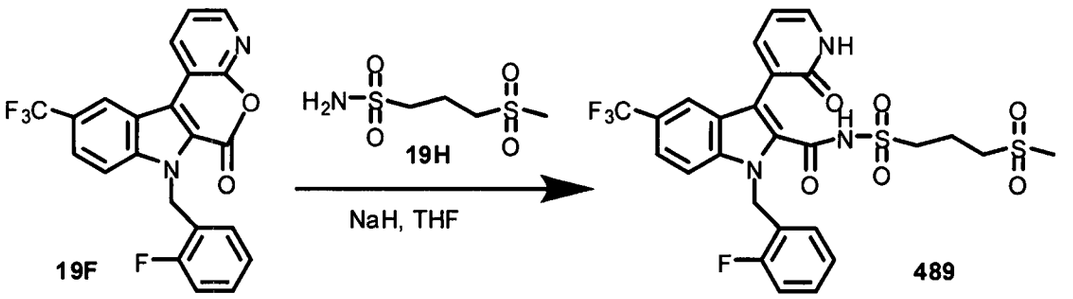
Paso 6:



Una solución acuosa de oxona (1,82 g, 3 ml agua) se agregó a la solución de metanol (3 ml) del sulfuro **19G** (0,1 g) a temperatura ambiente y la mezcla de reacción resultante se agitó hasta la mañana siguiente a temperatura ambiente. El metanol se eliminó bajo presión reducida y el residuo se repartió entre CH_2Cl_2 y agua. Las fases orgánicas se lavaron con agua, se secaron ($MgSO_4$) y se

concentró para proporcionar la sulfona **19H** (25,6 mg). ^{1}H RMN (400 MHz, d_6–DMSO) δ 6,90 (s, 2 H), 3,25 (t, J = 7,32 Hz, 2H), 3,10 (t, J = 7,32 Hz, 2H), 2,97 (s, 3H), 2,13–2,05 (m, 2H).

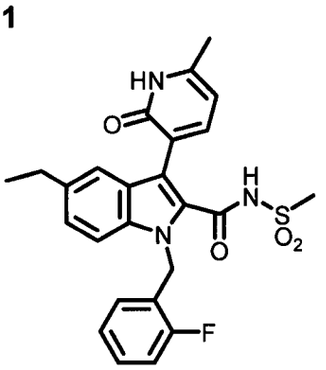
Paso 7:



Se agregó NaH (3,5 mg, 1,2 eq) en una porción a la solución agitada de la lactona **19F** (50 mg, 0,12 mmol) y sulfonamida **19H** (25 mg, 0,12 mmol) a temperatura ambiente bajo atmósfera de nitrógeno. La mezcla de reacción se dejó agitar durante 4 horas a temperatura ambiente. El producto de reacción en bruto se purificó usando cromatografía en columna de gel de sílice (CH_2Cl_2/MeOH=99:1 – 20:1) para proporcionar el compuesto **489** (22. 6 mg) como un sólido blanco. ^{1}H RMN (400 MHz, d_6–DMSO) δ 7,87 (d, J = 8,30 Hz, 1H), 7,82 (d, J = 6,35 Hz, 1H), 7,78 (s, 1H), 7,65–7,64 (m, 2H), 7,32 (q, J = 6,35 Hz, 1H), 7,22 (t, J = 8,79 Hz, 1H), 7,10 (t, J = 7,32 Hz, 1H), 6,93 (t, J = 7,32 Hz, 1H), 6,58 (bs, 1H), 5,83 (s, 2H), 3,54 (s, 2H), 3,26 (t, J =7,81 Hz, 2H), 2,97 (s, 3H), 2,06 (quinteto, J = 7,32 Hz, 2H). E. M. encontrada para C26H23F4N3O6S2: 614,3 $(M+H)^+$.

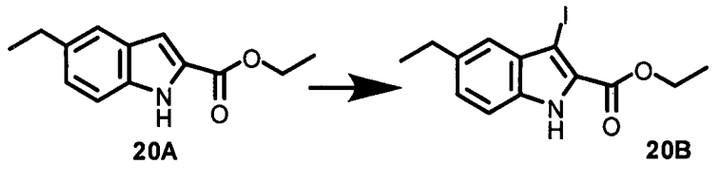
Ejemplo 20

Preparación del compuesto **71**



71

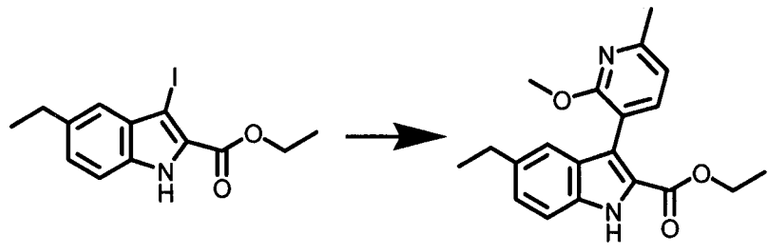
Paso 1:



20A **20B**

Los materiales de partida **20A** (15,0 g, 69,04 mmol) y THF (100 ml) se agregaron a un balón de 1000 ml. La solución resultante se enfrió con un baño de agua. A esta solución agitada, se agregó NIS (15,30 g, 68,80 mmol) lentamente. La solución resultante se dejó agitar a temperatura ambiente durante 5 horas antes de agregar 700 ml de agua. La mezcla resultante continuó con la agitación a temperatura ambiente durante 30 minutos y luego se filtró. La torta se lavó con agua (2X40 ml), se secó al aire, luego se secó con vacío para proporcionar el compuesto **20B** como sólido blancuzco (23,0 g, 97%). E. M. encontrada para $C_{13}H_{14}INO_2$: 344,2 $(M+H)^+$.

Paso 2:

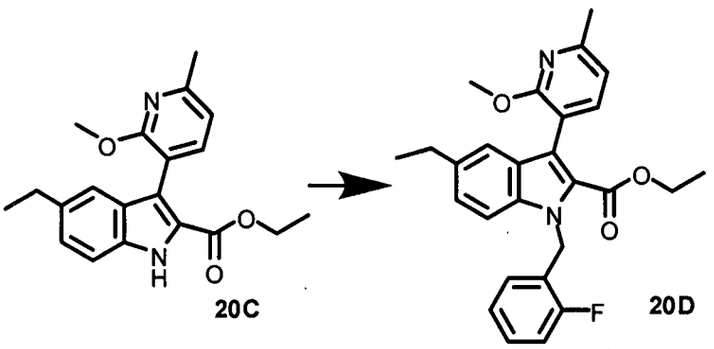


20B **20C**

Un balón de 200 ml se cargó con **20B** (2,45 g, 7,14 mmol), ácido 6–metil–2–metoxipiridina–3–borónico (0,98 g, 5,87 mmol), complejo [1,1' bis(difenilfosfin) ferroceno]dicloropaladio(II) con diclorometano (1:1) (0,58 g, 0,71 mmol), y DME (50 ml). A la solución agitada, se agregó una solución de carbonato de sodio (10 ml de 1,5 M, 15,0 mmol) a través de una jeringa. La mezcla de reacción se mantuvo a reflujo durante 4 horas antes de enfriar hasta la temperatura ambiente. Luego de la concentración, el residuo se absorbió con acetato de etilo (200 ml), se lavó con agua (3x100 ml), y se secó sobre sulfato de sodio. El solvente se eliminó

por centelleo bajo presión reducida y el residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–10% acetato de etilo en hexanos como el solvente para proporcionar el compuesto **20C** como un sólido blanco (1,51 g, 76%). E. M. encontrada para $C_{20}H_{22}N_2O_3$: 339,2 $(M+H)^+$.

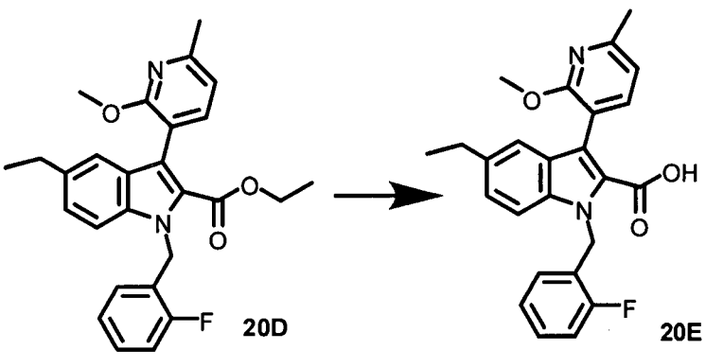
Paso 3:



20C **20D**

Los materiales de reacción **20C** (200 mg, 0,59 mmol), cloruro de 2-fluorobencilo (170 mg, 1,76 mmol), carbonato de cesio (700 mg, 2,16 mmol), y DMF (3 ml) se agregaron a un balón de 100 ml. La suspensión resultante se dejó agitar a temperatura ambiente durante 16 horas, se diluyó con acetato de etilo (100 ml), y se lavó con agua (3X40 ml). La solución orgánica se secó sobre sulfato de sodio y se concentró. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–10% acetato de etilo en hexanos como eluyente para proporcionar el compuesto **20D** as a gel (205 mg, 78%).

Paso 4:

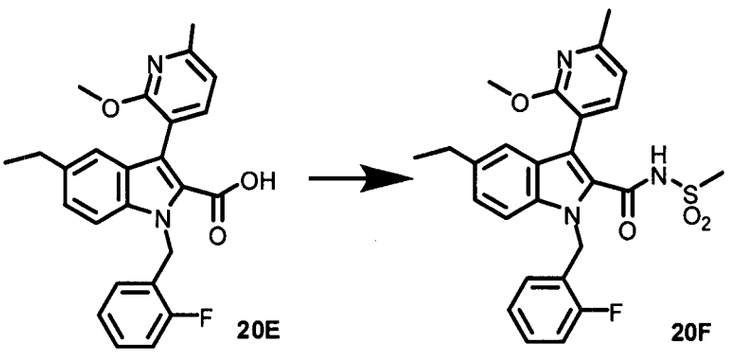


20D **20E**

A la mezcla agitada de **20D** (200 mg, 0,45 mmol) en THF (5 ml) en un balón de 100 ml se agregó con una solución de hidróxido de litio (2,5 ml de 1 M,

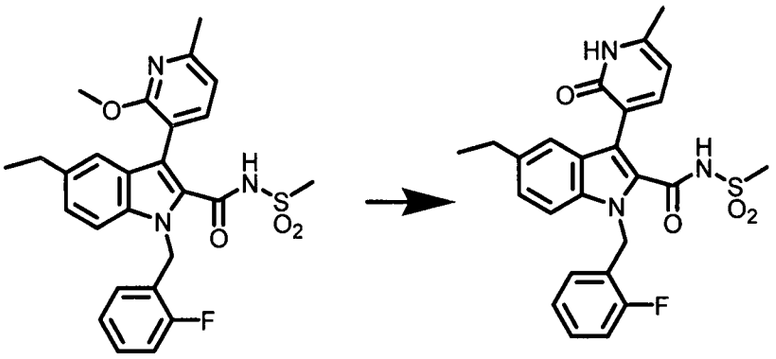
2,5 mmol). La solución resultante se mantuvo a reflujo durante 4 días antes de enfriar hasta la temperatura ambiente. Luego de la concentración *al vacío*, el residuo se disolvió en metanol (5 ml), se neutralizó con solución acuosa 1,0 M de HCl (2,5 ml, 2,5 mmol) y luego se concentró nuevamente. El residuo se extrajo con acetato de etilo (3x40 ml). Las soluciones orgánicas combinadas se concentraron y se secaron al vacío para proporcionar el compuesto **20E** como una cera blanca (190 mg, ~100%). E. M. encontrada para $C_{27}H_{25}ClFN_2O_3S$: 542,3 $(M+H)^+$.

Paso 5:



Una solución de **20E** (65 mg, 0,16 mmol) y 1,1'–carbonildiimidazol (37 mg, 0,23 mmol) en THF (5 ml) en un balón de 50 ml se reflujó durante 1 hora antes de enfriarse hasta la temperatura ambiente. Se agregaron metilsulfonamida (35 mg, 0,37 mmol) seguido de DBU (55 mg, 0,36 mmol). La mezcla de reacción resultante se dejó reflujar durante 3 horas antes de enfriarse hasta la temperatura ambiente y se concentró al vacío. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–2% metanol en diclorometano como eluyente para proporcionar el compuesto **20F** como una cera blanca (70 mg, 91%). E. M. encontrada para $C_{26}H_{26}FN_3O_4S$: 496,3 $(M+H)^+$.

Paso 6:

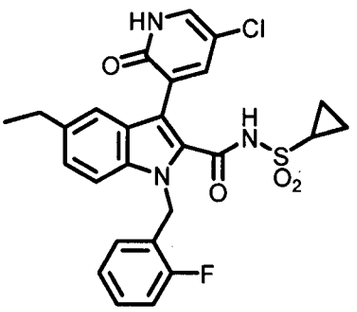


20F **71**

El material de partida **20F** (60 mg, 0,12 mmol) y HCl 4,0 M en 1,4–dioxano (3,0 ml, 12,0 mmol) se agregaron a un recipiente de presión de 15 ml. La solución resultante se dejó agitar a 90°C durante 1 hora antes de enfriarse hasta la temperatura ambiente. La mezcla se transfirió a un balón de 25 ml y se concentró en rotavapor. El residuo se purificó usando TLC preparativa sobre gel de sílice con 5% metanol en diclorometano como solvente de desarrollo para proporcionar el compuesto **71** como un sólido blanco (25 mg, 43%). ^{1}H RMN (400 MHz, d_6–DMSO) δ 7,72 (s, 1H), 7,33 (s, 1H), 7,30–7,25 (m, 1H), 7,25–7,18 (m, 1H), 7,18–7,11 (m, 1H), 7,09–7,05 (m, 1H), 7,00–6,94 (m, 1H), 6,94–6,84 (m, 1H), 6,33 (s, 1H), 5,78 (s, 2H), 2,95 (s, 3H), 2,72 (q, J = 7,57 Hz, 2H), 2,26 (s, 3H), 1,26 (t, J = 7,57 Hz, 3H). E. M. encontrada para $C_{25}H_{24}FN_3O_4S$: 482,3 $(M+H)^+$.

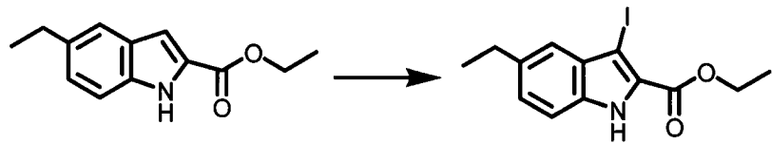
Ejemplo 21

Preparación del compuesto **263**



263

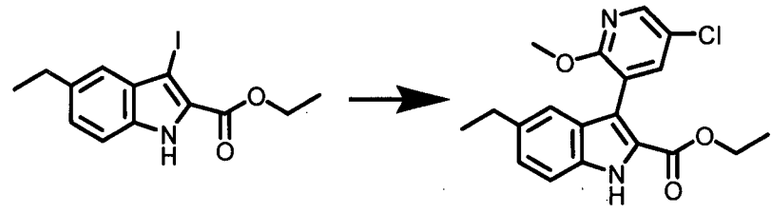
Paso 1:



21A **21B**

Los materiales de partida **21A** (15,0 g, 69,04 mmol) y THF (100 ml) se agregaron a un balón de 1000 ml. La solución resultante se enfrió con un baño de agua. A esta solución agitada, se agregó NIS (15,30 g, 68,80 mmol) lentamente. La solución resultante se dejó agitar a temperatura ambiente durante 5 horas antes de agregar 700 ml de agua. La mezcla resultante continuó con la agitación a temperatura ambiente durante 30 min y luego se filtró. La torta se lavó con agua (2 X 40 ml), se secó al aire y luego al vacío para proporcionar el compuesto **21B** como sólido blancuzco (23,0 g, 97%). MS encontrado 344,2 para $C_{13}H_{14}INO_2$ + H^+.

Paso 2:

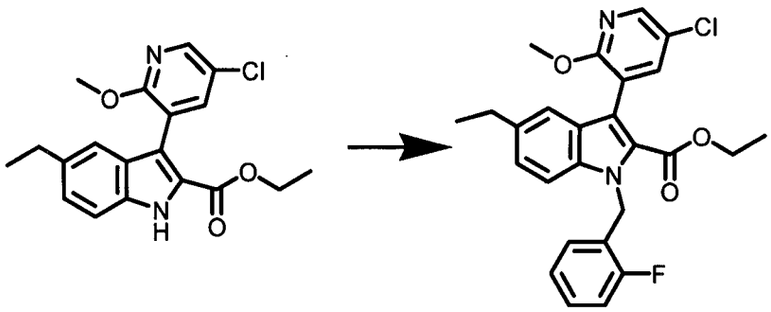


21B **21C**

Un balón de 250 ml se cargó con **21B** (3,60 g, 10,49 mmol), ácido 5–cloro–2–metoxipiridin–3–borónico (2,0 g, 10,67 mmol), complejo [1,1'–bis(difenilfosfin)ferroceno]dicloropaladio(II) con diclorometano (1:1) (0,87 g, 1,06 mmol), y DME (50 ml). A la solución agitada, una solución de carbonato de sodio (10 ml de 1,5 M, 15,0 mmol) se agregó a través de una jeringa. La mezcla de reacción se mantuvo a reflujo durante 6 horas antes de enfriarse hasta la temperatura ambiente. Luego de la concentración, el residuo se absorbió con acetato de etilo (200 ml), se lavó con agua (100 ml), y se secó sobre sulfato de sodio. El solvente se eliminó por centelleo bajo presión reducida y el residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–10%

acetato de etilo en hexanos as el solvente para proporcionar el compuesto **21C** como un sólido blanco (2,4 g, 64%). E. M. encontrada para $C_{19}H_{19}ClN_2O_3$: 359,2 $(M+H)^+$.

Paso 3:

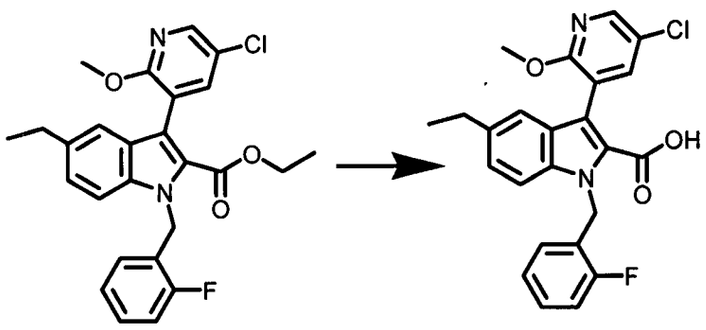


21C **21D**

Una suspensión de **21C** (280 mg, 0,78 mmol), cloruro de 2-fluorobencilo (300 mg, 2,07 mmol), carbonato de cesio (400 mg, 1,23 mmol) y DMF (3 ml) se dejó agitar a temperatura ambiente durante 19 horas, se diluyó con acetato de etilo (100 ml), y se lavó con agua (3X50 ml). La solución orgánica se secó sobre sulfato de sodio y se concentró. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–5% acetato de etilo en hexanos como eluyente para proporcionar el compuesto **21D** as a gel (318 mg, 87%).

Paso 4:

21D

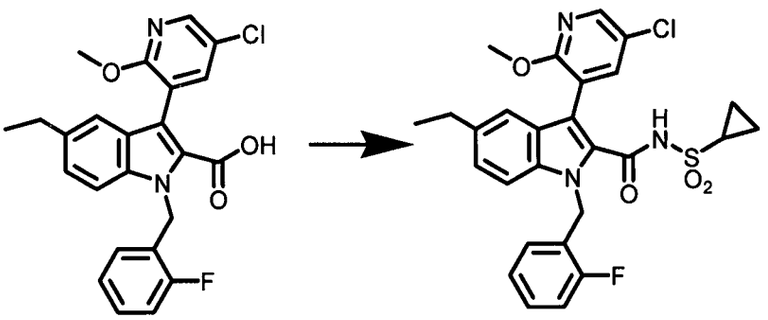


21D **21E**

A la mezcla agitada de **21D** (318 mg, 0,68 mmol) en THF (10 ml) en un balón de 100 ml se agregó con una solución de hidróxido de litio (2,0 ml de 1 M,

2,0 mmol). La solución resultante se mantuvo a reflujo durante 5 días antes de enfriar hasta la temperatura ambiente. Luego de la concentración *al vacío*, el residuo se disolvió en metanol (5 ml), se neutralizó con solución acuosa 1,0 M de HCl (2,0 ml, 2,0 mmol) y luego se concentró nuevamente. El residuo se extrajo con acetato de etilo (3x40 ml). Las soluciones orgánicas combinadas se concentraron y se secaron al vacío para proporcionar el compuesto **21E** como un sólido blanco (280 mg, 94%). E. M. encontrada para $C_{24}H_{20}ClFN_2O_3$: 439,2 $(M+H)^+$.

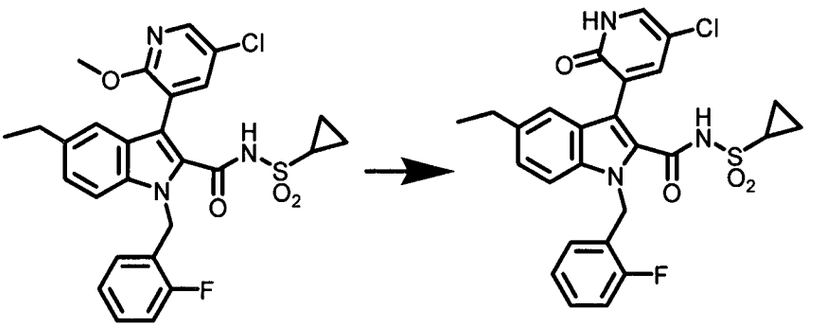
Paso 5:



21E **21F**

Una solución de **21E** (70 mg, 0,16 mmol) y 1,1'–carbonildiimidazol (40 mg, 0,25 mmol) en THF (3 ml) en un balón de 50 ml se reflujó durante 1,5 hora antes de enfriarse hasta la temperatura ambiente. Se agregaron ciclopropilsulfonamida (40 mg, 0,33 mmol) seguido de DBU (80 mg, 0,53 mmol). La mezcla de reacción resultante se dejó reflujar durante 4 horas antes de enfriarse hasta la temperatura ambiente y se concentró en rotavapor. El residuo se purificó usando Cromatografía Combi flash sobre gel de sílice usando 0–4% metanol en diclorometano como eluyente para proporcionar el compuesto **21F** as a gel (45 mg, 52%). E. M. encontrada para $C_{27}H_{25}ClFN_3O_4S$: 542,3 $(M+H)^+$.

Paso 6:

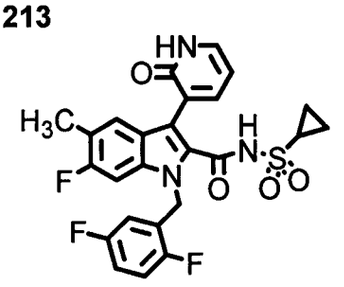


21F **263**

El material de partida **21F** (40 mg, 0,073 mmol) y HCl 4,0 M en 1,4–dioxano (5,0 ml, 20,0 mmol) se agregaron a un recipiente de presión de 15 ml. La solución resultante se dejó agitar a 90°C durante 2 horas antes de enfriarse hasta la temperatura ambiente. La mezcla se transfirió a un balón de 25 ml y se concentró al vacío. El residuo se purificó usando TLC preparativa sobre gel de sílice con 5% metanol en diclorometano como solvente de desarrollo para proporcionar el compuesto **263** como un sólido blanco (25 mg, 65%). ^{1}H RMN (400 MHz, d_6–DMSO) δ 7,80 (s, 1H), 7,69 (s, 1H), 7,46 (d, J = 8,51 Hz, 1H), 7,34 (s, 1H), 7,29–7,24 (m, 2H), 7,10 (t, J = 9,14 Hz, 1H), 7,04 (t, J = 7,25 Hz, 1H), 6,90 (t, J = 6,62 Hz, 1H), 5,79 (s, 2H), 2,94 (bs, 1H), 2,74 (q, J = 7,57 Hz, 2H), 1,26 (t, J = 7,57 Hz, 3H), 1,16 (bs, 2H), 1,04 (bs, 2H). E. M. encontrada para $C_{26}H_{23}ClFN_3O_4S$: 528,3 $(M+H)^+$.

Ejemplo 22

Preparación del compuesto **213**



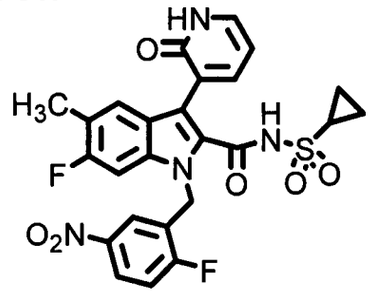
213

Usando el método descrito en el Ejemplo 1, Paso 7, y sustituyendo 2,5–difluorobencil bromuro en lugar de 3–bromometil–4–fluoro–benzonitrilo, se

preparó el compuesto **213**. E. M. encontrada para C25H20F3N3O4S: 516,3 $(M+H)^+$.

Ejemplo 23

Preparación del compuesto **317**



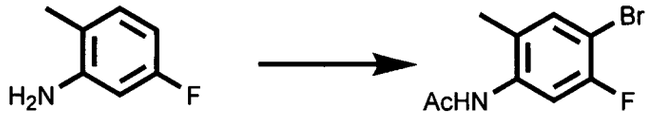
317

Usando el método descrito en el Ejemplo 1, Paso 7, y sustituyendo 3–bromometil–4–fluoro–nitrobenceno en lugar de 3–bromometil–4–fluoro–benzonitrilo, se preparó el compuesto **317**. E. M. encontrada para C25H20F2N4O6S: 543,3 $(M+H)^+$.

Ejemplo 24

Preparación del Compuesto Intermediario **24G**

Paso A – Síntesis del compuesto 24B

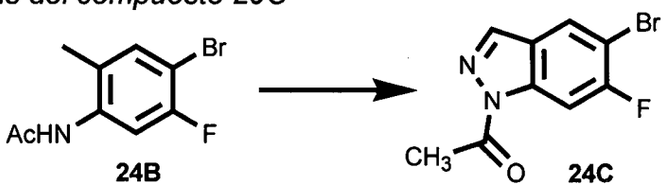


24A **24B**

Una solución de 5–fluoro–2–metilanilina (**24A**, 25 g, 200 mmol) en tolueno (250 ml) se trató con anhídrido acético (25 ml. 226 mmol) calentado a reflujo durante 1 hora. La mezcla de reacción se enfrió cuando un sólido incoloro se precipitó, el cual se filtró y se lavó con una mezcla de éter y hexanos. El sólido incoloro se absorbió en ácido acético (150 ml) y se trató gota a gota con una solución de bromo (9,6 ml, 186 mmol) en ácido acético (20 ml) y se agitó a temperatura ambiente durante 12 horas. La solución se diluyó con agua y el sólido

que se separó se filtró y se lavó para proporcionar N–(4–bromo–5–fluoro–2–metilfenil)acetamida (**24B**, 40 g) un sólido incoloro.

Paso B – Síntesis del compuesto 29C



24B **24C**

Una solución de N–(4–bromo–5–fluoro–2–metilfenil)acetamida (**24B**, 10,00 g, 40,64 mmol) en cloroformo (100 ml) se trató con anhídrido acético (11,5 ml, 122,0 mmol), acetato de potasio (8,00 g, 81,5 mmol), y 18–Crown–6 (540,00 mg, 2,0430 mmol) y luego con isoamil nitrito (12,3 ml, 871 mmol) y se calentó a 65°C durante 12 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se trató con EtOAc (500 ml), se lavó con agua, se secó ($MgSO_4$), se filtró, y luego se concentró al vacío. Un sólido amarillo pálido de 1–(5–bromo–6–fluoro–1H–indazol–1–il)etanona (**29C**) se precipitó. El filtrado inicial se concentró y el residuo se purificó usando cromatografía (SiO_2, EtOAc/Hexanos) para proporcionar más del producto **24C**.

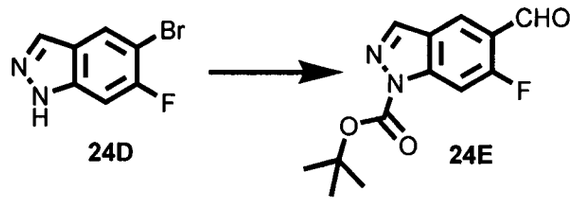
Paso C– Síntesis del compuesto 24D



24C **24D**

Una solución de 1–(5–bromo–6–fluoro–1H–indazol–1–il)etanona (**24C**, 5,0 g, 19,5 mmol) se trató con HCl ac. (Sol. 3M, 100 ml) y metanol (20 ml) y se calentó a 90°C durante 3h, cuando la reacción se torna homogénea. La mezcla de reacción se enfrió hasta la temperatura ambiente y se alcalinizó con NaOH ac.. Un sólido incoloro se precipitó, el cual se filtró y se secó para proporcionar 5–bromo–6–fluoro–1H–indazol (**24D**)

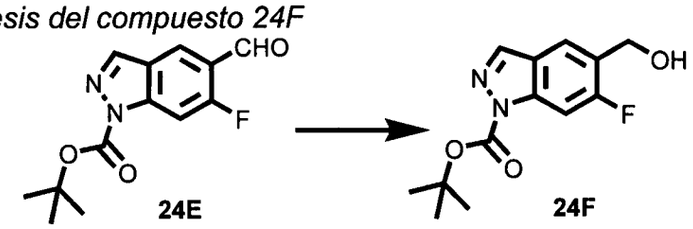
Paso D – Síntesis del compuesto 24E



24D **24E**

Una solución de 5–bromo–6–fluoro–1H–indazol (**24D**, 3,50 g, 16,28 mmol) en tetrahidrofurano (200,00 ml) se trató con yoduro de sodio (60% en aceite mineral, 1,172 g) a 0°C y se agitó a temperatura ambiente durante 20 minutos. La mezcla de reacción se enfrió hasta –78°C (hielo seco y acetona) y se trató con 2,5 M de n–butil litio en hexano (8,2 ml, 20,3 mmol) gota a gota. La mezcla de reacción se dejó agitar a esa temperatura durante 20 min y se trató con DMF (5,06 ml, 65,11 mmol). La mezcla de reacción se entibió lentamente hasta la temperatura ambiente cuando la solución viscosa se tornó fluida y la agitación fue eficiente. El análisis de TLC (40% EtOAc/Hexanos) indicó la conversión completa de material de partida en producto. La mezcla de reacción se acidificó con HCl ac. absorbido en EtOAc (500 ml) se lavó con HCl ac. (100 ml), salmuera (100 ml), se secó ($MgSO_4$), se filtró, se concentró al vacío y se usó como estaba en el paso siguiente. Una solución de producto 6–fluoro–1H–indazol–5–carbaldehído (2,3 g) en THF (100 ml) se trató con di–*ter*-butildicarbonato (3,56 g, 16,28 mmol) y DMAP (300 mg) y se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró *al vacío y* el residuo se purificó usando cromatografía (SiO_2, EtOAc/Hexanos gradiente 0–40%) para proporcionar [2e] 6–fluoro–5–formil-1H–indazol–1–carboxilato de *ter*-butilo (**24E**, 3,5 g; Rendimiento = 81%) un sólido incoloro.

Paso E – Síntesis del compuesto 24F

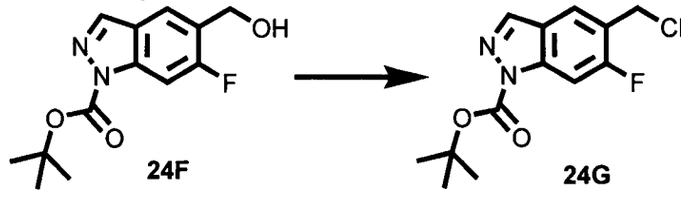


24E **24F**

Una solución de 6–fluoro–5–formil-1H–indazol–1–carboxilato de *ter*-butilo

(**29E**, 3,55 g, 13,4 mmol) en metanol (50,00 ml) se trató con $NaBH_4$ (1,02 g, 26,9 mmol) a 0°C y se dejó agitar durante 1h. La mezcla de reacción se diluyó con agua y EtOAc (500 ml). La fase orgánica se separó y se lavó con HCl ac. (1M, 200 ml), NaOH ac. (1M, 200 ml) salmuera (200 ml) se secó ($MgSO_4$), se filtró, se concentró al vacío y el residuo se purificó usando cromatografía (SiO_2, EtOAc/hexanos) para proporcionar 5–(hidroximetil)–6–fluoro–1H–indazol–1–carboxilato de *ter*-butilo (**29F**, 3,00 g; Rendimiento = 83,9%) un sólido incoloro.

Paso F – Síntesis del compuesto 24G

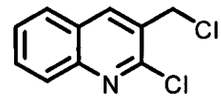


24F **24G**

Una solución de 5–(hidroximetil)–6–fluoro–1H–indazol–1–carboxilato de *ter*-butilo (**29F**, 3,0g, 11,27 mmol) en cloruro de metileno (50,00 ml, 780,0 mmol) a temperatura ambiente se trató con piridina (4,56 ml, 56,33 mmol) y cloruro de metansulfonilo (1,31 ml) y se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción se concentró al vacío y el residuo se disolvió en EtOAc (300 ml) se lavó con HCl ac. (100 ml), salmuera (100 ml), se secó ($MgSO_4$), se filtró, se concentró al vacío, y se purificó usando cromatografía (SiO_2, EtOAc/Hexanos) para proporcionar 5–(clorometil)–6–fluoro–1H–indazol–1–carboxilato de *ter*-butilo (**24G**, 1,9 g; Rendimiento = 59%)

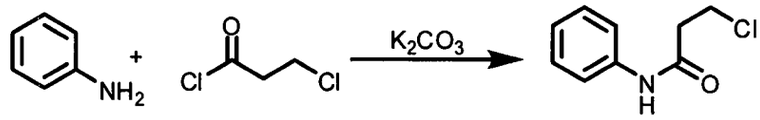
Ejemplo 25

Preparación del Compuesto Intermediario **25B**



25B

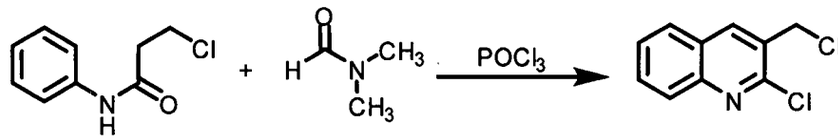
Paso A – Síntesis del compuesto 6A



25A

Una mezcla de anilina (65,04 ml, 713,8 mmol), carbonato de potasio (54,4 g, 394 mmol) y agua (300 ml) se agregaron 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 cloruro de 3–Cloro– propionilo (75,18 ml, 787,6 mmol) gota a gota a través de un embudo de incorporación y la suspensión resultante se dejó agitar a temperatura ambiente durante 3 horas. La mezcla de reacción se filtró y el sólido recolectado se lavó en forma consecutiva con agua (300 ml), HCl ac. (1M, 2 x 300 ml), y agua (300 ml), luego se secó para proporcionar el compuesto **25A**, que se usó sin purificación (114,5 g, 87%).

Paso B – Síntesis del compuesto 25B

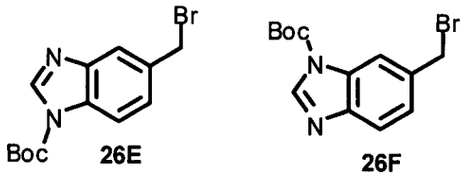


25A **25B**

Se cargó N,N–Dimetilformamida (53,7 ml, 694 mmol) en un matraz de tres bocas y se enfrió hasta 0°C y se trató con cloruro de fosforilo (177,7 ml, 1906 mmol) gota a gota. La reacción se dejó agitar a esa temperatura durante 10 min y se trató con 3–Cloro–N–fenilpropanamida **25A** (50,00 g, 272,3 mmol) y se agitó a temperatura ambiente durante 30 minutos. La mezcla de reacción se calentó a 80°C durante 3 h y lentamente se vertió en hielo. El sólido que se separó se filtró y se lavó extensivamente con agua (2x1000 ml), bicarbonato de sodio saturado acuoso (500 ml), y se absorbió en EtOAc (1L), la solución se secó ($MgSO_4$) se filtró se concentró al vacío y el residuo obtenido se recristalizó a partir de hexanos en ebullición para proporcionar el compuesto **25B** (20 g).

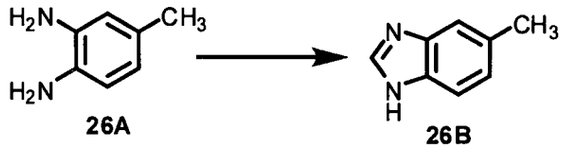
Ejemplo 26

Preparación de los Compuestos Intermediarios **26E y 26F**



26E **26F**

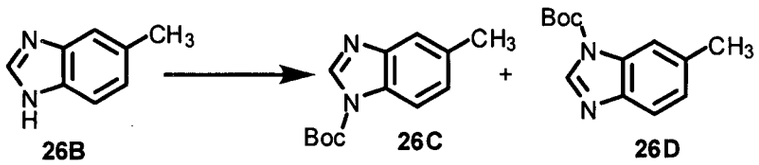
Paso A – Síntesis del compuesto 26B



26A **26B**

Una solución del compuesto **26A** (3 g, 24,5 mmol) en ortoformiato de trimetilo (15 ml) se trató con 2 gotas HCl conc. y se calentó hasta 80°C durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró al vacío para proporcionar el compuesto **26B** (3,65 g), que se usó sin purificación adicional. E. M. encontrada para $C_8H_8N_2$: 133,2 $(M+H)^+$.

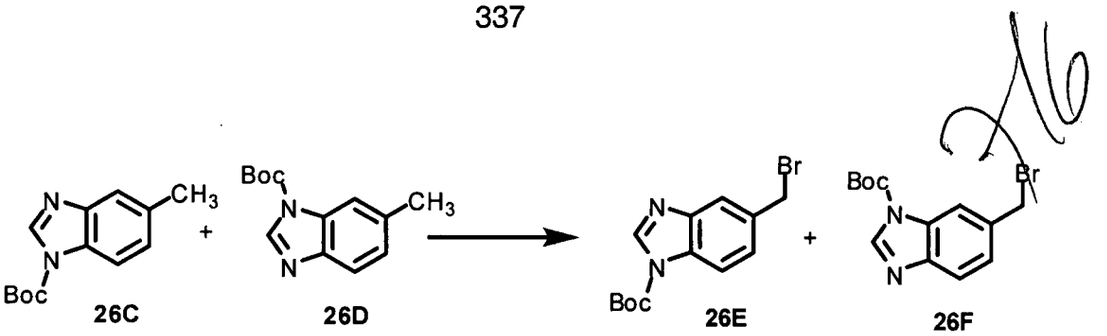
Paso B – Síntesis de Compuestos 26C y 26D



26B **26C** **26D**

A una solución del compuesto **26B** (24,5 mmol) en CH_3CN (65 ml) se agregó dicarbonato de di–tertulito (5,89 g, 27,0 mmol), trietilamina (3,76 ml, 27,0 mmol) y 4–dimetilamino piridina (300 mg, 2,45 mmol) y la reacción resultante se calentó hasta 80°C y se dejó agitar a esta temperatura durante 1,5 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío, y el residuo obtenido se purificó usando cromatografía flash en columna (gel de sílice, EtOAc/Hexanos 5–20%) para proporcionar una mezcla de compuestos isoméricos **26C** y **26D** (5,38 g, 94,3% de rendimiento en los pasos A y B).

Paso C – Síntesis de Compuestos 26E y 26F

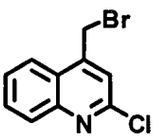


26C 26D 26E 26F

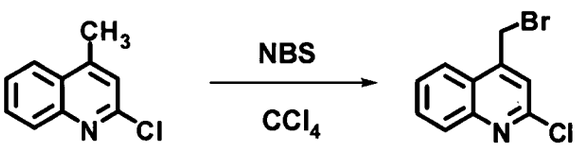
A una solución de compuestos **26C** y **26D** (2 g, 8,61 mmol) en tetracloruro de carbono (40 ml) se agregó N–bromosuccinimida (1,6 g, 9,04 mmol) y peróxido de dibenzoilo (41,7 mg, 0,1722 mmol) y la reacción resultante se calentó hasta 90°C y se dejó agitar a esta temperatura durante 12 horas. La reacción se enfrió hasta la temperatura ambiente, se eliminaron los sólidos por filtración y el filtrado se lavó con agua, se secó sobre sulfato de sodio y se concentró al vacío para proporcionar compuestos **26E** y **26F** (2,58 g) que se usó sin purificación adicional. E. M. encontrada para $C_{13}H_{15}BrN_2O_2$: 334,7 $(M+Na)^+$.

Ejemplo 27

Preparación del Compuesto Intermediario **27B**



27B



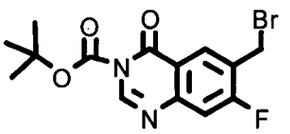
27A **27B**

Una mezcla del compuesto **27A** (1,5 g, 8,44 mmol), NBS (1,8 g, 10,11 mmol) en tetracloruro de carbono (50 ml) se calentó hasta reflujo, luego se agregó peróxido de benzoilo (0,21 g, 0,866 mmol). La suspensión resultante se dejó agitar a reflujo durante 19 horas, luego se enfrió hasta la temperatura ambiente y se filtró. El filtrado se lavó con carbonato de sodio saturado, se secó sobre sulfato de sodio y se concentró al vacío para proporcionar una mezcla (1,7 g) que

contiene aproximadamente 50% del compuesto **27B**, y se usó sin purificación adicional.

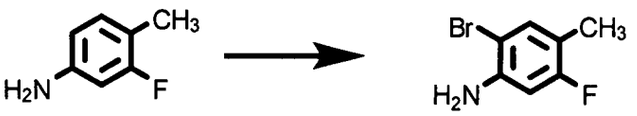
Ejemplo 28

Preparación del Compuesto Intermediario **28G**



28G

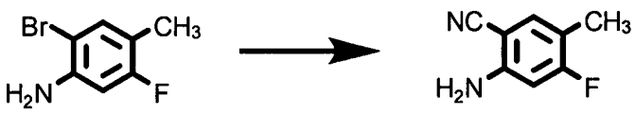
Paso A – Síntesis del compuesto 9B



28A **28B**

Una mezcla del compuesto **28A** (6,00 g, 47,9 mmol) y carbonato de potasio anhidro (6,70 g, 48,5 mmol) en diclorometano anhidro (130 ml) se enfrió hasta –15°C en un baño de hielo-sal y luego se agregó gota a gota a una solución de bromo (7,70 g, 48,2 mmol) en diclorometano anhidro (80 ml). Luego de completar la incorporación, la reacción se dejó agitar a –15°C durante 1 hora. Se agregó agua helada (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 sobre $MgSO_4$ y se concentró al vacío para proporcionar el compuesto **28B** (11,0 g, cuanto.), que se usó sin purificación adicional.

Paso B – Síntesis del compuesto 28C

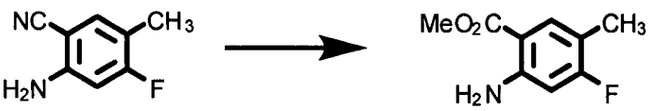


28B **28C**

El Compuesto **28B** 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 hasta 160°C y se dejó agitar a esta temperatura durante 20 horas. Luego de que se enfrió hasta la temperatura ambiente, con agua (200 ml), se agregaron cloruro de hierro (III) (42,0 g, 155 mmol) y ácido clorhídrico concentrado (20 ml) a la mezcla de

reacción y la reacción resultante se dejó agitar durante 45 minutos. La mezcla de reacción luego se alcalinizó hasta un pH > 10 usando solución comercial de hidróxido de amonio. La solución alcalina luego se extrajo con acetato de etilo (4 x 400 ml). Los extractos orgánicos combinados se lavaron con agua, se secaron sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo obtenido se purificó usando cromatografía flash para proporcionar el compuesto **28C** (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).

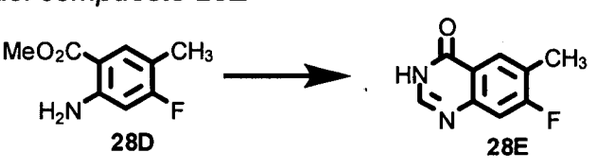
Paso C – Síntesis del compuesto 28D



28C **28D**

A una solución de **28C** (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 hasta 70°C y se dejó agitar durante cuatro días. Luego de que se enfrió hasta la temperatura ambiente, se vertió en agua helada. Luego se diluyó la mezcla con acetato de etilo (200 ml) y se alcalinizó (pH > 10) con solución de hidróxido de amonio comercial. Se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 100 ml). La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en bruto que se purificó usando cromatografía flash para proporcionar el compuesto **28D** (1,0 g, 41%) y algo recuperado de **28C**. ^{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).

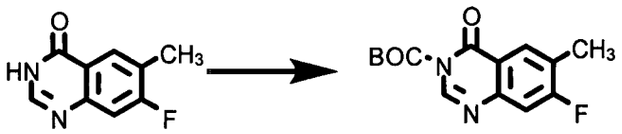
Paso D – Síntesis del compuesto 28E



28D **28E**

La solución del compuesto **28D** (500 mg, 2,73 mmol) en formamida (6,0 ml) se calentó hasta 150°C en un baño de aceite y se dejó agitar durante 18 horas. Luego de que se enfrió hasta la temperatura ambiente, se agregaron acetato de etilo (100 ml) y agua (100 ml) y se separaron las fases. La solución orgánica se lavó con agua (2 x 60 ml), se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en bruto **28E** (0,50 g, cuanto.) el cual se usó sin purificación adicional. EM encontrada para $C_9H_7FN_2O$: 179,0 $(M+H)^+$.

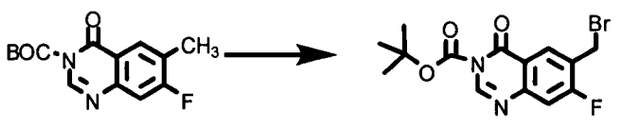
Paso E – Síntesis del compuesto 28F



28E **28F**

A una solución de **28E** (del Paso 4) en THF anhidro (20 ml) a temperatura ambiente se agregó dicarbonato de di–*ter*-butilo (1,84 g, 8,43 mmol), 4–dimetilaminopiridina (350 mg, 2,86 mmol) y trietil amina (0,40 ml, 2,87 mmol). La mezcla de reacción se dejó agitar durante 18 horas. Se agregaron acetato de etilo (100 ml) y agua (100 ml) y se separaron las fases. La fase acuosa se extrajo con acetato de etilo (2 x 50 ml). La solución orgánica combinada se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en bruto el cual se purificó usando cromatografía flash para proporcionar el compuesto **28F** (285 mg, 36%). EM encontrada para $C_{14}H_{15}FN_2O_3$: 179,0 $(M+H–100)^+$.

Paso F – Síntesis del compuesto 28G



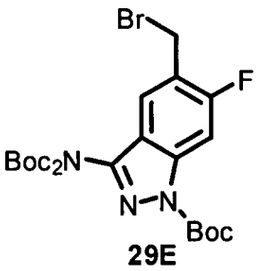
28F **28G**

La mezcla de **28F** (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 hasta 90°C en un baño de aceite y se dejó agitar durante 4 horas. Luego de que se enfrió hasta la temperatura ambiente y se concentró al vacío, el residuo se

disolvió en acetato de etilo (100 ml) y agua (100 ml). Se separaron las fases. La solución orgánica se lavó con agua (100 ml), se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en bruto **28G** (453 mg, cuanto.) el cual se usó sin purificación adicional.

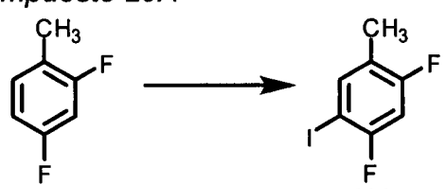
Ejemplo 29

Preparación del Compuesto Intermediario **29E**



29E

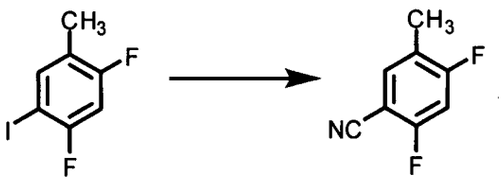
Paso A – Síntesis del compuesto 29A



29A

Una solución de 2,4–difluorotolueno (4,72 g, 36,8 mmol) en ácido trifluoroacético (12,29 ml, 159,5 mmol) se enfrió hasta 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 al vacío y el residuo obtenido se disolvió en hexanos (100 ml), se lavó con tiosulfato de sodio acuoso (100 ml), salmuera (100 ml), luego se secó ($MgSO_4$), se filtró y se concentró al vacío. El residuo resultante se purificó usando destilación bombilla a bombilla para proporcionar el compuesto **29A** (7,2 g, 77%) como un aceite incoloro.

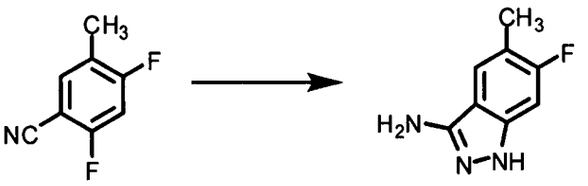
Paso B – Síntesis del compuesto 29B



29A **29B**

Una solución del compuesto **29A** (7,11 g, 28,0 mmol), cianuro de zinc (1,97 g, 16,8 mmol) y tetrakis(trifenilfosfin)paladio(0) (3,23 g, 2,80 mmol) en DMF (30 ml) se calentó hasta 90°C y se dejó agitar a esta temperatura durante 1,5 horas. La mezcla de reacción se concentró *al vacío* y el residuo obtenido se absorbió en agua (400 ml) y se extrajo con éter (400 ml). El extracto orgánico se lavó con solución acuosa de hidróxido de amonio (1N). La fase orgánica se secó ($MgSO_4$) se filtró, se concentró al vacío para proporcionar un residuo que se purificó usando cromatografía flash en columna (SiO_2, EtOAc/Hexanos) para proporcionar una mezcla que contenía producto y trifenilfosfina. Esta mezcla se purificó en forma adicional usando sublimación 1 mm/Hg a 45°C para proporcionar el compuesto **29B** (1,8 g; Rendimiento = 42%).

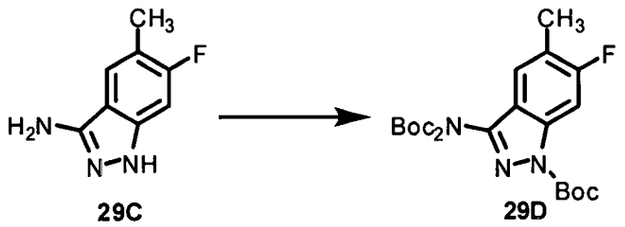
Paso C – Síntesis del compuesto 29C



29B **29C**

Una solución del compuesto **29B** (1,400 g, 9,154 mmol) y hidrazina (0,700 ml, 22,3 mmol) en alcohol isopropílico (50 ml, 653,1 mmol), se calentó hasta reflujo y se dejó agitar a esta temperatura durante 24 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío y el residuo obtenido se purificó usando cromatografía flash en columna (SiO_2, Acetona/Hexanos 0→ 50%) para proporcionar el compuesto **29C** (330 mg, 22%).

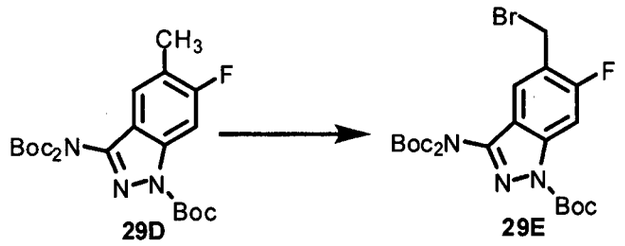
Paso D – Síntesis del compuesto 29D



29C 29D

Una solución del compuesto **29C** (330,00 mg, 1,998 mmol), di–ter-butildicarbonato (2,6163 g, 11,98 mmol) y 4–dimetilaminopiridina (48,817 mg, 0,39959 mmol) en acetonitrilo (15ml, 287,2 mmol) se calentó hasta reflujo y se dejó agitar a esta temperatura durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío, y el residuo resultante se purificó usando cromatografía flash en columna (SiO_2, EtOAc/Hexanos 0– 20%) para proporcionar el compuesto **29D** (640,00 mg, 68%) como un aceite incoloro.

Paso E – Síntesis del compuesto 29E

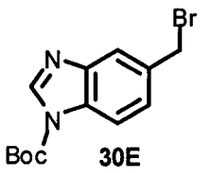


29D 29E

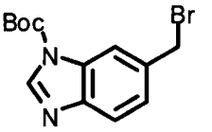
Una solución del compuesto **29D** (630,00 mg, 1,3533 mmol), N–bromosuccinimida (337,22 mg, 1,8947 mmol) y peróxido de benzoilo (65,563 mg, 0,27067 mmol) en tetracloruro de carbono (20 ml) se calentó hasta reflujo y se dejó agitar a esta temperatura durante 3 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío y el residuo obtenido se disolvió en EtOAc (300 ml). La solución resultante se lavó con tiosulfato de sodio acuoso (100 ml), salmuera (100 ml), se secó ($MgSO_4$), se filtró, y se concentró al vacío. El residuo obtenido se purificó usando cromatografía flash en columna (SiO_2, EtOAc/Hexanos) para proporcionar el compuesto **29E** como un aceite incoloro.

Ejemplo 30

Preparación de los Compuestos Intermediarios **30E y 30F**

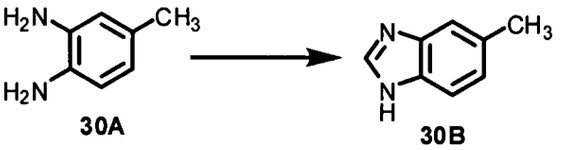


30E



30F

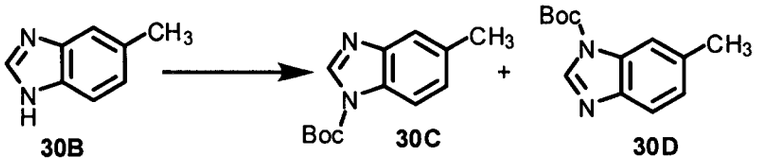
Paso A – Síntesis del compuesto 30B



30A **30B**

Una solución del compuesto **8A** (3 g, 24,5 mmol) en ortoformiato de trimetilo (15 ml) se trató con 2 gotas HCl conc. y se calentó hasta 80°C durante 2 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente y se concentró al vacío para proporcionar el compuesto **8B** (3,65 g), que se usó sin purificación adicional. E. M. encontrada para $C_8H_8N_2$: 133,2 $(M+H)^+$.

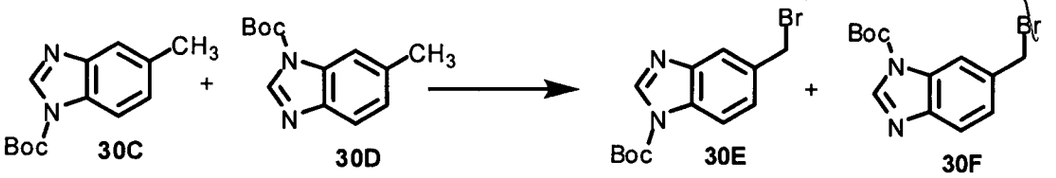
Paso B – Síntesis de Compuestos 30C y 30D



30B **30C** **30D**

A una solución del compuesto **30B** (24,5 mmol) en CH_3CN (65 ml) se agregó dicarbonato de di–tertulito (5,89 g, 27,0 mmol), trietilamina (3,76 ml, 27,0 mmol) y 4–dimetilamino piridina (300 mg, 2,45 mmol) y la reacción resultante se calentó hasta 80°C y se dejó agitar a esta temperatura durante 1,5 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío, y el residuo obtenido se purificó usando cromatografía flash en columna (gel de sílice, EtOAc/Hexanos 5–20%) para proporcionar una mezcla de compuestos isoméricos **30C** y **30D** (5,38 g, 94,3% de rendimiento en los pasos A y B).

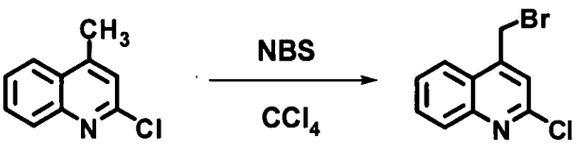
Paso C – Síntesis de Compuestos 30E y 30F



A una solución de compuestos **30C** y **30D** (2 g, 8,61 mmol) en tetracloruro de carbono (40 ml) se agregó N–bromosuccinimida (1,6 g, 9,04 mmol) y peróxido de dibenzoilo (41,7 mg, 0,1722 mmol) y la reacción resultante se calentó hasta 90°C y se dejó agitar a esta temperatura durante 12 horas. La reacción se enfrió hasta la temperatura ambiente, se eliminaron los sólidos por filtración y el filtrado se lavó con agua, se secó sobre sulfato de sodio y se concentró al vacío para proporcionar compuestos **30E y 30F** (2,58 g) que se usó sin purificación adicional. E. M. encontrada para $C_{13}H_{15}BrN_2O_2$: 334,7 $(M+Na)^+$.

Ejemplo 31

Preparación del Compuesto Intermediario **31B**



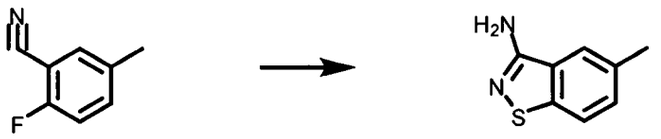
31A **31B**

Una mezcla del compuesto **31A** (1,5 g, 8,44 mmol), NBS (1,8 g, 10,11 mmol) en tetracloruro de carbono (50 ml) se calentó hasta reflujo, luego se agregó peróxido de benzoilo (0,21 g, 0,866 mmol). La suspensión resultante se dejó agitar a reflujo durante 19 horas, luego se enfrió hasta la temperatura ambiente y se filtró. El filtrado se lavó con carbonato de sodio saturado, se secó sobre sulfato de sodio y se concentró al vacío para proporcionar una mezcla (1,7 g) que contiene aproximadamente 50% del compuesto **31B**, y se usó sin purificación adicional.

Ejemplo 32

Preparación del Compuesto Intermediario **32D**

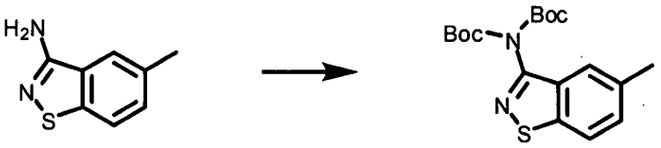
Paso A – Síntesis del compuesto 32B



32A **32B**

Una mezcla de 2–fluoro–5–metilbenzonitrilo (**32A**, 2,0 g; 14,799 mmol) y sulfuro de sodio (1,0 eq, 1,15 g) se disolvió en 150 ml de DMSO y se calentó a 70°C hasta la mañana siguiente. La mezcla se colocó en un baño de agua helada y se trató con hidróxido de amonio acuoso concentrado (20 ml) e hipoclorito de sodio acuoso (20 ml). La mezcla de reacción se dejó entibiar hasta la temperatura ambiente y se dejó agitar durante 5 horas. La mezcla se diluyó con acetato de etilo (300 ml) y se lavó con agua (2 x 60 ml) y salmuera (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre una columna Biotage 40–M de gel de sílice (gradiente: 0 hasta 30% acetona en hexanos) para proporcionar el compuesto **32B** (860 mg; 36%) como un sólido blanco. ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 7,68 (1H, d, J = 8,54 Hz), 7,48 (1H, s), 7,33 (1H, d, J = 8,54 Hz), 4,89 (2H, s amplio), 2,50 (3H, s).

Paso B – Síntesis del compuesto 32C

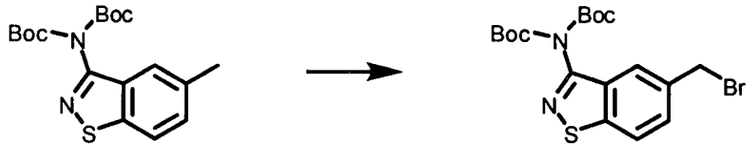


32B **32C**

Una solución de 5–metilbenzo[d]isotiazol–3–ilamina, (**10B**, 850 mg; 5,176 mmol) en acetonitrilo anhidro (50 ml) se trató con Boc–anhídrido (2,1 eq, 2,37 g) y se calentó hasta 50°C. Todo el material de partida se había consumido luego de 2 h y la mezcla se concentró *al vacío* hasta un tercio de su volumen. El residuo se disolvió en acetato de etilo (100 ml) y se lavó con hidrógeno sulfato de sodio acuoso (20 ml), y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de

sílice y se purificó sobre una columna Biotage 40—M de gel de sílice (gradiente: 0 hasta 10% acetato de etilo en hexanos) para proporcionar el compuesto **10C** (1,7 g; 91%) como un polvo blanco. ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 7,77 (1H, d, J = 8,54 Hz), 7,55 (1H, s), 7,38 (1H, dd, J = 1,83, 8,54 Hz), 2,51 (3H, s), 1,36 (18H, s). LR–MS (ESI): cálculo analítico para $C_{18}H_{25}N_2O_4S$ $[M+H]^+$ 365,15; experimental 365,23.

Paso C – Síntesis del compuesto 32D



32C **32D**

Una solución de N,N–bis–Boc–5–metil–benzo[d]isotiazol–3–ilamina (**32D**, 500 mg; 1,371 mmol) en 15 ml de tetracloruro de carbono se trató con N–bromosuccinimida (1,05 eq, 256 mg) y peróxido de benzoilo (10% en moles; 33 mg). La solución se desgasificó (vacío/enjuague de argón) y luego se calentó hasta 75°C durante 5 horas. La mezcla de reacción se concentró hasta un tercio de su volumen *al vacío* y el residuo se disolvió en acetato de etilo (50 ml). La solución se lavó con solución acuosa saturada de bicarbonato de sodio (2 x 10 ml) y salmuera (10 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre una columna de gel de sílice Biotage 40-S (gradiente: hexanos luego 0 hasta 10% acetato de etilo en hexanos) para proporcionar el compuesto **32D** (396 mg; 69%) como un sólido blanco. ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 7,87 (1H, d, J = 8,54 Hz), 7,78 (1H, s), 7,58 (1H, dd, J = 1,83, 8,54 Hz), 4,63 (2H, s), 1,37 (18H, s). LR–MS (ESI): cálculo analítico para $C_{18}H_{24}BrN_2O_4S$ $[M+H]^+$ 445,06; experimental 445,24.

Ejemplo 33

Preparación del Compuesto Intermediario **33D**

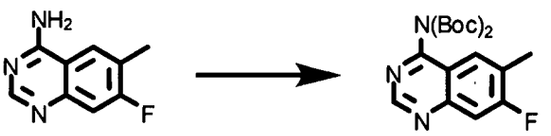
Paso A – Síntesis del compuesto 33B



33A **33B**

Una solución de **33A** (0,20 g, 1,33 mmol) en formamida (15 ml) se calentó hasta 150ºC y se dejó agitar durante 18 horas. Luego de que se enfrió hasta la temperatura ambiente, se agregaron acetato de etilo (60 ml) y agua (30 ml) y se separaron las fases. La solución orgánica se lavó con agua (3x20 ml), se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar el producto en bruto **33B** (0,22 g, 93%). EM encontrada para $C_9H_8FN_3$: 178,2 $(M+H)^+$.

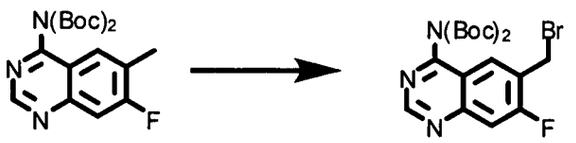
Paso B – Síntesis del compuesto 11C



33B **33C**

Se trató **33B** con 3,0 equivalentes de $(Boc)_2O$ para proporcionar **33C.** EM encontrada para $C_{19}H_{24}FN_3O_4$: 378,4 $(M+H)^+$.

Paso C – Síntesis del compuesto 33D



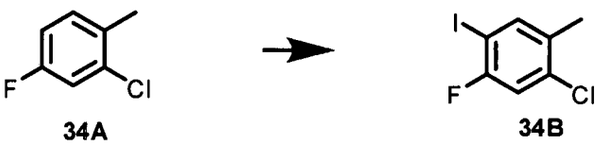
33B **33C**

La bromación de **33C** en condiciones de N–bromo succinimida estándar produjo **33D**. EM encontrada para $C_{19}H_{23}BrFN_3O_4$: 458,3 $(M+H)^+$.

Ejemplo 34

Preparación del Compuesto Intermediario **34F**

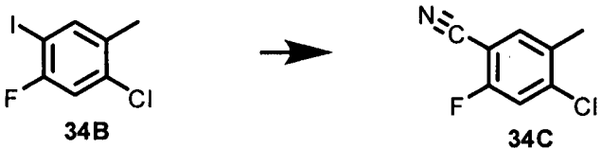
Paso A – Síntesis del compuesto 34B



34A **34B**

La N–yodosuccinimida (1,1 eq; 17,1 g) se agregó a una solución de 2,4–difluoro tolueno (**34A**, 10,0 g; 69,17 mmol; Alfa Aesar) en ácido trifluoroacético (46 ml). La reacción se dejó agitar durante 12 horas. Los volátiles se retiraron bajo presión reducida; la emulsión resultante se diluyó con éter (400 ml) y se lavó con tiosulfato de sodio acuoso al 5% (5x40 ml), agua (2x30 ml), y salmuera (40 ml). La fase orgánica se recolectó, se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. La reacción se purificó por destilación bomba a bomba para proporcionar producto **34B** como un líquido incoloro (17 g; 91%)

Paso B – Síntesis del compuesto 34C



34B **34C**

Una solución del intermediario **34B** (13,0 g; 48,06 mmol) y cianuro de zinc (1 eq; 5,644 g) en N,N–dimetliformamida (50 ml) se trató con tetrakis (trifenilfosfin) paladio(0) (0,1 eq; 5,55 g) y se calentó a 90°C durante 12 horas. La mezcla de reacción se diluyó con éter (600 ml) e hidróxido de amonio (1:1 hidróxido de amonio concentrado: agua 200 ml). La fase orgánica se separó y se lavó con agua (100 ml) y salmuera (100 ml), se secó sobre sulfato de magnesio, se filtró, se concentró bajo presión reducida, y se purificó sobre gel de sílice eluyendo primero con hexanos, luego con 20% acetato de etilo/hexanos. El Producto 34**C** (4,48 g; 33%) se generó como un aceite incoloro.

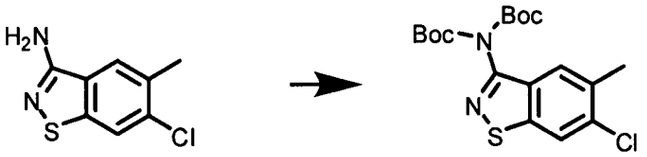
Paso C – Síntesis del compuesto 34D



34C **34D**

Una solución de **34C** (2,25 g; 13,27 mmol) y sulfuro de sodio (1 eq; 1,035 g) se preparó en DMSO (130 ml) y se calentó a 70°C hasta la mañana siguiente. La mezcla se colocó en un baño de agua helada y se trató con hidróxido de amonio acuoso concentrado (30 ml) e hipoclorito de sodio acuoso (30 ml). La mezcla de reacción se dejó agitar durante 5 h (temp desde 0 hasta 25°C). La mezcla se diluyó con acetato de etilo (400 ml) y se lavó con agua (2x40 ml) y salmuera (50 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre una columna ISCO 330G (gradiente: 0–30% acetona en hexanos), generando el producto **34D** (800 mg; 30,3%) como un sólido blanco.

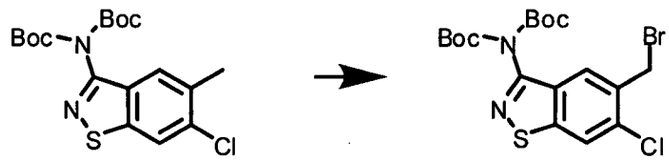
Paso D – Síntesis del compuesto 34E



34D **34E**

Una solución del intermediario **34D** (780 mg; 3,93 mmol) en acetonitrilo anhidro (39 ml) se trató con Boc–anhídrido (2,2 eq; 1,885 g) y se calentó hasta 50°C. Todo el material de partida se había consumido luego de 2 h y la mezcla se concentró *al vacío* hasta un tercio de su volumen. El residuo se disolvió en acetato de etilo (100 ml) y se lavó con hidrógeno sulfato de sodio acuoso (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre una columna ISCO de 80 gramos (gradiente: 0 hasta 10% acetato de etilo en hexanos) para proporcionar el compuesto **34E** (1,03 g; 66% de rendimiento) como un sólido blanco.

Paso E – Síntesis del compuesto 34F



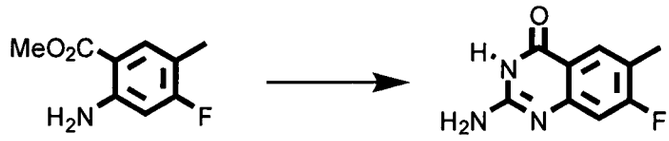
34E **34F**

Una solución del intermediario **34E** (400 mg; 1,003 mmol), N–Bromosuccinimida (1,05 eq; 187,4 mg), y peróxido de benzoilo (0,1 eq; 24,3 mg) en tetracloruro de carbono anhidro (10 ml) se preparó y se calentó a reflujo durante 12 horas. La TLC (30% acetato de etilo en hexanos) reveló que la reacción había progresado parcialmente. La mezcla de reacción se concentró bajo presión reducida, se diluyó con acetato de etilo (100 ml), se lavó con bicarbonato de sodio acuoso saturado (25 ml) y salmuera (25 ml), se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. El residuo luego se diluyó con diclorometano, se adsorbió sobre gel de sílice, y se purificó sobre ISCO (Columna 25–M; 0–40% acetato de etilo en hexanos). Las fracciones que contenían producto se concentraron bajo presión reducida generando el intermediario **34F** (278 mg; 58%) como un aceite amarillo translúcido.

Ejemplo 35

Preparación del Compuesto Intermediario **35C**

Paso A – Síntesis del compuesto 31A

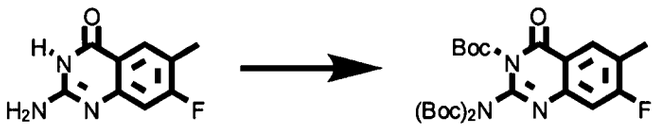


35A

Una mezcla sólida de 2–amino–4–fluoro–5–metilbenzoato de metilo (2,66 g, 14,5 mmol), clorhidrato de cloroformamidinio (2,6 g, 22,6 mmol) y metil sulfona (8,5 g, 90,3 mmol) se calentó hasta 150–160°C en un baño de aceite con agitación vigorosa. Se tornó una solución translúcida luego de aproximadamente 10 minutos. Se continuó aplicando calor durante un total de 2 horas. Cuando se enfrió hasta la temperatura ambiente, se solidificó. El material se absorbió con

agua (200 ml), se alcalinizó con hidróxido de amonio comercial. Luego de agitar durante 1 hora, el sólido se recolectó por filtración. Se lavó con agua (20 ml) y se secó al vacío para proporcionar producto en bruto **35A** (2,93 g, cuanto.). EM encontrada para $C_9H_8FN_3O$: 194,2 $(M+H)^+$.

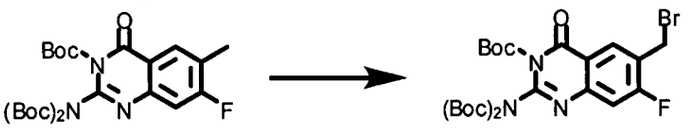
Paso B – Síntesis del compuesto 35B



35A **35B**

El Compuesto **35B** se preparó a partir de **35A** de acuerdo con los procedimientos descritos, y usando 4 equivalentes de $(Boc)_2O$. EM encontrada para $C_{24}H_{32}FN_3O_7$: 394,3 $(M+H-100)^+$.

Paso C – Síntesis del compuesto 35C



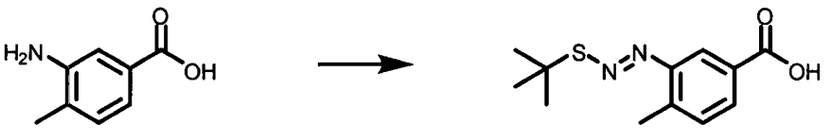
35B **35C**

Una solución del compuesto **35B** (4,83 g, 9,8 mmol), N–bromosuccinimida (2,70 g, 15,2 mmol) y peróxido de benzoilo (600 mg, 2,48 mmol) en tetracloruro de carbono (300 ml) se calentó hasta reflujo y se dejó agitar a esta temperatura durante 18 horas. La mezcla de reacción se enfrió hasta la temperatura ambiente, se concentró al vacío y el residuo obtenido se disolvió en EtOAc (300 ml). La solución resultante se lavó con tiosulfato de sodio acuoso (100 ml), salmuera (100 ml), se secó ($MgSO_4$), se filtró, y se concentró al vacío para proporcionar el compuesto intermediario **35C**, que se usó sin purificación adicional. EM encontrada para $C_{24}H_{31}BrFN_3O_7$: 472,3 $(M+H-100)^+$.

Ejemplo 36

Preparación del compuesto intermediario **36G**

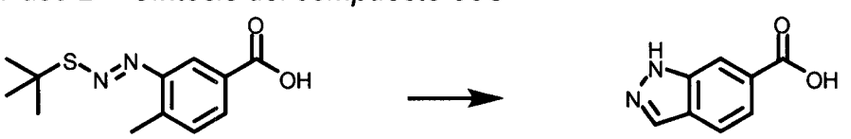
Paso A – Síntesis del compuesto 36B



36A **36B**

A una solución agitada de HCl acuoso (15 ml de HCl conc en 50 ml de agua) se agregó ácido 3–amino–4–metilo benzoico (**36 A**, 5,0 g; 33,0 mmol). La mezcla se enfrió en un baño de agua helada seguido de la lenta incorporación de una solución de nitrito de sodio (1,1 eq, 2,50 g) en agua (12 ml). La mezcla se dejó agitar durante 30 min momento en el cual la mezcla fue una solución oscura homogénea. Se agregó una solución saturada acuosa de acetato de sodio hasta que se logró un pH 6. Se agregó t-butiltiolato de sodio (0,5 eq, 1,85 g) en una porción. La reacción se dejó agitar durante 2 h y el precipitado resultante se recolectó por filtración (whatman #1), se lavó con agua (20 ml) y se secó al vacío para proporcionar el compuesto **36B** (2,7 g; 64%) como un sólido tostado.

Paso B – Síntesis del compuesto 36C



36B **36C**

A una solución agitada de ter-butóxido de potasio (10,0 eq, 12,0 g) en DMSO (50 ml) se agregó una solución de ácido t–butildiazaenil benzoico **36B** (2,7 g; 10,70 mmol) en DMSO (30 ml). La mezcla se dejó agitar durante 6 h y luego se diluyó con hielo y se acidificó con HCl 1M acuoso hasta que se logró el pH 5–6. La mezcla se extrajo con acetato de etilo (3 x 50 ml) y las fases orgánicas combinadas se lavaron con agua (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto **36C** como un sólido levemente amarillo que se usó sin purificación adicional.

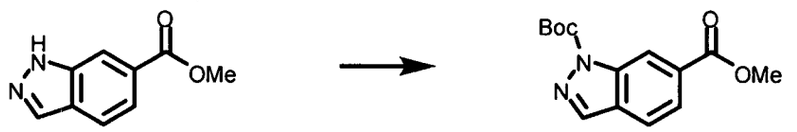
Paso C – Síntesis del compuesto 36D



36C **36D**

Una solución de ácido 1H–indazol–6–carboxílico **36C** (1,73 g; 10,70 mmol) en tolueno (80 ml) y metanol (30 ml) se trató con una solución de TMS–diazometano (Sol. 2 M en éter) hasta que se detuvo la evolución de gas. La mezcla de reacción se concentró *al vacío* y el residuo se adsorbió sobre gel de sílice. El producto se purificó en una columna Biotage 40—M de gel de sílice (gradiente: 0 a 20% acetona en hexanos) para proporcionar el compuesto **36D** (950 mg; 50% para dos pasos) como un sólido amarillo. ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 8,28 (1H, s), 8,16 (1H, s), 7,86 (1H, d, J = 8,54 Hz), 7,81 (1H, d, J = 8,54 Hz), 3,98 (3H, s). LR–MS (ESI): cálculo analítico para $C_9H_9N_2O_2$ $[M+H]^+$ 177,07; experimental 177,20.

Paso D – Síntesis del compuesto 36E

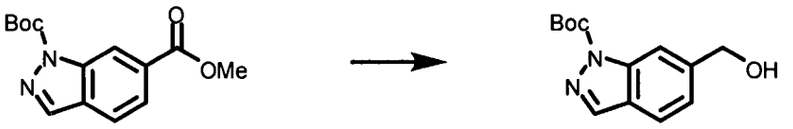


36D **36E**

Una solución de metil éster del ácido 1H–indazol–6–carboxílico **36D** (840 mg; 4,76 mmol) en 25 ml de acetonitrilo se trató con Boc–anhídrido (1,05 eq, 1,09 g) y una cantidad catalítica de DMAP (punta de espátula). La mezcla se dejó agitar a 60°C durante 3 horas. La mezcla se concentró hasta la mitad de su volumen *al vacío*, luego se diluyó con acetato de etilo (100 ml) y se lavó con solución saturada acuosa de bicarbonato de sodio (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó en una columna Biotage 40—M de gel de sílice (gradiente: 0 hasta 20% acetato de etilo en hexanos) para proporcionar el compuesto **36E** (1,2 g; 93%) como un aceite incoloro. ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 8,91 (1H, s), 8,22

(1H, s), 7,99 (1H, dd, J = 1,22, 8,54 Hz), 7,78 (1H, d, J = 8,54 Hz), 3,97 (3H, s), 1,74 (9H, s).

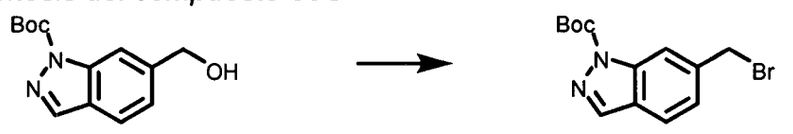
Paso E – Síntesis del compuesto 36F



36E **36F**

Una solución de indazol **36E** (460 mg; 1,66 mmol) en 16 ml de THF anhidro se enfrió hasta – 78°C y se trató con trietilborohidruro de litio (2,5 eq, 4,15 ml de a sol. 1 M en THF). La mezcla de reacción se dejó agitar a –78°C y seguido de TLC (25% acetato de etilo en hexanos). La reacción se completó en aproximadamente 1 h y se desactivó con la incorporación de hidrógeno sulfato de sodio saturado acuoso (3 ml). La mezcla se extrajo con acetato de etilo (100 ml) y se lavó con agua (20 ml) y salmuera (20 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío para proporcionar el producto en bruto como un aceite incoloro. El residuo se cromatografió en una columna de gel de sílice Biotage 40-S (0 hasta 40% acetato de etilo en hexanos) para proporcionar el compuesto **36F** (160 mg; 40%). ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 8,19 (1H, s), 8,13 (1H, s), 7,67 (1H, d, J = 7,93 Hz), 7,30 (1H, d, J = 7,93 Hz), 5,13 (2H, s), 1,71 (9H, s).

Paso F – Síntesis del compuesto 36G



36F **36G**

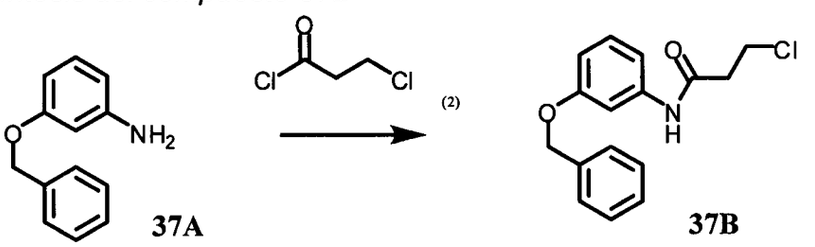
Una solución de alcohol **36F** (160 mg; 0,644 mmol) en cloroformo anhidro (12 ml) se colocó en un baño de agua helada y se trató con piridina (4,0 eq, 0,208 ml, d 0,978) y una solución de bromuro de tionilo (1,2 eq, 0,060 ml, d 2,683) en 1 ml de cloroformo. El baño de agua hielo se eliminó y la mezcla de reacción se dejó agitar a temperatura ambiente durante 30 minutos. La TLC (30% acetato de

etilo en hexanos) mostró aproximadamente 40% de conversión y se agregó más bromuro de tionilo (0,2 eq). La mezcla se calentó hasta 70°C durante 10 minutos. Luego de enfriar la mezcla se diluyó con acetato de etilo (30 ml) y se lavó con bicarbonato de sodio acuoso saturado (5 ml), hidrógeno sulfato de sodio acuoso (5 ml) y salmuera (5 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se purificó en a Columna de gel de sílice Biotage 25—S (gradiente: 0 hasta 40% acetato de etilo en hexanos) para proporcionar el compuesto **36G** (76 mg; 38%) como un aceite incoloro junto con material de partida sin reaccionar (25 mg; 24%). ^{1}H–RMN ($CDCl_3$; 400 MHz): δ 8,23 (1H, s), 8,14 (1H, s), 7,72 (1H, d, J = 8,54 Hz), 7,32 (1H, dd, J = 1,22, 8,54 Hz), 5,21 (1H, d, J = 12,20 Hz), 5,09 (1H, d, J = 12,20 Hz), 1,71 (9H, s).

Ejemplo 37

Preparación del Compuesto Intermediario **37C**

Paso A – Síntesis del compuesto 37B



37A **37B**

El Compuesto **37A** (disponible en el mercado) (10,0 g, 50,25 mmol) se disolvió en agua a temperatura ambiente y a la suspensión resultante se agregó K_2CO_3 (3,8 g, 27,64 mmol). Se agregó 3–Cloro propionilcloruro (7,0 g, 55,28 mmol) gota a gota durante 30 minutos y se dejó agitar durante 2 horas a temperatura ambiente . El precipitado se filtró y se lavó con agua, HCl 1 N, se secó a 50°C al vacío hasta la mañana siguiente para proporcionar 7,2 g del compuesto **37B**.

Paso B – Síntesis del compuesto 37C



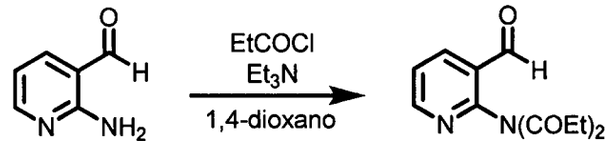
37B 37C

A N,N–Dimetilformamida (3,6 g, 49,66 mmol) a 0 ^{0}C se agregó gota a gota $POCl_3$ (26,6 g, 173,8 mmol) y se dejó agitar durante 60 minutos, durante cuyo tiempo se formó un precipitado blanco. Los 7,2 g del compuesto **37B** se agregaron en porciones en la mezcla de reacción y se dejó agitar durante 24 horas a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo y lentamente se agregó a un vaso de precipitados con hielo, luego de que el hielo se fundió, la fase orgánica se separó y se lavó con NaOH 0,5 N y agua, salmuera, se secó sobre sulfato de sodio, y se concentró al vacío, se purificó usando flash cromatografía, para proporcionar el compuesto **37C** (5,5 g , 34% luego de dos pasos). M.S. experimental: 318,04 $(M+H)^+$.

Ejemplo 38

Preparación del Compuesto Intermediario **38E**

Paso A – Síntesis del compuesto 38B

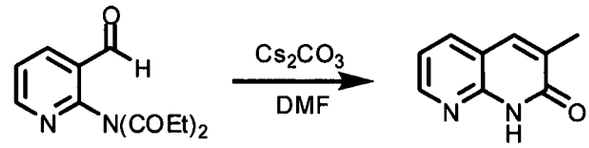


38A **38B**

A una solución de **38A** (7,2 g, 58,8 mmol) en 1,4–dioxano (39 ml) a 0°C se agregó cloruro de propionilo (37,8 ml, 176,5 mmol) y Et_3N (24,6 ml, 176,5 mmol) con agitación. La mezcla de reacción se dejó agitar a temperatura ambiente durante hasta la mañana siguiente. El solvente se eliminó bajo presión reducida, y el residuo resultante se absorbió en EtOAc. La fase orgánica se lavó con agua,

se secó sobre $MgSO_4$, se filtró, y se concentró al vacío para obtener el compuesto **38B**, que se usó sin purificación adicional.

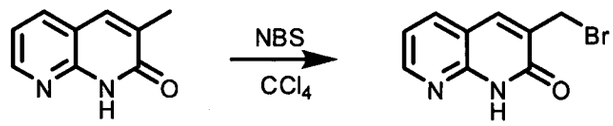
Paso B– Síntesis del compuesto 38C



38B **38C**

A una suspensión de **38B** (residuo en bruto del paso anterior) en DMF (60 ml) se agregó carbonato de cesio (38 g, 117,6 mmol), y la mezcla resultante se calentó a 65°C durante hasta la mañana siguiente. La reacción se enfrió hasta la temperatura ambiente, y el granel de DMF se eliminó bajo presión reducida. Luego se agregó agua al residuo en bruto y la mezcla se filtró. La torta del filtro se lavó con agua y EtOAc. Se recolectaron 5,2 g de **38C** como un sólido amarillo pálido.

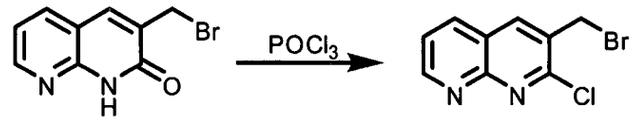
Paso C – Síntesis del compuesto 38D



38C **38D**

A una suspensión de **38C** (0,8 g, 5 mmol) en CCl_4 (25 ml) se agregó NBS (38 g, 117,6 mmol), y peróxido de benzoilo (61 mg, 0,25 mmol), y la mezcla resultante luego se calentó a 90°C durante 4 horas. Se enfrió la reacción hasta la temperatura ambiente, y se agregó 300 ml de CH_2Cl_2. La mezcla se filtró, y el filtrado se secó sobre $MgSO_4$, se filtró, y se concentró al vacío para proporcionar 2 g del compuesto **38D**, que se usó sin purificación adicional.

Paso D – Síntesis del compuesto 38E



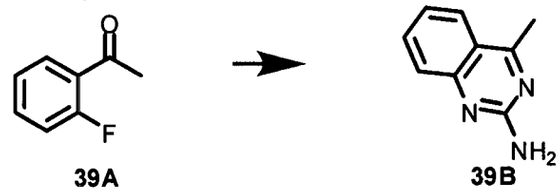
38D **38E**

Se agregó $POCl_3$ a un balón de 100 ml que contenía **38D** en bruto. La suspensión resultante luego se calentó a 88°C durante 4 horas. Se enfrió la reacción hasta la temperatura ambiente, y luego se vertió en un vaso de precipitados de 1 litro que contenía hielo. La solución resultante se neutralizó hasta ph 8 usando solución 6 *N* de NaOH. El sólido que se precipitó a partir de la solución se recolectó para proporcionar 0,82 g de residuo en bruto que se purificó usando cromatografía en columna sobre gel de sílice (ISCO Combi–Flash Rf; gradiente: 5 hasta 50% acetato de etilo en hexanos) para proporcionar 330 mg del compuesto **38E**.

Ejemplo 39

Preparación del Compuesto Intermediario **39D**

Paso A – Síntesis del compuesto 39B

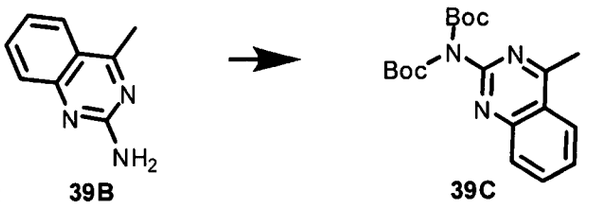


39A **39B**

Una mezcla de orto–fluoroacetofenona (**39A**, 3,45 g; 25 mmol) y carbonato de guanidina (2 eq; 9,0 g) se preparó en 250 ml de N,N–dimetil acetamida, se dejó agitar, y se calentó a 135°C bajo purga de nitrógeno hasta la mañana siguiente. El solvente se eliminó bajo presión reducida y se diluyó con acetato de etilo (600 ml). La solución se lavó con agua (2x100 ml) y salmuera (40 ml). La fase orgánica se separó, se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. El sólido se disolvió en dicloruro de metileno, se cargó sobre gel de sílice y se secó bajo presión reducida. El material se purificó en ISCO (columna de 80 g; 0–70% THF en hexanos). Las fracciones que contenían

producto se recolectaron y se concentró al vacío para proporcionar el producto **39B** como un sólido de color crema (880 mg; 22%)

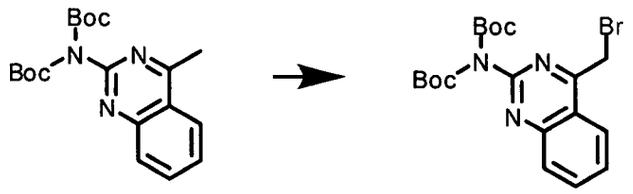
Paso B – Síntesis del compuesto 39C



360-219 **39B** **39C**

Una solución de 4–Metil–quinazolin–2–ilamina **39B** (640 mg; 4,02 mmol) en 10 ml de acetonitrilo anhidro se trató con una solución de Boc–anhídrido (2,5 eq; 2,19 g) en 10,0 ml de acetonitrilo anhidro. La solución resultante se trató con DMAP (0,2 eq; 98,2 mg). La mezcla se dejó agitar hasta la mañana siguiente. La TLC (50% THF en hexanos) mostró una reacción completa. La mezcla se diluyó con acetato de etilo (500 ml) y se lavó con agua (3x30 ml), y Salmuera (40 ml). La fase orgánica se secó sobre sulfato de magnesio, se filtró y se concentró al vacío. El residuo se adsorbió sobre gel de sílice y se purificó sobre un columna ISCO (120 g) (0% a 60% THF en hexanos). Las fracciones con producto se recolectaron y se concentraron al vacío para proporcionar producto **39C** como un sólido blanco - amarillo claro (1,3 g; 90%).

Paso C – Síntesis del compuesto 39D



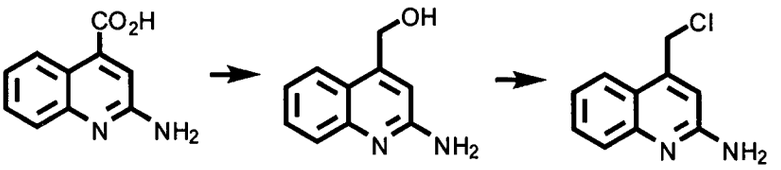
39C **39D**

El intermediario **39C** (1,11 g; 3,09 mmol), N–Bromosuccinimida (1,05 eq; 577 mg), y peróxido de benzoilo (0,1 eq; 75 mg) se combinaron en un balón y se diluyó con tetracloruro de carbono anhidro (31 ml). La reacción se dejó agitar a temperatura ambiente durante 10 minutos y luego se calentó a reflujo hasta la mañana siguiente. La TLC (30% acetato de etilo en hexanos) reveló que la

reacción ha progresado parcialmente. La mezcla de reacción se concentró bajo presión reducida, se diluyó con acetato de etilo (300 ml), y se lavó con bicarbonato de sodio acuoso saturado (40 ml) y salmuera (40 ml), se secó sobre sulfato de magnesio, se filtró, se concentró bajo presión reducida, se diluyó con dicloruro de metileno, se adsorbió sobre gel de sílice, y se purificó sobre ISCO (Columna 25–M; 0–40% acetato de etilo en hexanos). Las fracciones que contenían producto se concentraron bajo presión reducida y produjeron producto como un aceite incoloro en una mezcla 2:1 del compuesto **39D** y material de partida (Total : 440 mg; 33%).

Ejemplo 40

Preparación del Compuesto Intermediario **40C**



40A **40B** **40C**

Los materiales de partida **40A** (2,0 g, 10,6 mmol), hidruro doble de litio y aluminio (2,0 g, 52,7 mmol), y THF (100 ml) se agregaron a un balón de 250 ml. La suspensión resultante se dejó agitar a temperatura ambiente durante 18 horas. La reacción se desactivó con 10 ml de solución saturada de cloruro de amonio seguido de 200 ml de acetato de etilo. Luego de la filtración, la fase orgánica se lavó con salmuera (2x100 ml), se secó sobre sulfato de sodio, y se concentró al vacío para proporcionar **40B** un sólido amarillento (1,05 g, 59%).

Un balón de 250 ml se cargó con **40B** (1,05 g, 6,03 mmol) y cloruro de tionilo (10 ml). La mezcla resultante se dejó agitar a 60°C durante 4 horas antes de enfriarse hasta la temperatura ambiente. Luego de la eliminación del exceso de cloruro de tionilo, el residuo se secó al vacío para proporcionar **40C** como un sólido naranja (1,45 g). Este material en bruto se usó sin purificación adicional.

Ejemplo 41

Ensayo de Inhibición de la Polimerasa NS5B del VHC

Se ha demostrado que un ARN heteropolimérico transcripto in vitro conocido como D–ARN o DCoH es un patrón eficiente para la polimerasa NS5B del VHC (S.–E. Behrens *et al.*, *EMBO J.* 15:12–22 (1996); WO 96/37619). Una versión 75-mer sintetizada químicamente, designada DCoH75, cuya secuencia equivale al extremo terminal 3' del D–ARN, y DCoH75ddC, donde la citidina del extremo terminal 3' DCoH75 está reemplazada por didesoxicitidina, se usaron para evaluar la actividad enzimática de NS5B como se describe en Ferrari *et al.*, *12th International Symposium on VHC and Related Viruses*, P–306 (2005). Se produjo y se purificó una forma enzimática de NS5B soluble de 21 aminoácidos C–terminal (NS5BDeltaCT21) de Escherichia coli como proteína de fusión rotulada con polihistidina 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 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 patrón de ARN, 20 µCi/ml [^{33}P]–CTP, 2% DMSO, y 30 o 150 nM de enzima NS5B. Las reacciones se incubaron a 22°C durante 2 horas, luego se interrumpió agregando 150 mM de EDTA, se lavó en la placa de filtro DE81 en buffer de fosfato di-básico de sodio 0,5M, pH 7,0, y se realizó el recuento usando Packard TopCount luego de la incorporación del coctail de centelleo. Se monitoreó la síntesis de polinucleótido por la incorporación del CTP radio-rotulado. El efecto de los derivados indólicos 2,3 sustituidos sobre la actividad de polimerasa se evaluó agregando varias concentraciones de un derivado indólico 2,3 sustituido, normalmente en 10 diluciones seriales a la mitad, a la mezcla del ensayo. Las concentraciones iniciales de los derivados indólicos osciló desde 200 µM hasta 1 µM. Un valor de IC_{50} para el inhibidor, definido como la concentración de compuesto que provee un 50% de inhibición de actividad de polimerasa, se

determinó adaptando los datos de cpm a la ecuación de Hill Y=100/(1+10^((LogIC50–X)*Inclinación de Hill)), donde X es el logaritmo de concentración de compuesto e Y es el % de inhibición. Ferrari *et al.*, *12th International Symposium on HCV and Related Viruses*, P–306 (2005) describió este procedimiento de ensayo en detalle. Debe observarse que dicho ensayo como se describe es ejemplificativo y no pretende limitar el alcance de la invención. El practicante experimentado puede apreciar que pueden realizarse modificaciones incluyendo sin carácter limitativo patrón de ARN, cebador, nucleótidos, forma de polimerasa NS5B, composición del buffer, para desarrollar análisis similares que generen el mismo resultado para determinar la eficacia de los compuestos y las composiciones descritos en la invención.

Los datos de inhibición de la polimerasa de NS5B para los derivados indólicos 2,3 sustituidos seleccionados de la presente invención se obtuvieron usando el método anterior y los valores calculados de IC_{50} oscilaron desde aproximadamente 0,001 µM hasta aproximadamente 14000 µM.

Ejemplo 42

Ensayo de Replicón de VHC basado en células

Para medir la actividad anti-VHC basada en células de los derivados indólicos 2,3 sustituidos de la presente invención, se sembraron células de replicón a razón de 5000 células/pocillo, en placas Nunc recubiertas por colágeno I de 96 pocillos en presencia del derivado indólico 2,3 sustituido. Se agregaron varias concentraciones de un derivado indólico 2,3 sustituido, normalmente en 10 diluciones seriales a la mitad, a la mezcla de ensayo, donde la concentración inicial del compuesto variaba desde 250 µM hasta 1 µM. La concentración final de DMSO fue del 0,5%, el suero de feto de bovino fue del 5%, en los medios de ensayo. Se cosecharon las células el día 3 con la incorporación de 1x buffer de lisis celular (Cat Ambion #8721). El nivel de ARN del replicón se midió usando

PCR de tiempo real (análisis Taqman). El amplicón se ubicó en 5B. Los cebadores de PCR fueron: 5B,2F, ATGGACAGGCGCCCTGA; 5B,2R, TTGATGGGCAGCTTGGTTTC; la secuencia de la sonda fue CACGCCATGCGCTGCGG rotulada con FAM. Se usó ARN de GAPDH como control endógeno y se amplificó en la misma reacción como NS5B (PCR multiplexada) usando los cebadores y la sonda rotulada con VIC recomendados por el fabricante (PE Applied Biosystem). Las reacciones por PCT-RT en tiempo real se corrieron en un sistema ABI PRISM 7900HT Sequence Detection System usando el siguiente programa: 48°C durante 30 minutos, 95°C durante 10 minutos, 40 ciclos de 95°C durante 15 seg, 60°C durante 1 minuto. Los valores de ΔCT (CT_{5B}–CT_{GAPDH}) se graficaron contra la concentración de compuesto experimental y se adaptaron al modelo sigmoidal de dosis - respuesta usando XLfit4 (MDL). Se definió EC_{50} como la concentración de inhibidor necesaria para lograr $\Delta CT=1$ sobre la línea de base proyectada; EC_{90} la concentración necesaria para lograr $\Delta CT=3,2$ sobre la línea de base. En forma alternativa, para cuantificar la cantidad absoluta de ARN del replicón, se estableció una curva estándar incluyendo transcripciones T7 diluidas serialmente de ARN de replicón en el ensayo Taqman. Todos los reactivos de Taqman fueron de PE Applied Biosystems. Dicho procedimiento de análisis se escribió en detalle en por ej. Malcolm *et al., Antimicrobial Agents and Chemotherapy* 50: 1013–1020 (2006).

Los datos de replicón de VHC para los derivados indólicos 2,3 sustituidos seleccionados de la presente invención se obtuvieron usando el método anterior y los valores calculados de EC_{50} oscilaron desde aproximadamente 1 μM hasta aproximadamente 14000 μM.

Usos de los derivados indólicos 2,3 sustituidos

Los derivados indólicos 2,3 sustituidos son útiles en la medicina humana y veterinaria para tratar o prevenir una infección viral o un trastorno relacionado con

un virus en un paciente. De acuerdo con la invención, los derivados indólicos 2,3 sustituidos pueden administrarse a un paciente que necesite tratamiento o prevención de una infección viral o un trastorno relacionado con un virus.

En consecuencia, en una realización, la invención provee métodos para el tratamiento de una infección viral en un paciente que comprenden administrar al paciente una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico. En otra realización, la invención provee métodos para el tratamiento de un trastorno relacionado con un virus en un paciente que comprenden administrar al paciente una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

Tratamiento o prevención de una infección viral

Los derivados indólicos 2,3 sustituidos pueden usarse para tratar o prevenir una infección viral. En una realización, los derivados indólicos 2,3 sustituidos pueden ser inhibidores de replicación viral. En una realización específica, los derivados indólicos 2,3 sustituidos pueden ser inhibidores de replicación del VHC. En consecuencia, los derivados indólicos 2,3 sustituidos son útiles para el tratamiento de enfermedades virales y trastornos relacionados con la actividad de un virus, tales como polimerasa del VHC.

Ejemplos de infecciones virales que pueden tratarse o prevenirse usando los presentes métodos, incluyen sin carácter limitativo, infección por hepatitis A, infección por hepatitis B y infección por hepatitis C.

En una realización, la infección viral es infección por hepatitis C (VHC).

En una realización, la infección por hepatitis C es hepatitis C aguda. En otra realización, la infección por hepatitis C es hepatitis C crónica.

Las composiciones y combinaciones de la presente invención pueden ser útiles para el tratamiento de un paciente que sufre de una infección relacionada con cualquier genotipo del VHC. Los tipos y sub-tipos de VHC pueden diferir en antigenicidad, nivel de viremia, severidad de la enfermedad producida, y respuesta al tratamiento con interferón como se describe en Holly *et al.*, *Pathology*, 30(2):192–195 (1998). La nomenclatura establecida en Simmonds *et al.*, *J Gen Virol*, 74(Pt11):2391–2399 (1993) se usa ampliamente y clasifica los aislados en seis genotipos principales, 1 hasta 6, con dos o más sub-tipos relacionados, por ej., 1a, 1b. Se han propuesto los genotipos adicionales 7–10 y 11, sin embargo, la base filogenética sobre la cual se basa esta clasificación se ha cuestionado, y de este modo los aislados de tipos 7, 8, 9 y 11 se han re-asignado como tipo 6, y aislados tipo 10 como tipo 3 (ver Lamballerie *et al, J Gen Virol*, 78(Pt1):45–51 (1997)). Los genotipos principales también se han definido como poseedores de similitudes de secuencia de entre 55 y 72% (promedio 64,5%), y los sub-tipos dentro de los tipos como poseedores de una similitud del 75%–86% (promedio 80%) cuando se realizaba la secuencia 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 un virus

Los derivados indólicos 2,3 sustituidos pueden usarse para tratar o prevenir un trastorno relacionado con un virus. En consecuencia, los derivados indólicos 2,3 sustituidos son útiles para el tratamiento de trastornos relacionados con la actividad de un virus, tales como cirrosis o inflamación hepática. Los trastornos relacionados con un virus incluyen, sin carácter limitativo, trastornos relacionados con la polimerasa que depende del ARN y trastornos relacionados con infección por VHC.

Tratamiento o prevención de un trastorno relacionado con la polimerasa que depende del ARN

Los derivados indólicos 2,3 sustituidos son útiles para tratar o prevenir un trastorno relacionado con la polimerasa que depende del ARN (RdRp) en un paciente. Dichos trastornos incluyen infecciones virales en los cuales el virus inefectivo contiene una enzima RdRp.

En consecuencia, en una realización, la presente invención provee un método para el tratamiento de un trastorno relacionado con la polimerasa que depende del ARN en un paciente, que comprenden administrar al paciente una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

Tratamiento o prevención de un trastorno relacionado con infección por VHC

Los derivados indólicos 2,3 sustituidos también pueden ser útiles para tratar o prevenir un trastorno relacionado con una infección por VHC. Ejemplos de dichos trastornos incluyen, sin carácter limitativo, cirrosis, hipertensión portal, ascitis, dolor de huesos, várices, ictericia, encefalopatía hepática, tiroiditis, porfiria cutánea tardía, crioglobulinemia, glomerulonefritos, síndrome seco, trombocitopenia, líquenes planos y diabetes mellitus.

En consecuencia, en una realización, la invención provee métodos para el tratamiento de un trastorno relacionado con el VHC en un paciente, en los cuales el método comprende administrar al paciente a cantidad efectiva para fines terapéuticos de por lo menos un derivado indólico 2,3 sustituido, o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

Tratamiento combinado

En otra realización, los presentes métodos para tratar o prevenir una infección viral pueden comprender en forma adicional la administración de uno o

más agentes terapéuticos adicionales que no son derivados indólicos 2,3 sustituidos.

En una realización, el agente terapéutico adicional es un agente antiviral.

En otra realización, el agente terapéutico adicional es un agente inmunomodulador tal como un agente inmunosupresor.

En consecuencia, en una realización, la presente invención provee métodos para el tratamiento de una infección viral en un paciente, el método comprende administrar al paciente: (i) por lo menos un derivado indólico 2,3 sustituido, o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico, y (ii) por lo menos un agente antiviral distinto que es distinto de un derivado indólico 2,3 sustituido, en los cuales las cantidades administradas son efectivas juntas para tratar o prevenir una infección viral.

Cuando se administra un tratamiento combinado de la invención a un paciente, el agente terapéutico en la combinación o una composición o composiciones farmacéuticas que comprenden los agentes terapéuticos, pueden administrarse en cualquier orden tal como, por ejemplo, en forma secuencial, concurrente, juntos, simultáneamente y similares. Las cantidades de los arios activos en dicha terapia combinada (diferentes cantidades de dosificación) o las mismas cantidades (las mismas cantidades de dosificación). De este modo, para fines ilustrativos no limitativos, un derivado indólico 2,3 sustituido y un agente terapéutico adicional pueden estar presentes en cantidades fijas (cantidades posológicas) en una unidad de dosificación individual (por ej., una cápsula, un comprimido y similares). Un ejemplo comercial de dicha unidad de dosificación que contiene cantidades fijas de dos compuestos activos diferentes es VYTORIN® (provisto por Merck Schering–Plough Pharmaceuticals, Kenilworth, New Jersey).

En una realización, el por lo menos un derivado indólico 2,3 se administra durante un tiempo en el cual el(los) agente(s) antiviral(es) ejercen su efecto profiláctico o terapéutico, o *viceversa.*

En otra realización, el por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) se administran en dosis comúnmente empleadas cuando dichos agentes se usan como monoterapia para el tratamiento de una infección viral.

En otra realización, el por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) se administran en dosis más bajas que las dosis comúnmente empleadas cuando dichos agentes se usan como monoterapia para el tratamiento de una infección viral.

Incluso en otra realización, el por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) actúan en forma sinergística y se administran en dosis más bajas que las dosis comúnmente empleadas cuando dichos agentes se usan como monoterapia para el tratamiento de una infección viral.

En una realización, el por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) están presentes en la misma composición. En una realización, esta composición es apropiada para administración oral. En otra realización, esta composición es apropiada para administración endovenosa.

Infecciones virales y los trastornos relacionados con un virus que pueden tratarse o prevenirse usando los métodos de tratamiento combinado de la presente invención incluyen, sin carácter limitativo, aquellos mencionados con anterioridad.

En una realización, la infección viral es infección por VHC.

El por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) pueden actuar en forma adicional o sinergística. Una combinación sinérgica puede permitir el uso de dosificaciones más bajas de uno o más agentes y/o la administración menos frecuente de uno o más agentes de un tratamiento combinado. Una dosificación más baja o la administración menos frecuente de uno o más agentes pueden reducir la toxicidad del tratamiento sin reducir la eficacia del mismo.

En una realización, la administración de por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es) puede inhibir la resistencia de una infección viral a estos agentes.

Ejemplos no limitativos de otros agentes terapéuticos útiles en las presentes composiciones y métodos incluyen un inhibidor de polimerasa de VHC, un interferón, un nucleósido, un inhibidor de la replicación viral, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ADN.

En una realización, el otro agente antiviral es un inhibidor de proteasa viral.

En otra realización, el otro agente antiviral es un inhibidor de la proteasa del VHC.

En otra realización, el otro agente antiviral es un interferón.

Incluso en otra realización, el otro agente antiviral es un inhibidor de la replicación viral.

En una realización, el otro agente antiviral es un inhibidor de la replicación viral, el cual es un inhibidor de replicasa del VHC.

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 de viriones.

En otra realización, el otro agente antiviral es terapia con anticuerpos.

En otra realización, los otros agentes antivirales comprenden un inhibidor de proteasa y un inhibidor de polimerasa.

Incluso en otra realización, los otros agentes antivirales comprenden un inhibidor de proteasa y un agente inmunosupresor.

Además en 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 polimerasa del VHC útiles en los presentes métodos y composiciones incluyen, sin carácter limitativo VP–19744 (Wyet/ViroPharma), VHC–796 (Wyet/ViroPharma), NM–283 (Idenix/Novartis), R–1626 (Roche), MK–0608 (Merck), A848837 (Abbott), GSK–71185 (Glaxo SmithKline), XTL–2125 (XTL Biopharmaceuticals), y aquellos descritos 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 presentes métodos y composiciones incluyen, sin carácter limitativo, interferón alfa–2a, interferón alfa–2b, interferón alfacon–1 y conjugados PEG-interferón alfa. "Conjugados PEG-interferón alfa" son moléculas de interferón unidas en forma covalente a una molécula de PEG. Los conjugados PEG-interferón alfa ilustrativos incluyen interferón alfa–2a (Roferon™, Hoffman La–Roche, Nutley, New Jersey) en forma de interferón alfa–2a pegilado (*por ej.*, como el que se comercializa con el nombre comercial Pegasys™), interferón alfa–

2b (Intron™, de Schering–Plough Corporation) en forma de interferón alfa–2b pegilado (*por ej.*, como el que se comercializa con el nombre comercial PEG–Intron™), interferón alfa–2c (Berofor Alfa™, Boehringer Ingelheim, Ingelheim, Germany), polipéptidos de fusión de interferón alfa, o interferón de consenso como lo define la determinación de una secuencia de consenso de interferones alfa naturales (Infergen™, Amgen, Thousy Oaks, California).

Los agentes de terapia con anticuerpos útiles en los presentes métodos y composiciones incluyen, sin carácter limitativo, anticuerpos específicos para IL–10 (tales como aquellos descritos en la Publicación de Patente de Estados Unidos No. US2005/0101770, 12G8 humanizado, un anticuerpo monoclonal humanizado contra IL–10 humano, plásmidos que contienen los ácidos nucleicos que codifican las cadenas liviana y pesada de 12G8 humanizado se depositaron en la American Type Culture Collection (ATCC) como números de depósito PTA–5923 y PTA–5922, respectivamente), y similares). Los inhibidores de proteasa viral útiles en los presentes métodos y composiciones incluyen, sin carácter limitativo, inhibidores de serina proteasa NS3 (incluyendo, sin carácter limitativo, aquellos descritos en Patentes de EE UU 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 Patentes de EE UU Nos. US20020160962, US20050176648 y US20050249702), inhibidores de proteasa del 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.

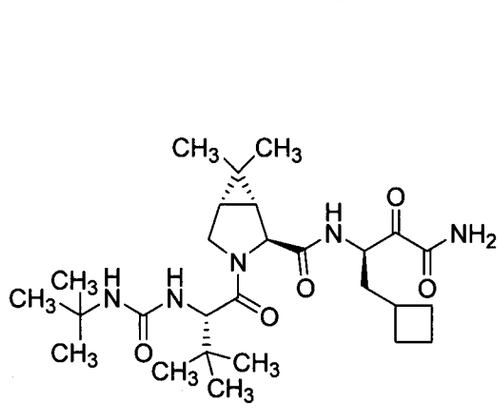
Los inhibidores de replicación viral útiles en los presentes métodos y composiciones incluyen, sin carácter limitativo, inhibidores de replicasa de VHC, inhibidores de helicasa de NS3, inhibidores de NS5A, ribavirina, viramidina, A–831 (Arrow Therapeutics); un agente antisentido o una vacuna terapéutica.

En una realización, los inhibidores de replicación viral útiles en los presentes métodos y composiciones incluyen, sin carácter limitativo, inhibidores de helicasa de NS3 o inhibidores de NS5A.

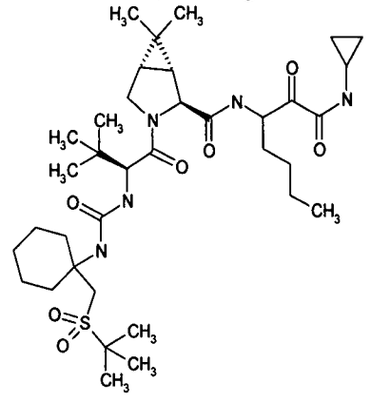
Ejemplos de inhibidores de proteasa útiles en los presentes métodos incluyen, sin carácter limitativo, un inhibidor de la proteasa del VHC y un inhibidor de serina proteasa NS–3.

Ejemplos de inhibidores de proteasa del VHC útiles en los presentes métodos incluyen, sin carácter limitativo, aquellos descritos 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); Publicación de Patentes de EE UU Nos. US2005/0249702 y US 2007/0274951; y Publicaciones Internacionales Nos. WO 98/14181; WO 98/17679, WO 98/17679, WO 98/22496 y WO 99/07734 y WO 05/087731.

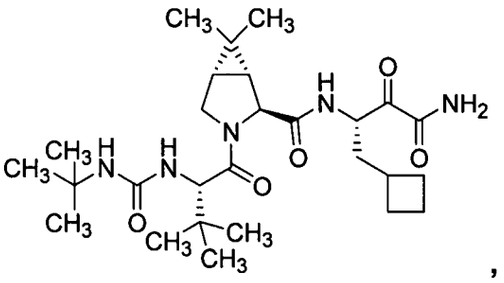
Ejemplos adicionales de inhibidores de proteasa de VHC útiles en los presentes métodos incluyen, sin carácter limitativo, los siguientes compuestos:



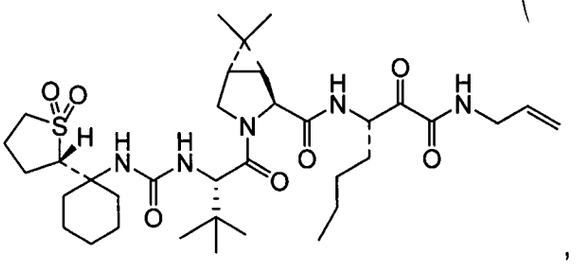
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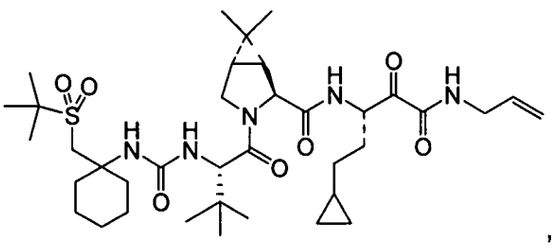
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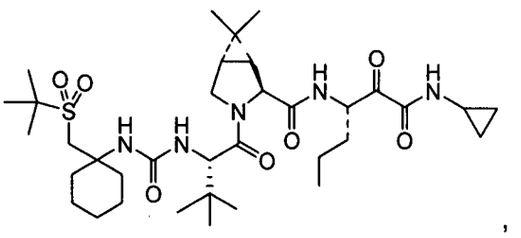
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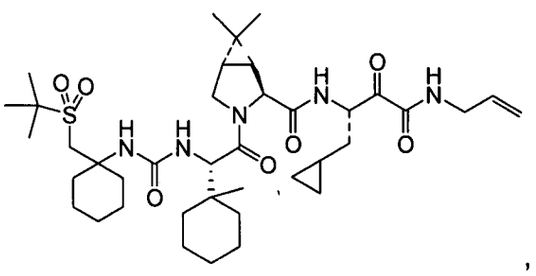
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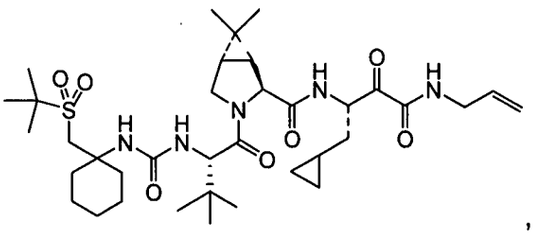
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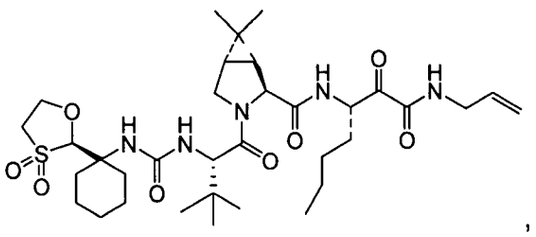
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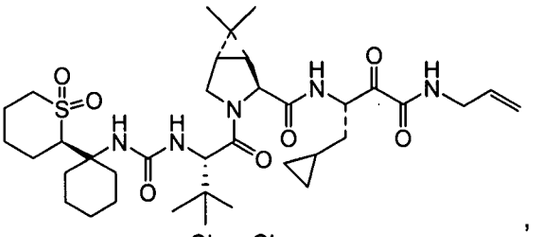
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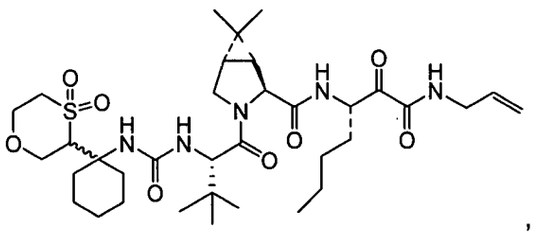
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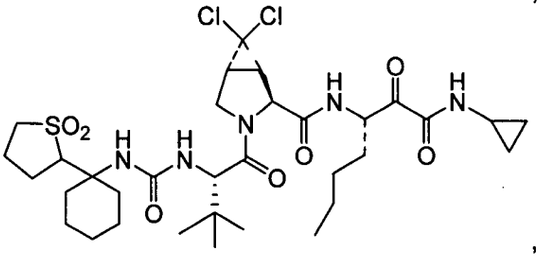
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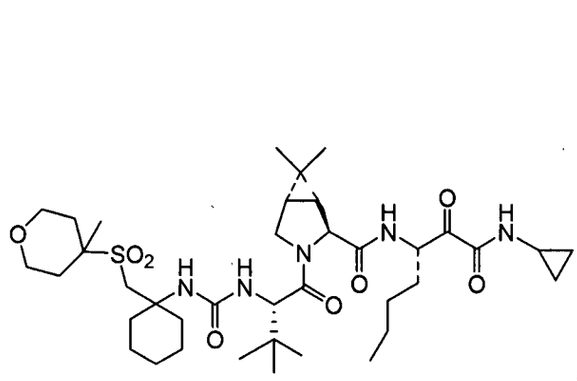
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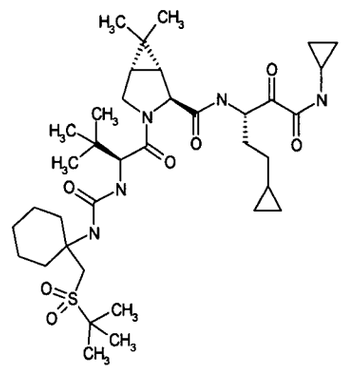
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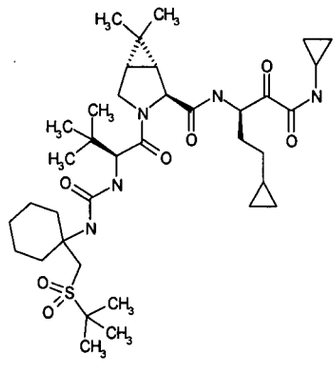
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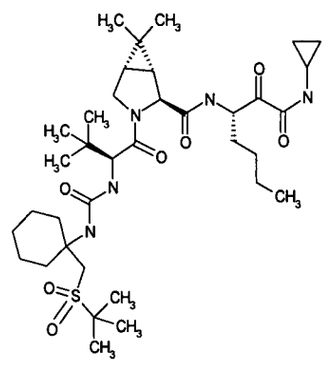
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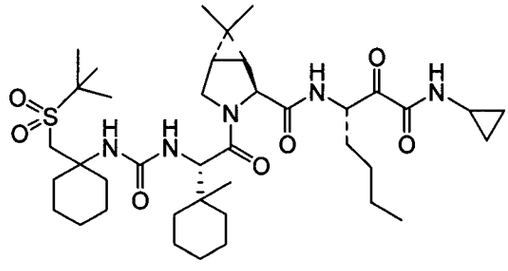
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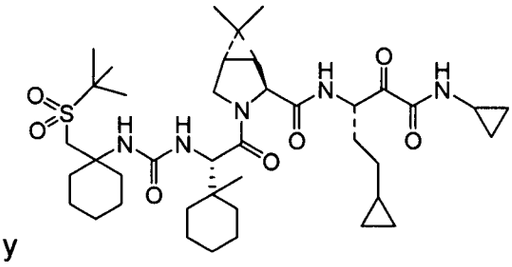
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Ejemplos adicionales de otros agentes terapéuticos útiles en los presentes métodos incluyen, sin carácter limitativo, Levovirin™ (ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (Ribozyme Pharmaceuticals, Boulder, Colorado), VX–950™ (Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (SciClone

Pharmaceuticals, San Mateo, California), Maxamina™ (Maxim Pharmaceuticals, San Diego, California), NKB–122 (JenKen Bioscience Inc., North Carolina), micofenolato mofetil (Hoffman–LaRoche, Nutley, New Jersey).

Las dosis y regímenes de dosificación de los otros agentes usados en los tratamientos combinados de la presente invención para el tratamiento o prevención de una infección viral pueden determinarlos el médico que realiza el tratamiento, teniendo en consideración las dosis aprobadas y el régimen de dosificación que aparece en el prospecto del envase; la edad, el sexo, y la salud general del paciente; y el tipo y la severidad de la infección viral o enfermedad o trastorno relacionado. Cuando se administra en forma combinada, el(los) derivado(s) indólico(s) 2,3 sustituido(s) y el(los) otro(s) agente(s) para el tratamiento de las enfermedades o afecciones enumeradas anteriormente pueden administrarse en forma simultánea (*es decir,* en la misma composición o en composiciones separadas, una después de la otra) o en forma consecutiva. Esto resulta particularmente útil cuando los componentes de la combinación se administran en diferentes cronogramas de administración, *por ej.*, un principio se administra una vez por día y el otro cada seis horas, o cuando las composiciones preferidas son diferentes, *por ej.* una es un comprimido y la otra una cápsula. Por lo tanto es ventajoso un kit que comprende las formas de dosificación separadas.

En general, una dosificación diaria total del por lo menos un derivado indólico 2,3 sustituido y el(los) agente(s) antiviral(es) adicional(es), cuando se administran en el tratamiento combinado, pueden oscilar desde aproximadamente 0,1 hasta aproximadamente 2000 mg por día, aunque necesariamente ocurrirán variaciones dependiendo del blanco del tratamiento, el paciente y la vía de administración. En una realización, la dosificación es desde aproximadamente 10 hasta aproximadamente 500 mg/día, administrados en una dosis única o en 2-4 dosis divididas. En otra realización, la dosificación es desde aproximadamente 1

hasta aproximadamente 200 mg/día, administrados en una dosis única o en 2-4 dosis divididas. Incluso en otra realización, la dosificación es desde aproximadamente 1 hasta aproximadamente 100 mg/día, administrados en una dosis única o en 2-4 dosis divididas. Además en otra realización, la dosificación es desde aproximadamente 1 hasta aproximadamente 50 mg/día, administrados en una dosis única o en 2-4 dosis divididas. En una realización adicional, la dosificación es desde aproximadamente 1 hasta aproximadamente 20 mg/día, administrados en una dosis única o en 2-4 dosis divididas. En otra realización, la dosificación es desde aproximadamente 500 hasta aproximadamente 1500 mg/día, administrados en una dosis única o en 2-4 dosis divididas. Incluso en otra realización, la dosificación es desde aproximadamente 500 hasta aproximadamente 1000 mg/día, administrados en una dosis única o en 2-4 dosis divididas. Además en otra realización, la dosificación es desde aproximadamente 100 hasta aproximadamente 500 mg/día, administrados en una dosis única o en 2-4 dosis divididas.

En una realización, cuando el otro agente terapéutico es INTRON–A interferón alfa 2b (provisto al mercado por Schering–Plough Corp.), este agente se administra por inyección subcutánea a 3MIU(12 mcg)/0,5 ml/TIW es durante 24 semanas o 48 semanas para el primer tratamiento.

En otra realización, cuando el otro agente terapéutico es PEG–INTRON interferón alfa 2b pegilado (provisto al mercado por Schering–Plough Corp.), este agente se administra por inyección subcutánea a 1,5 mcg/kg/semana, dentro de un rango de 40 hasta 150 mcg/semana, durante por lo menos 24 semanas.

En otra realización, cuando el otro agente terapéutico es ROFERON A inteferón alfa 2a (provisto al mercado por Hoffmann–La Roche), este agente se administra por inyección subcutánea o intramuscular a 3MIU(11,1 mcg/ml)/TIW

durante por lo menos 48 a 52 semanas, o alternativamente 6MIU/TIW durante 12 semanas seguido de 3MIU/TIW durante 36 semanas.

Incluso en otra realización, cuando el otro agente terapéutico es PEGASUS interferón alfa 2a pegilado (provisto al mercado por Hoffmann–La Roche), este agente se administra por inyección subcutánea a 180mcg/1ml o 180mcg/0,5ml, once a semana durante por lo menos 24 semanas.

Además en otra realización, cuando el otro agente terapéutico es INFERGEN interferón alfacon–1 (provisto al mercado por Amgen), este agente se administra por inyección subcutánea a 9mcg/TIW es 24 semanas durante para el primer tratamiento y hasta 15 mcg/TIW durante 24 semanas para tratamiento sin respuesta o recaída.

En una realización adicional, cuando el otro agente terapéutico es Ribavirina (disponible en el mercado como ribavirina REBETOL de Schering–Plough o ribavirina COPEGUS de Hoffmann–La Roche), este agente se administra a una dosis diaria de desde aproximadamente 600 hasta aproximadamente 1400 mg/día durante por lo menos 24 semanas.

En una realización, uno o más compuestos de la presente invención se administran con uno o más agentes terapéuticos adicionales seleccionados de un inhibidor de la proteasa del VHC, un inhibidor de replicasa del VHC, un nucleósido, un interferón, un interferón pegilado y ribavirina. Los tratamientos combinados pueden incluir cualquier combinación de estos agentes terapéuticos adicionales.

En otra realización, uno o más compuestos de la presente invención se administran con un agente terapéutico adicional seleccionado de un inhibidor de la proteasa del VHC, un inhibidor de replicasa del VHC, un nucleósido, un interferón, un interferón pegilado y ribavirina.

En otra realización, uno o más compuestos de la presente invención se administran con dos agentes terapéuticos adicionales seleccionados de un inhibidor de la proteasa del VHC, un inhibidor de replicasa del VHC, un nucleósido, un interferón, un interferón pegilado y ribavirina.

Incluso en otra realización, uno o más compuestos de la presente invención se administran con dos agentes terapéuticos adicionales seleccionados de un inhibidor de la proteasa del VHC, un inhibidor de replicasa del VHC, un nucleósido, un interferón, un interferón pegilado y ribavirina. En una realización específica, uno o más compuestos de la presente invención se administran con un inhibidor de la proteasa del VHC y ribavirina. En otra realización específica, uno o más compuestos de la presente invención se administran con un interferón pegilado y ribavirina.

En otra realización, uno o más compuestos de la presente invención se administran con tres agentes terapéuticos adicionales seleccionados de un inhibidor de la proteasa del VHC, un inhibidor de replicasa del VHC, un nucleósido, un interferón, un interferón pegilado y ribavirina.

En una realización, uno o más compuestos de la presente invención se administran con uno o más agentes terapéuticos adicionales seleccionados de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, y un inhibidor de la replicación viral. En otra realización, uno o más compuestos de la presente invención se administran con uno o más agentes terapéuticos adicionales seleccionados de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, y ribavirina. En una realización, un compuesto de la presente invención se administra con un agente terapéutico adicional seleccionado de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, y un inhibidor de la replicación viral. En otra realización, un compuesto de la presente invención se

administra con dos agentes terapéuticos adicionales seleccionados de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, y un inhibidor de la replicación viral. En otra realización, un compuesto de la presente invención se administra con ribavirina. Incluso en otra realización, un compuesto de la presente invención se administra con ribavirina y otro agente terapéutico. Incluso en otra realización, un compuesto de la presente invención se administra con ribavirina y otro agente terapéutico, en los cuales el otro agente terapéutico se selecciona de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, y un inhibidor de la replicación viral.

Composiciones y Administración

Debido a su actividad, los derivados indólicos 2,3 sustituidos son útiles en la medicina humana y veterinaria. Como se describió con anterioridad, los derivados indólicos 2,3 sustituidos son útiles para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente que lo necesita.

Cuando se administra a un paciente, los IDs pueden administrarse como componente de una composición que comprende un vehículo aceptable desde el punto de vista farmacéutico o portador. La presente invención provee composiciones farmacéuticas que comprenden una cantidad efectiva de por lo menos un derivado indólico 2,3 sustituido y un vehículo aceptable desde el punto de vista farmacéutico. En las composiciones farmacéuticas y métodos de la presente invención, los principios activos se administrarán normalmente en una mezcla con materiales vehículo apropiados seleccionados con respecto a la forma pretendida de administración, es decir comprimidos orales, cápsulas (ya sea con relleno sólido, relleno semi sólido o relleno líquido), polvos para constitución, geles orales, elixires, gránulos dispersables, jarabes, suspensiones, y similares, y consistente con las prácticas farmacéuticas convencionales. Por ejemplo, para administración oral en forma de comprimidos o cápsulas, el principio

farmacológico activo puede combinarse con un vehículo inerte, oral, no tóxico aceptable desde el punto de vista farmacéutico, tales como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato de dicalcio, sulfato de calcio, talco, manitol, alcohol etílico (formas líquidas) y similares. Las preparaciones de forma sólida incluyen polvos, comprimidos, gránulos dispersables, cápsulas, cachés y supositorios. Los polvos y comprimidos pueden estar formados por desde aproximadamente 5 hasta aproximadamente 95 por ciento de la composición de la invención. Los comprimidos, polvos, cachés y cápsulas pueden usarse como formas de dosificación sólida apropiadas para administración oral.

Más aun, cuando se desee o se necesite, pueden incorporarse en la mezcla también aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes apropiados. Los aglutinantes apropiados incluyen almidón, gelatina, azúcares naturales, edulcorantes a base de maíz, gomas naturales y sintéticas tales como acacia, alginato de sodio, carboximetilcelulosa, polietilen glicol y ceras. Entre los lubricantes pueden mencionarse para usar en estas formas de dosificación ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegradores incluyen almidón, metilcelulosa, goma guar y similares. Los agentes edulcorantes y saborizantes y conservantes también pueden incluirse cuando resulte apropiado.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones y pueden incluir agua o soluciones de agua–propilenglicol para inyección parenteral.

Las preparaciones de forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden encontrarse en combinación

con un vehículo aceptable desde el punto de vista farmacéutico, tales como un gas comprimido inerte.

También se incluyen preparaciones de forma sólida que pretenden convertirse, inmediatamente antes de usar, en preparaciones de forma líquida ya sea para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Para preparar supositorios, primero se funde una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácido graso o manteca de cacao, y se dispersa el principio activo en forma homogénea por ejemplo por agitación. La mezcla homogénea fundida luego se vierte en moldes de tamaño conveniente, se deja enfriar y por consiguiente solidificar.

Los derivados indólicos 2,3 sustituidos de la presente invención también pueden administrarse por vía transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o reservorio que son convencionales en el arte para este fin.

Adicionalmente, las composiciones de la presente invención pueden formularse en forma de liberación prolongada para brindar la velocidad de liberación controlada de uno o más de los componentes o principios activos para optimizar los efectos terapéuticos, es decir actividad anti-inflamatoria y similares. Las formas de dosificación apropiadas para liberación prolongada incluyen comprimidos estratificados de índices variables de desintegración o matrices poliméricas de liberación controlada impregnadas con los principios activos y con forma de comprimido o cápsula que contiene dichas matrices poliméricas porosas impregnadas o encapsuladas.

En una realización, el o los derivados indólicos 2,3 sustituidos se administran por vía oral.

En otra realización, el o los derivados indólicos 2,3 sustituidos se administran por vía endovenosa.

En otra realización, el o los derivados indólicos 2,3 sustituidos se administran en forma tópica.

Incluso en otra realización, el o los derivados indólicos 2,3 sustituidos se administran por vía sublingual.

En una realización, una preparación farmacéutica que comprende por lo menos un derivado indólico 2,3 sustituido está en forma de dosificación unitaria. En dicha forma, la preparación se subdivide en dosis unitarias que contienen las cantidades apropiadas del principio activo, por ej., una cantidad efectiva para lograr el efecto deseado.

Las composiciones pueden prepararse de acuerdo con métodos convencionales de mezclado, granulación y recubrimiento, respectivamente, y las presentes composiciones pueden contener, en una realización, desde aproximadamente 0,1% hasta aproximadamente 99% del derivado indólico 2,3 sustituido(s) en peso o volumen. En varias realizaciones, las presentes composiciones pueden contener, en una realización, desde aproximadamente 1% hasta aproximadamente 70% o desde aproximadamente 5% hasta aproximadamente 60% del derivado indólico 2,3 sustituido(s) en peso o volumen.

La cantidad de derivado indólico 2,3 sustituido en una dosis unitaria de preparación puede variarse o ajustarse desde aproximadamente 0,1 mg hasta aproximadamente 2000 mg. En varias realizaciones, la cantidad es desde aproximadamente 1 mg hasta aproximadamente 2000 mg, 100 mg hasta aproximadamente 200 mg, 500 mg hasta aproximadamente 2000 mg, 100 mg hasta aproximadamente 1000 mg, y 1 mg hasta aproximadamente 500 mg.

Por conveniencia, la dosificación diaria total puede dividirse y administrarse en porciones durante el día si se desea. En una realización, la dosificación diaria

se administra en una porción. En otra realización, la dosificación diaria total se administra en dos dosis divididas durante un período de 24 horas. En otra realización, la dosificación diaria total se administra en tres dosis divididas durante un período de 24 horas. Incluso en otra realización, la dosificación diaria total se administra en cuatro dosis divididas durante un período de 24 horas.

La cantidad y la frecuencia de administración de los derivados indólicos 2,3 sustituidos se regularán de acuerdo con el criterio del médico a cargo del tratamiento considerando factores tales como la edad, la condición y el tamaño del paciente como también la severidad de los síntomas sometidos a tratamiento. Generalmente, una dosificación total de los derivados indólicos 2,3 sustituidos varía desde aproximadamente 0,1 hasta aproximadamente 2000 mg por día, aunque necesariamente ocurrirán variaciones dependiendo del blanco del tratamiento, el paciente y la vía de administración. En una realización, la dosificación es desde aproximadamente 1 hasta aproximadamente 200 mg/día, administrados en una dosis única o en 2-4 dosis divididas. En otra realización, la dosificación es desde aproximadamente 10 hasta aproximadamente 2000 mg/día, administrados en una dosis única o en 2-4 dosis divididas. En otra realización, la dosificación es desde aproximadamente 100 hasta aproximadamente 2000 mg/día, administrados en una dosis única o en 2-4 dosis divididas. Incluso en otra realización, la dosificación es desde aproximadamente 500 hasta aproximadamente 2000 mg/día, administrados en una dosis única o en 2-4 dosis divididas.

Las composiciones de la invención pueden comprender en forma adicional uno o más agentes terapéuticos adicionales, seleccionados de aquellos mencionados aquí con anterioridad. En consecuencia, en una realización, la presente invención provee composiciones que comprenden: (i) por lo menos un derivado indólico 2,3 sustituido o una de sus sales, solvatos, ésteres o prodrogas

aceptables desde el punto de vista farmacéutico; (ii) uno o más agentes terapéuticos adicionales que no son un derivado indólico 2,3 sustituido; y (iii) un vehículo aceptable desde el punto de vista farmacéutico, en los cuales las cantidades presentes en la composición son juntas efectivas para tratar una infección viral o un trastorno relacionado con un virus.

Kits

En un aspecto, la presente invención provee un kit que comprende una cantidad efectiva para fines terapéuticos de por lo menos un derivado indólico 2,3 sustituido, o una de las sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico de dicho compuesto y un vehículo, portador o diluyente aceptables desde el punto de vista farmacéutico.

En otro aspecto la presente invención provee un kit que comprende una cantidad de por lo menos un derivado indólico 2,3 sustituido, o una de las sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico de dicho compuesto y una cantidad de por lo menos un agente terapéutico adicional enumerado anteriormente, en los cuales las cantidades de los dos o más principios producen un efecto terapéutico deseado.

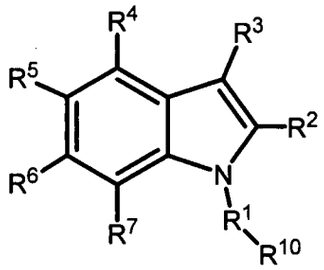
La presente invención es no queda limitada por las realizaciones específicas mencionadas en los ejemplos que pretenden ser ilustrativos de algunos aspectos solamente de la invención y cualquier realización que sea funcionalmente equivalente se encuentra dentro del alcance de esta invención. Por cierto, varias modificaciones de la invención además de aquellas que se muestran y se describen aquí resultarán obvias para los expertos en el arte y pretenden caer dentro del alcance de las reivindicaciones anexas.

Aquí se ha citado una cantidad de referencias, cuyas revelaciones completas se incorporan a la presente a modo de referencia.

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un compuesto que tiene la fórmula:



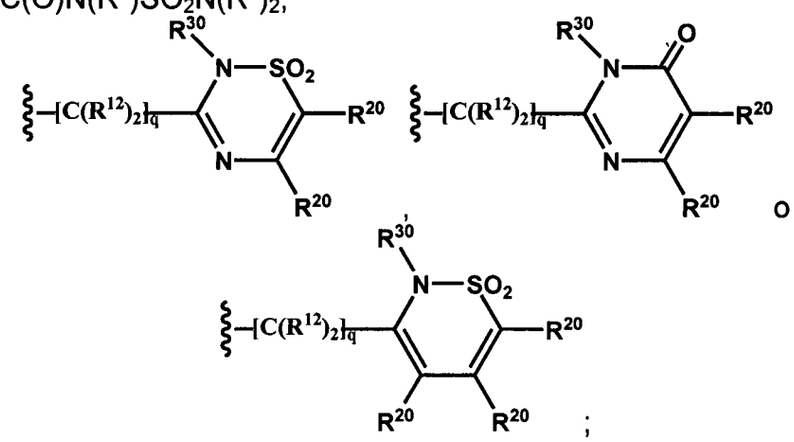
(I)

o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico,

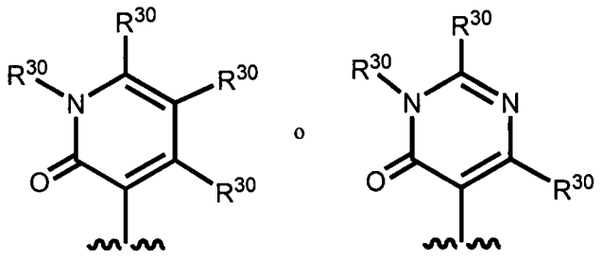
en los cuales:

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 $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$,



R^3 es:



;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, 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 vez que ocurre R^8 es en forma independiente 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 vez que ocurre R^9 es en forma independiente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q-O-$alquilo, $-[C(R^{12})_2]_q-N(alquil)_2$, $-[C(R^{12})_2]_q-$arilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$cicloalquenilo, $-[C(R^{12})_2]_q-$heterocicloalquilo, $-[C(R^{12})_2]_q-$heterocicloalquenilo, $-[C(R^{12})_2]_q-$heteroarilo, haloalquilo o hidroxialquilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 vez que ocurre R^{12} es en forma independiente H, halo, –$N(R^9)_2$, –OR^9, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan en forma independiente de alquilo, halo, haloalquilo, hidroxialquilo, –OH, –CN, –C(O)alquilo, –C(O)Oalquilo, –C(O)NH–alquilo, –C(O)N(alquil)$_2$, –O–alquilo, –NH_2, –NH(alquilo), –N(alquil)$_2$, –NHC(O)alquilo, –$NHSO_2$alquilo, –SO_2alquilo o –SO_2NH–alquilo, o dos grupos

R_{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

cada vez que ocurre R^{20} es en forma independiente alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los cuales 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, que se seleccionan 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 vez que ocurre R^{30} es en forma independiente 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 cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

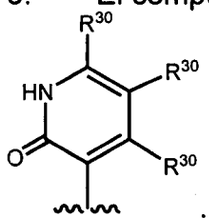
cada vez que ocurre p es en forma independiente 0, 1 o 2;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4; y

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4.

2. El compuesto de la reivindicación 1, en el cual R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en los cuales R^9 es H, alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

3. El compuesto de la reivindicación 2, en el cual R^3 es :



4. El compuesto de la reivindicación 2, en el cual R^1 es $-[C(R^{12})_2]_r-$.

5. El compuesto de la reivindicación 4, en el cual R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o

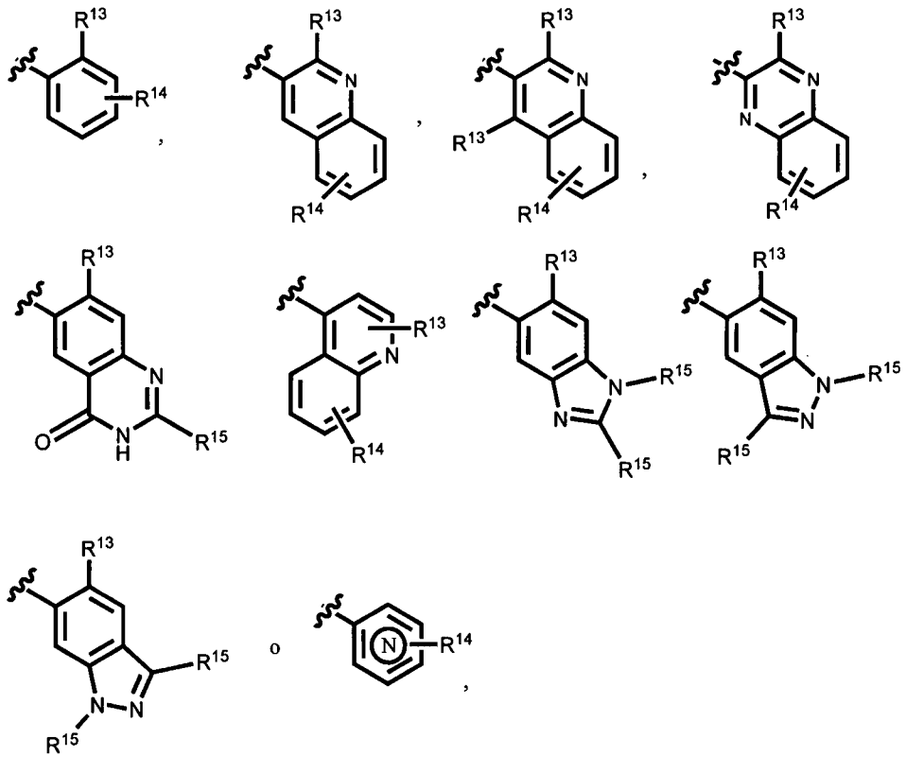


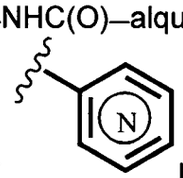
6. El compuesto de la reivindicación 5, en el cual R^1 es $-CH_2-$.

7. El compuesto de la reivindicación 2, en el cual R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o –OH; R^5 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN; y R^6 es H, alquilo, –O–alquilo, –O–haloalquilo, cicloalquilo, halo, haloalquilo, –OH, hidroxialquilo, $-NH_2$ o –CN.

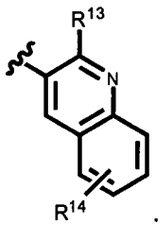
8. El compuesto de la reivindicación 2, en el cual R^{10} es arilo o heteroarilo.

9. El compuesto de la reivindicación 8, en el cual R^{10} es:

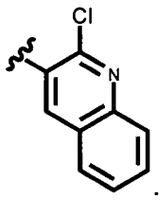


en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

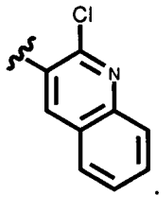
10. El compuesto de la reivindicación 9, en el cual R^{10} es:



11. El compuesto de la reivindicación 10, en el cual R^{10} es:



12. El compuesto de la reivindicación 6, en el cual R^{10} es:



13. El compuesto de la reivindicación 9, en el cual R^1 es -CH_2—, —CH_2CH_2—, —CH(CH_3)— o

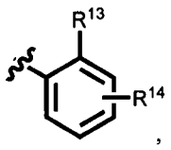
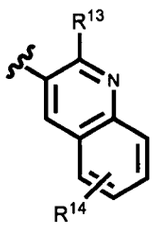
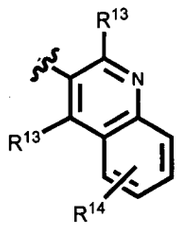
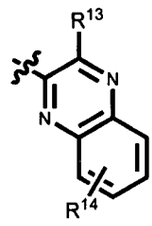
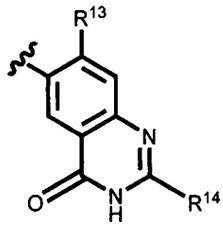
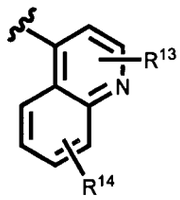
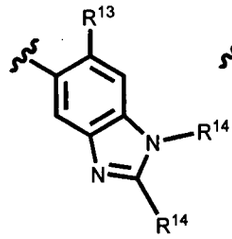
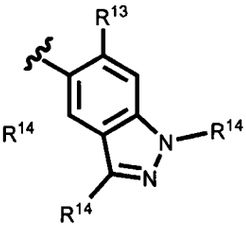
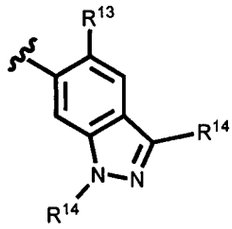
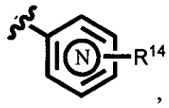


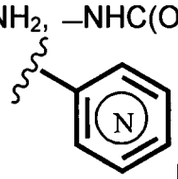
14. El compuesto de la reivindicación 13, en el cual R^1 es -CH_2—.

15. El compuesto de la reivindicación 9, en el cual R^4 y R^7 son cada uno en forma independiente H, alquilo, halo o —OH, R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o —CN, y R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o —CN.

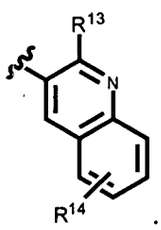
16. El compuesto de la reivindicación 15, en el cual R^{10} es arilo o heteroarilo.

17. El compuesto de la reivindicación 16, en el cual R^{10} es:

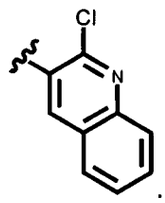

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o

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en los cuales R^{13} es H, F, Br o Cl; R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo; y  representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

18. El compuesto de la reivindicación 17, en el cual R^{10} es:


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19. El compuesto de la reivindicación 18, en el cual R^{10} es:

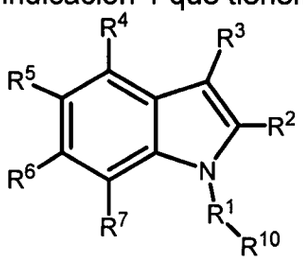


20. El compuesto de la reivindicación 3, en el cual cada vez que ocurre R^{30} es H.

21. El compuesto de la reivindicación 9, en el cual cada vez que ocurre R^{30} es H.

22. El compuesto de la reivindicación 17, en el cual cada vez que ocurre R^{30} es H.

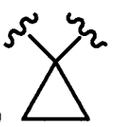
23. El compuesto de la reivindicación 1 que tienen la fórmula:



(Ia)

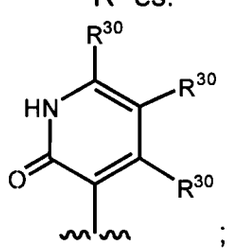
o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico,

en los cuales:

R^1 es $-CH_2-$, $-CH_2CH_2-$, $-CH(CH_3)-$ o  ;

R^2 es $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alquil)SO_2R^{11}$ o $-C(O)N(alquil)SO_2N(R^9)_2$;

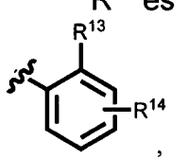
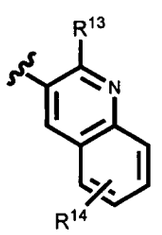
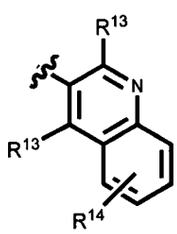
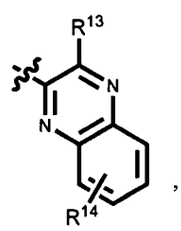
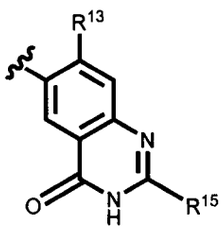
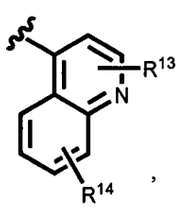
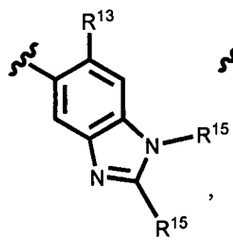
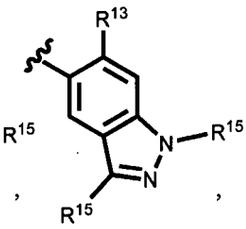
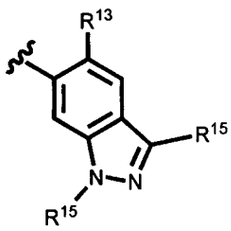
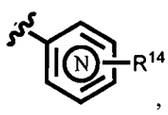
R^3 es:

 ;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, H, alquilo, –$[C(R^{12})_2]_q$–cicloalquilo, –$[C(R^{12})_2]_q$–heterocicloalquilo, haloalquilo, halo, –OH, –OR^9 o –$N(R^9)_2$;

cada vez que ocurre R^9 es en forma independiente H, alquilo, –alquil-$N(alquil)_2$, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo;

R^{10} es:


,

,

,

,

,

,

,

,

o

,

de manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, –alquil-$N(alquil)_2$, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo;

cada vez que ocurre R^{12} es en forma independiente H, halo, –$N(alquil)_2$, –OH, –O–alquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R_{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

R^{13} es H, F, Br o Cl;

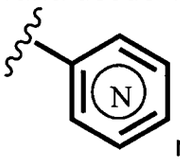
R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo;

cada vez que ocurre R^{15} es en forma independiente alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo,–$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo o heteroarilo;

cada vez que ocurre R^{30} es en forma independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4;

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4; y



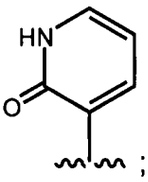
representa un grupo piridilo, en los cuales el átomo de nitrógeno del anillo puede estar en cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

24. El compuesto de la reivindicación 23 en el cual

R^1 es -CH_2–;

R^2 es –$C(O)NHSO_2R^{11}$ o –$C(O)NHSO_2N(R^9)_2$;

R^3 es:



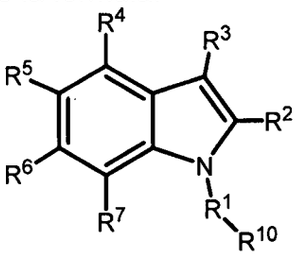
;

R^4, R^5, R^6 y R^7 son cada uno en forma independiente H, alquilo, haloalquilo o halo;

cada vez que ocurre R^9 es en forma independiente H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo; y

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo o cicloalquilo.

25. Un compuesto que tiene la fórmula:



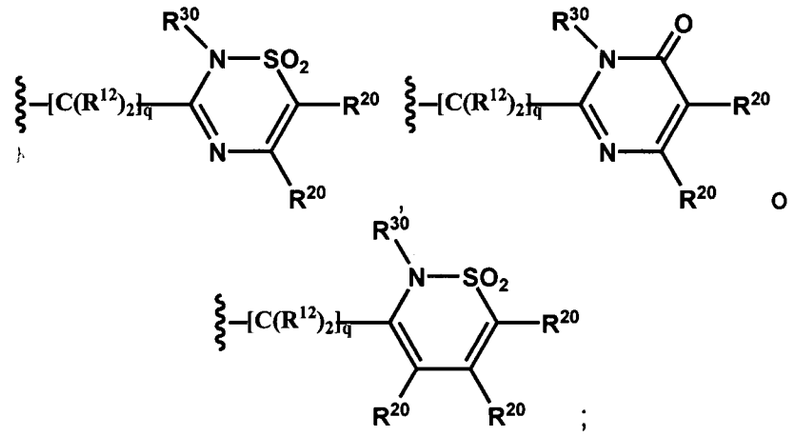
(II)

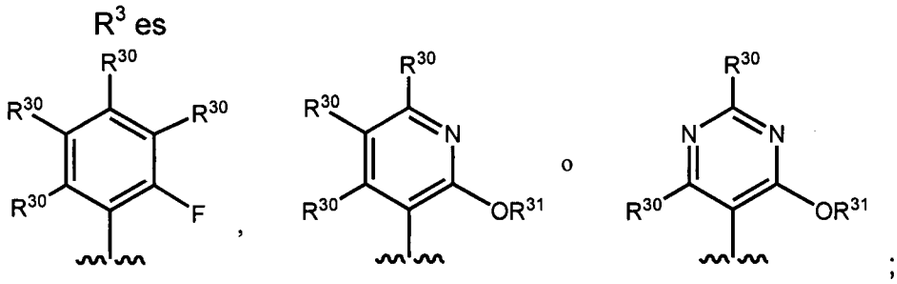
y sus sales, solvatos, ésteres y prodrogas aceptables desde el punto de vista farmacéutico,

en el cual:

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 $-[C(R^{12})_2]_q-C(O)N(R^9)SOR^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2R^{11}$, $-[C(R^{12})_2]_q-C(O)N(R^9)SO_2N(R^9)_2$,





R^3 es

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, 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 vez que ocurre R^8 es en forma independiente 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 vez que ocurre R^9 es en forma independiente H, alquilo, alquenilo, alquinilo, $-[C(R^{12})_2]_q-O-$alquilo, $-[C(R^{12})_2]_q-N(alquil)_2$, $-[C(R^{12})_2]_q-$arilo, $-[C(R^{12})_2]_q-$cicloalquilo, $-[C(R^{12})_2]_q-$cicloalquenilo, $-[C(R^{12})_2]_q-$heterocicloalquilo,

$-[C(R^{12})_2]_q-$heterocicloalquenilo, $-[C(R^{12})_2]_q-$heteroarilo, haloalquilo o hidroxialquilo;

R^{10} es H, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo, heteroarilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, heteroarilo, haloalquilo, hidroxi o hidroxialquilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo, heterocicloalquenilo, arilo o heteroarilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan 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 vez que ocurre R^{12} es en forma independiente H, halo, $-N(R^9)_2$, $-OR^9$, alquilo, cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo, donde un grupo cicloalquilo, cicloalquenilo, heterocicloalquilo o heterocicloalquenilo puede estar sustituido en forma independiente y opcional con hasta 4 sustituyentes, que se seleccionan en forma independiente de alquilo, halo, haloalquilo, hidroxialquilo, –OH, –CN, –C(O)alquilo, –C(O)Oalquilo, –C(O)NH–alquilo, $-C(O)N(alquil)_2$, –O–alquilo, $-NH_2$, –NH(alquilo), $-N(alquil)_2$, $-NHC(O)alquilo$, $-NHSO_2alquilo$, $-SO_2alquilo$ ° $-SO_2NH-alquilo$, o dos grupos R_{12}, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo cicloalquilo, heterocicloalquilo o C=O;

cada vez que ocurre R^{20} es en forma independiente alquilo, arilo, cicloalquilo, heterocicloalquilo o heteroarilo, o ambos grupos R^{20} y los átomos de carbono a los cuales 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, que se seleccionan 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 vez que ocurre R^{30} 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 $-SO_2N(R^9)C(O)N(R^9)_2$, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un anillo de 3 a 7 miembros seleccionado de arilo, cicloalquilo, heteroarilo y heterocicloalquilo;

R^{31} es 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 o $-[C(R^{12})_2]_q-$hidroxialquilo;

cada vez que ocurre p es en forma independiente 0, 1 o 2;

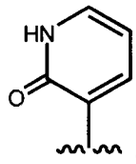
cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4; y

cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4.

26. El compuesto de la reivindicación 25, en el cual R^2 es $-C(O)NHSO_2R^{11}$ o $-C(O)NHSO_2N(R^9)_2$, en el cual R^9 es H, alquilo, arilo, cicloalquilo, heteroarilo o heterocicloalquilo y R^{11} es alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo.

27. El compuesto de la reivindicación 26, en el cual cada vez que ocurre R^{30} es en forma independiente, H, halo, $-N(alquil)_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo.

28. El compuesto de la reivindicación 27, en el cual R^3 es :



29. El compuesto de la reivindicación 28, en el cual R^1 es -$[C(R^{12})_2]_r$—.

30. El compuesto de la reivindicación 29 en el cual R^1 es -CH_2—, —CH_2CH_2—, —$CH(CH_3)$— o



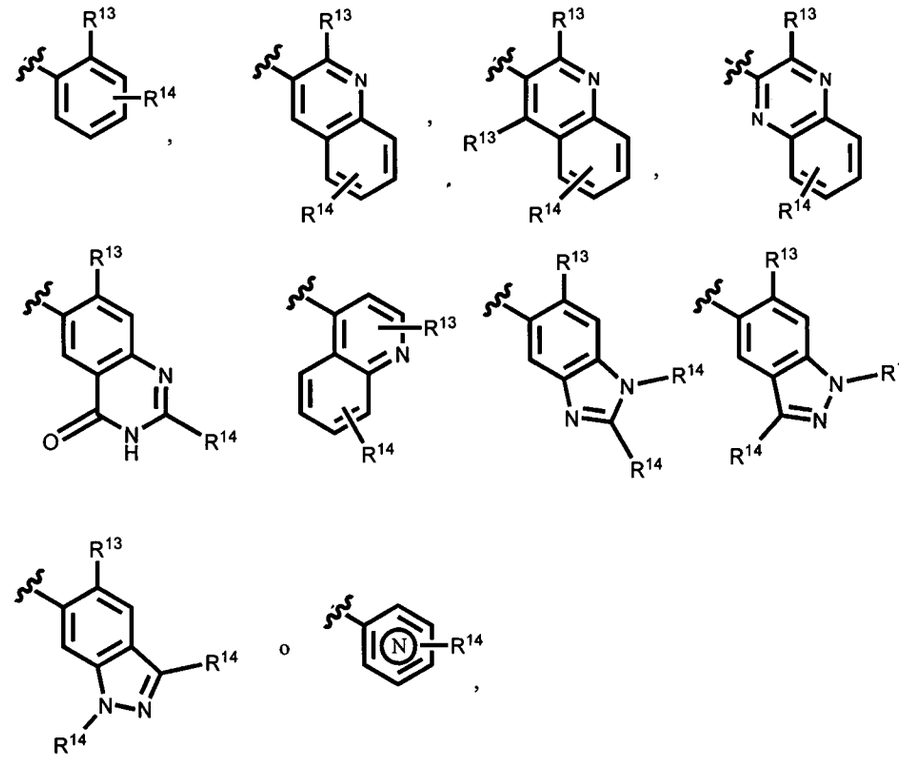
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31. El compuesto de la reivindicación 30 en el cual R^1 es -CH_2—.

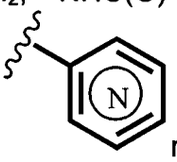
32. El compuesto de la reivindicación 29, en el cual R^4 y R^7 son cada uno en forma independiente H, halo o —OH, R^5 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o —CN, y R^6 es H, alquilo, —O—alquilo, —O—haloalquilo, cicloalquilo, halo, haloalquilo, —OH, hidroxialquilo, —NH_2 o —CN.

33. El compuesto de la reivindicación 32, en el cual R^{10} es arilo o heteroarilo.

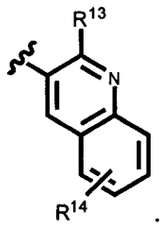
34. El compuesto de la reivindicación 33, en el cual R^{10} es:



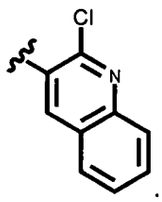
en el cual R^{13} es H, F, Br o Cl, R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo,

cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2–alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo, y  representa un grupo piridilo, en el cual el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

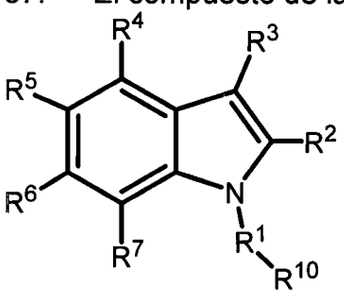
35. El compuesto de la reivindicación 34, en el cual R^{10} es:



36. El compuesto de la reivindicación 35, en el cual R^{10} es:



37. El compuesto de la reivindicación 25 que tienen la fórmula:



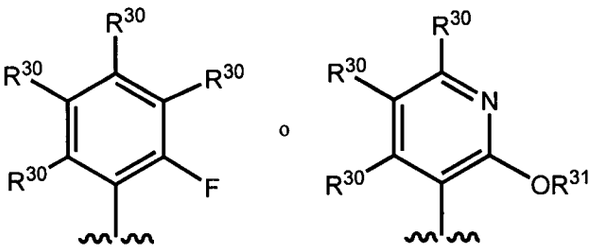
o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico,

en el cual:

R^1 es -CH_2–, –CH_2CH_2–, –$CH(CH_3)$— o  ;

R^2 es $-C(O)NHSO_2R^{11}$, $-C(O)NHSO_2N(R^9)_2$, $-C(O)N(alquil)SO_2R^{11}$ o $-C(O)N(alquil)SO_2N(R^9)_2$;

R^3 es:

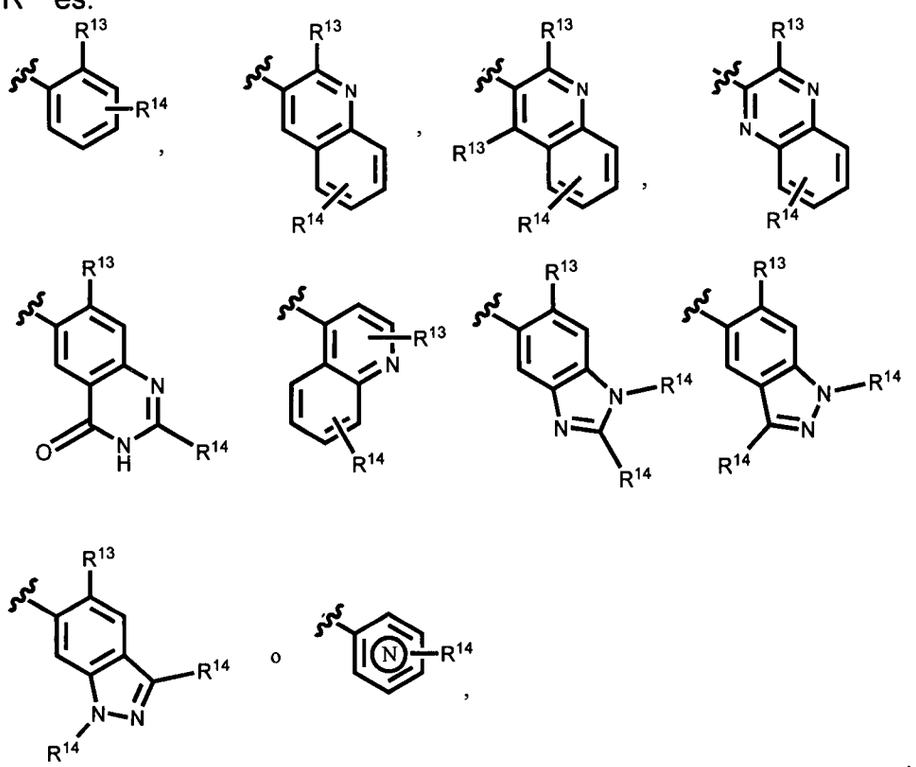


;

R^4, R^5, R^6 y R^7 son cada uno, en forma independiente, H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo, halo, –OH, –OH, –O–alquilo, –O–haloalquilo, $-NH_2$, –NH–alquilo o $-N(alquil)_2$;

cada vez que ocurre R^9 es en forma independiente H, alquilo, cicloalquilo, heterocicloalquilo, haloalquilo o hidroxialquilo;

R^{10} es:



de manera tal que cuando R^1 es un enlace, R^{10} no es H;

cada vez que ocurre R^{11} es en forma independiente alquilo, arilo, cicloalquilo, haloalquilo, heteroarilo, heterocicloalquilo o hidroxialquilo;

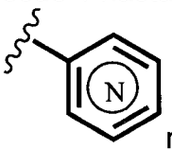
R^{13} es H, F, Br o Cl;

R^{14} representa hasta 4 sustituyentes opcionales y adicionales, cada uno seleccionado en forma independiente de alquilo, cicloalquilo, CF_3, –CN, halo, –O–alquilo, –O–haloalquilo, –$NHSO_2$–alquilo, –NO_2, –$C(O)NH_2$, –C(O)NH–alquilo, –C(O)OH, –OH, –NH_2, –SO_2alquilo, –SO_2NH–alquilo, –S–alquilo, –CH_2NH_2, –CH_2OH, –SO_2NH_2, –NHC(O)–alquilo, –C(O)O–alquilo, –C(O)–heterocicloalquilo y heteroarilo;

cada vez que ocurre R^{30} es en forma independiente, H, halo, –N(alquil)$_2$, –OH, –O–alquilo, –O–haloalquilo, alquilo, cicloalquilo o heterocicloalquilo, o dos grupos R^{30} adyacentes, junto con los átomos de carbono a los cuales están unidos, se unen para formar un grupo arilo, cicloalquilo, heteroarilo o heterocicloalquilo;

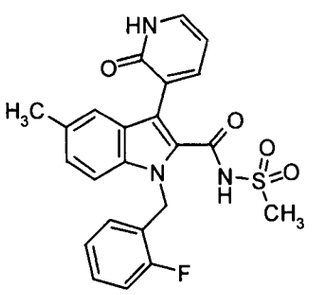
cada vez que ocurre q es en forma independiente un número entero que varía desde 0 hasta 4;

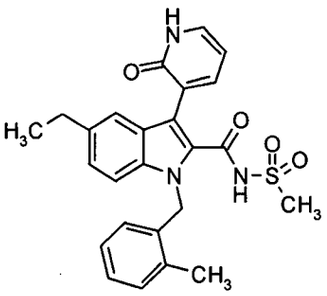
cada vez que ocurre r es en forma independiente un número entero que varía desde 1 hasta 4; y

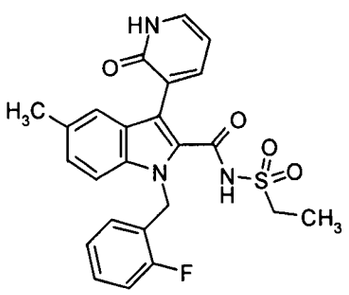


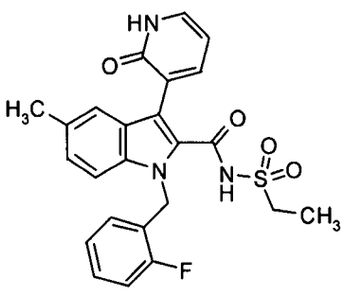
representa un grupo piridilo, en el cual el átomo de nitrógeno del anillo puede ser cualquiera de las cinco posiciones de átomos del anillo no sustituidos.

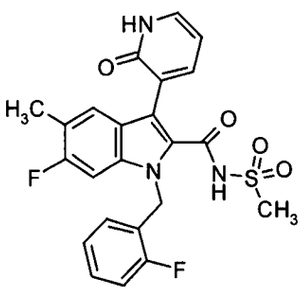
38. Un compuesto que tiene la estructura:

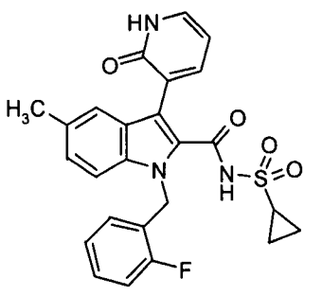


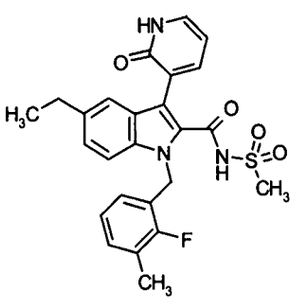


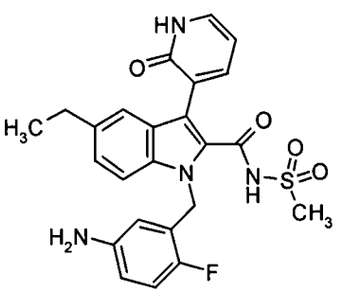


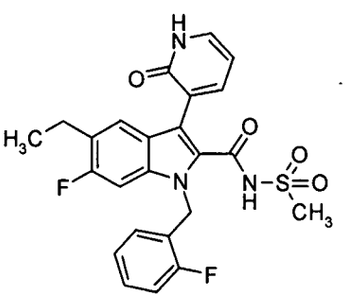


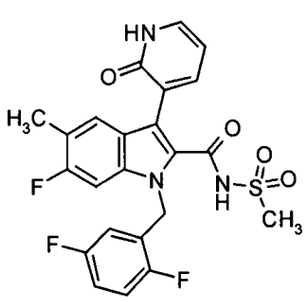


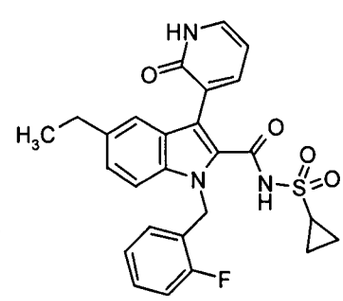


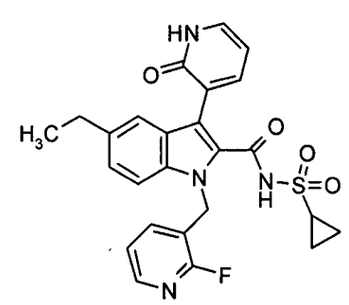


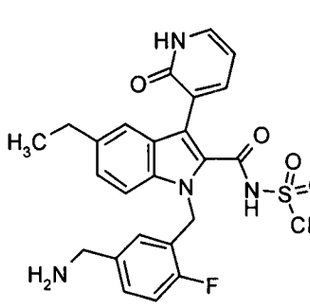


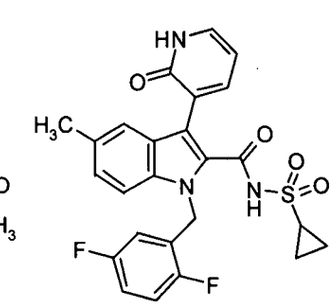


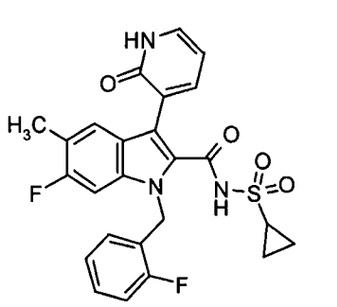


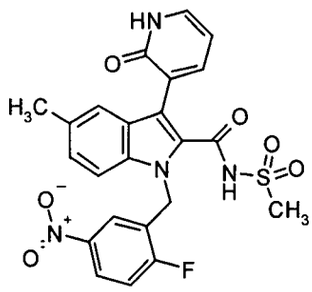


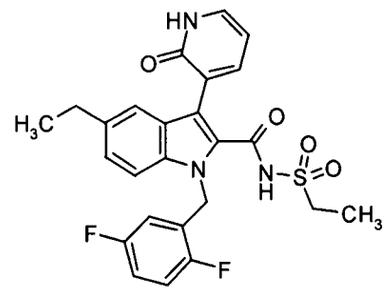


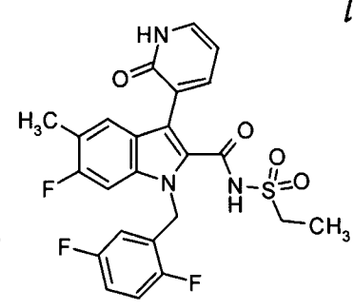


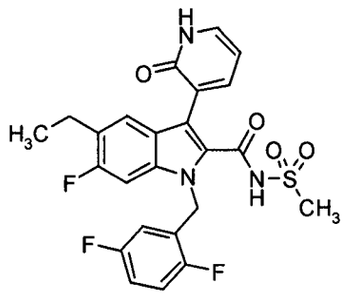


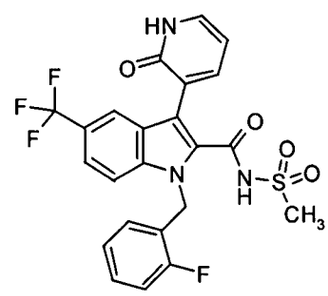


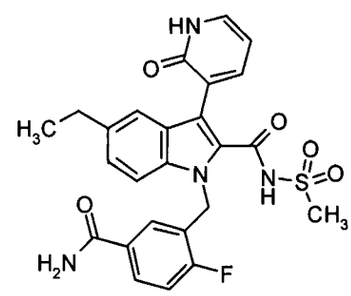


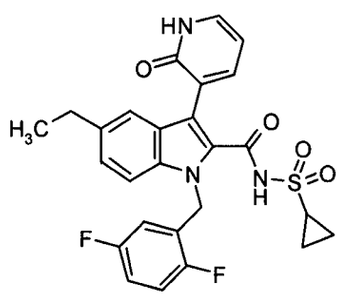


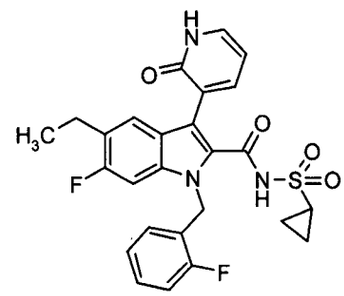


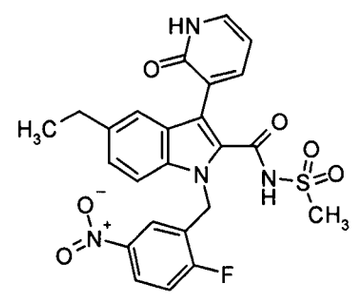


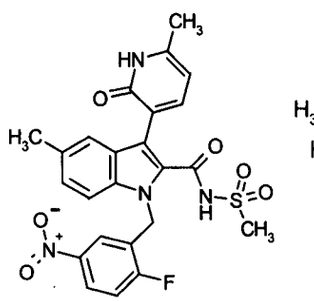


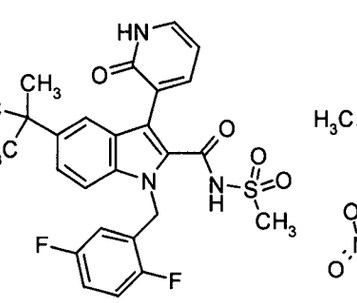


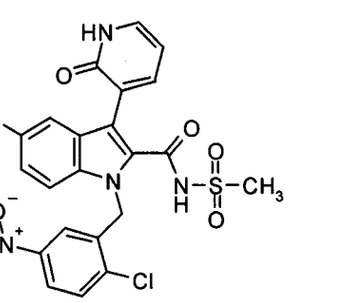


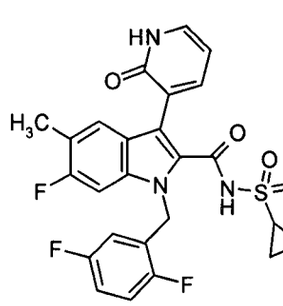


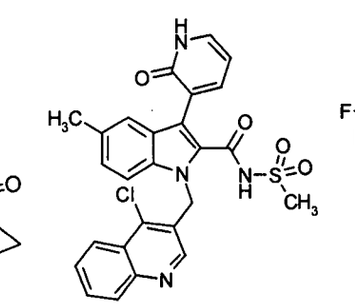


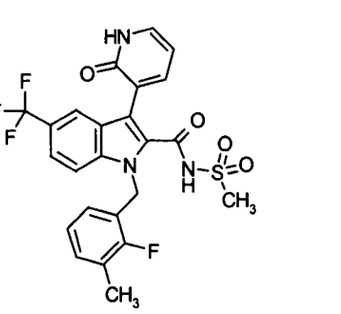




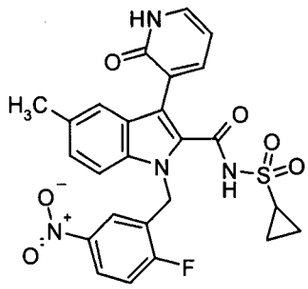


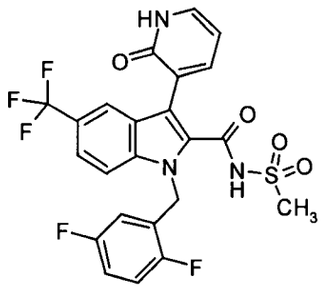


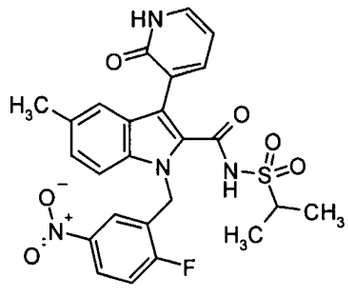


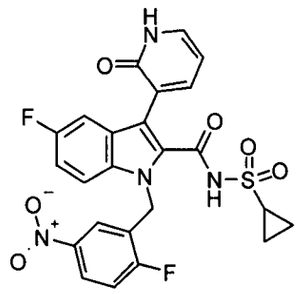


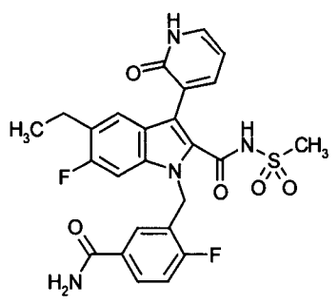


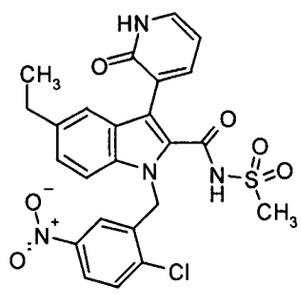


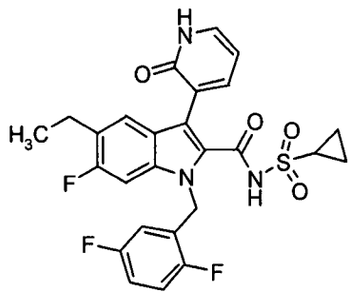


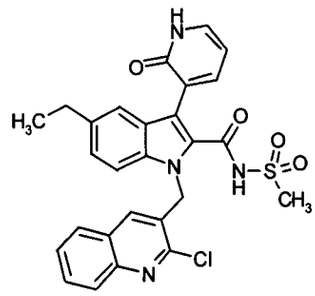


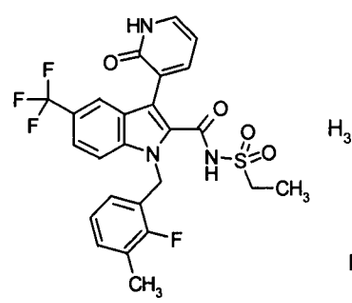


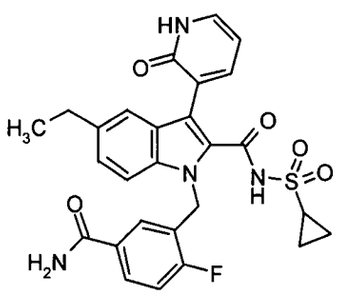


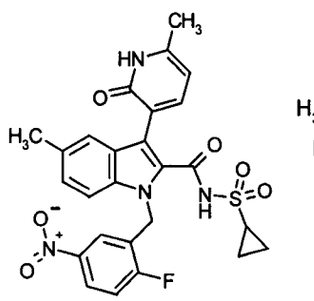


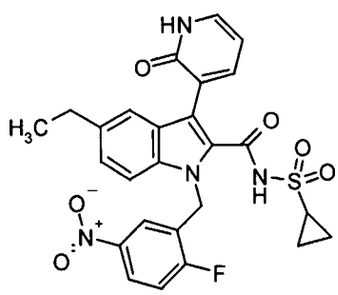


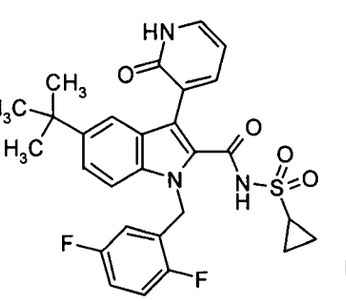


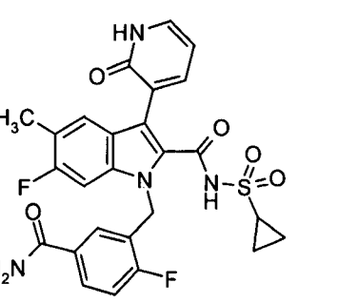


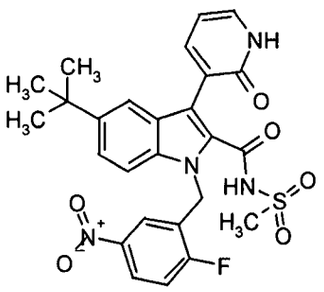


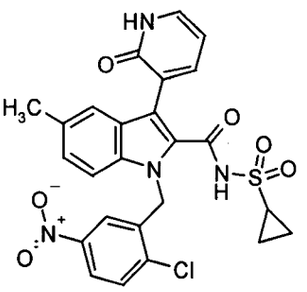


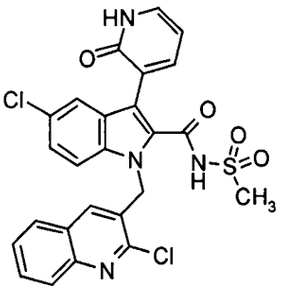


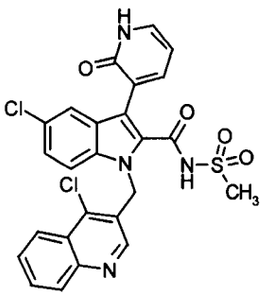


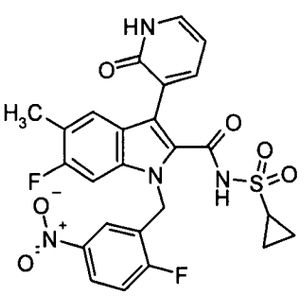


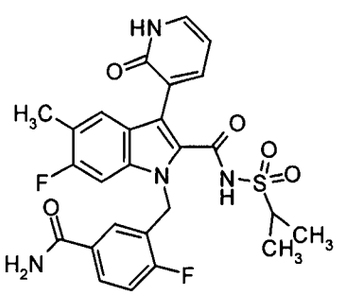


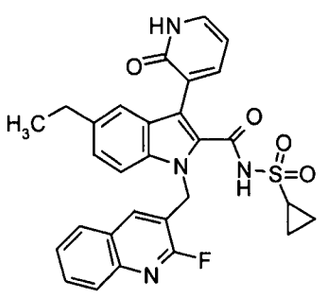


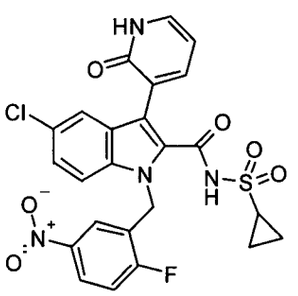


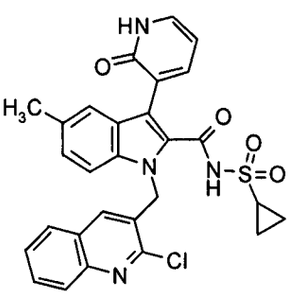


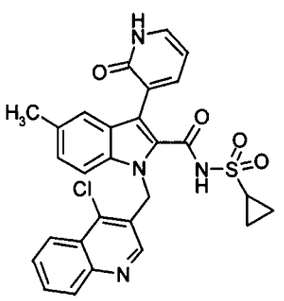


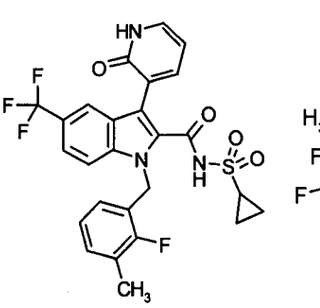


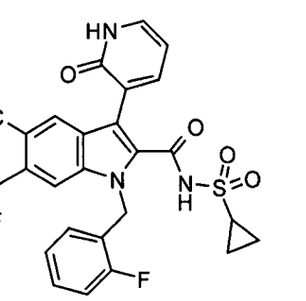


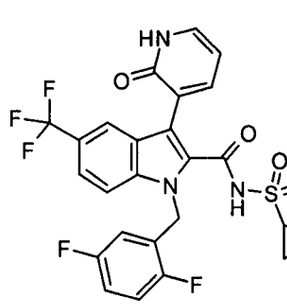


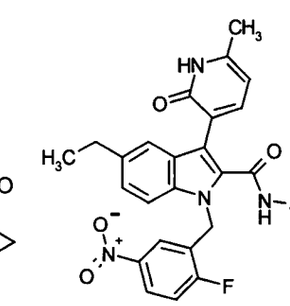


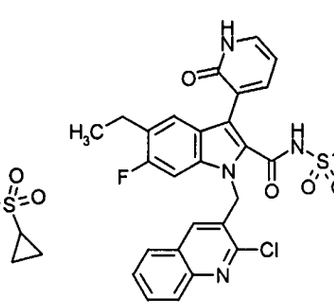


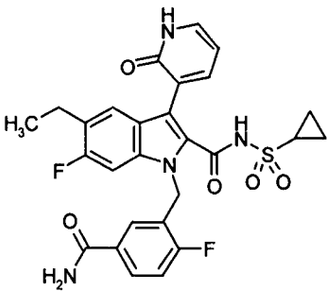


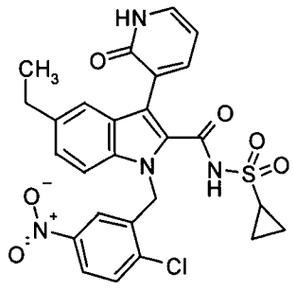


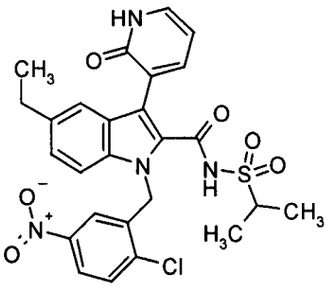


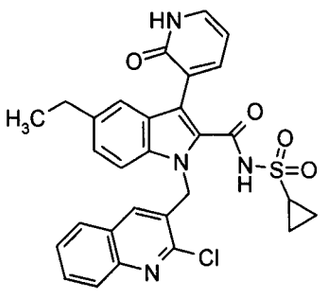


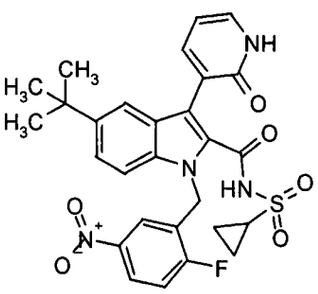


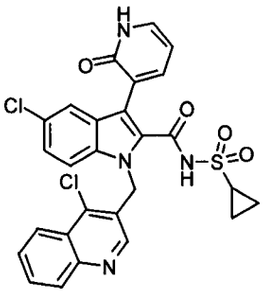


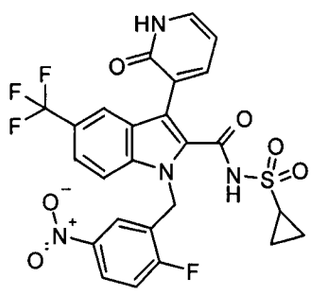


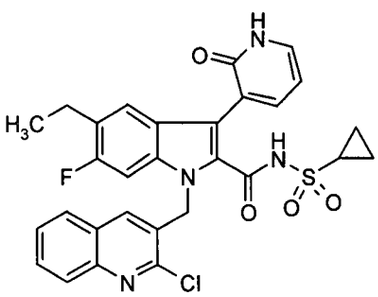


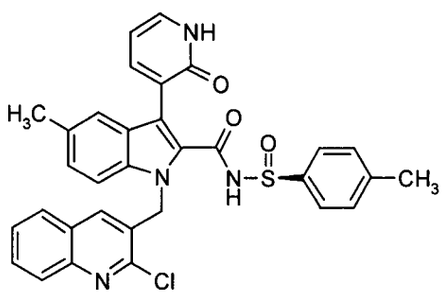


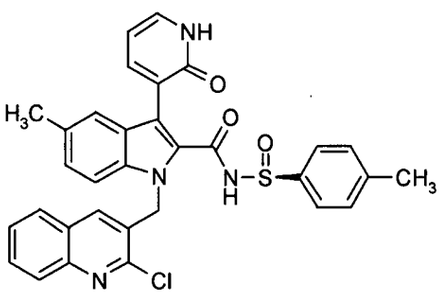


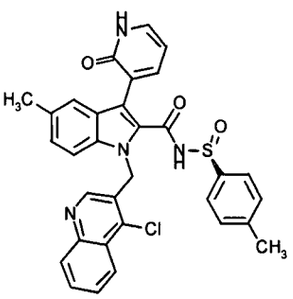


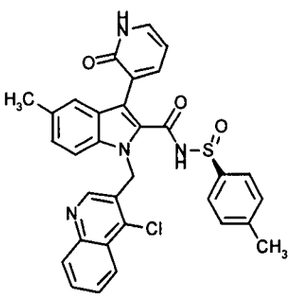


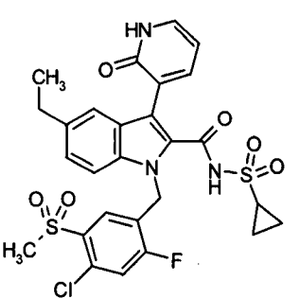


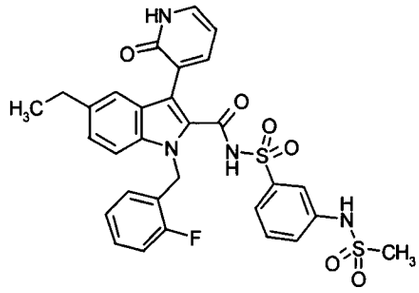


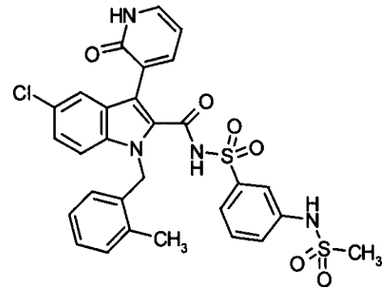


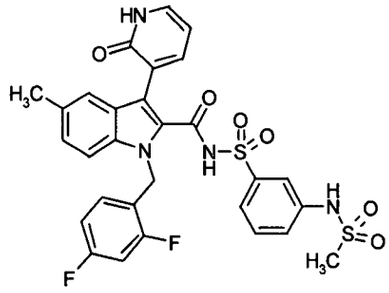


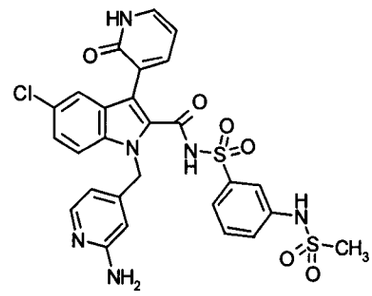


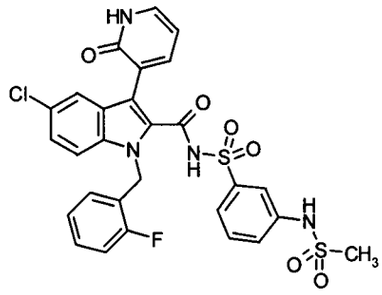


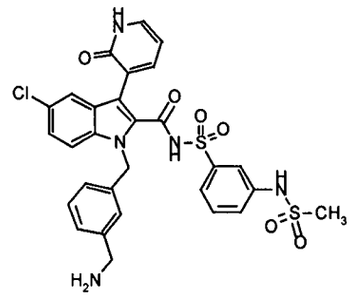


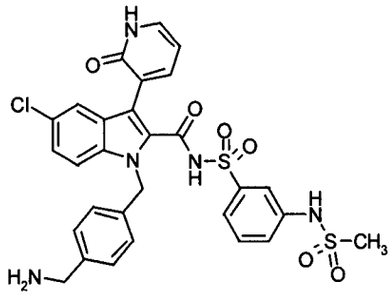


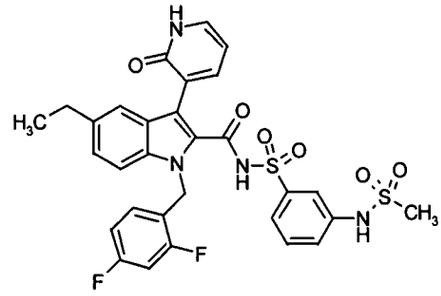


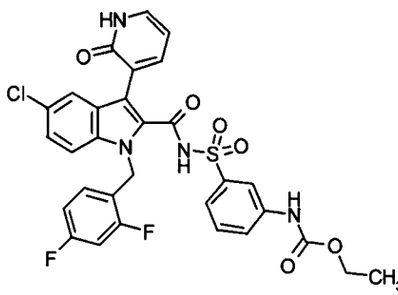


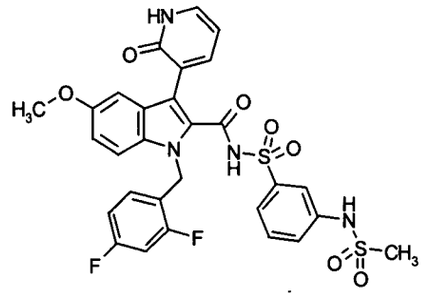


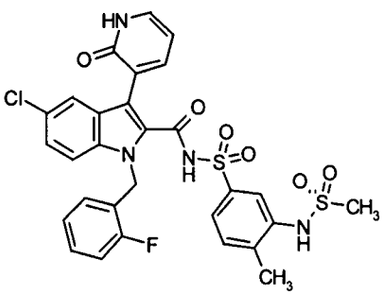


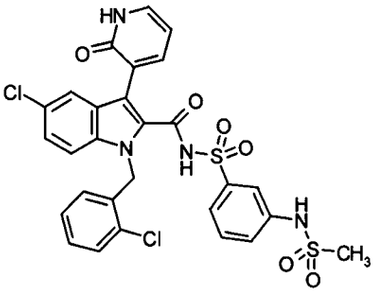


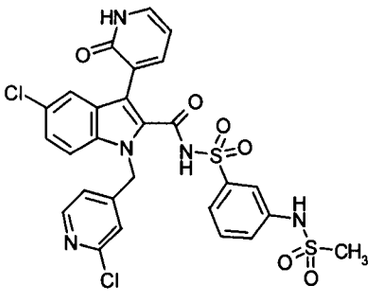


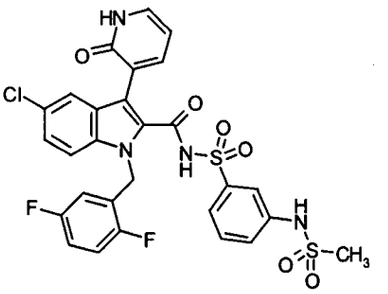


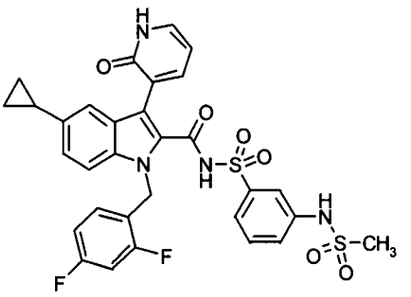


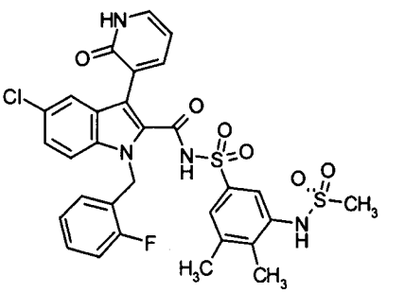


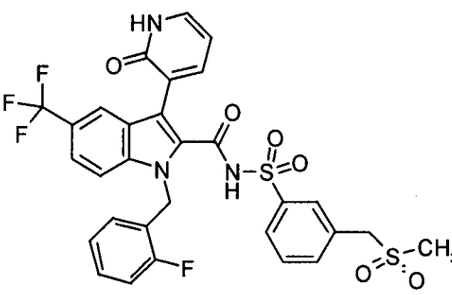


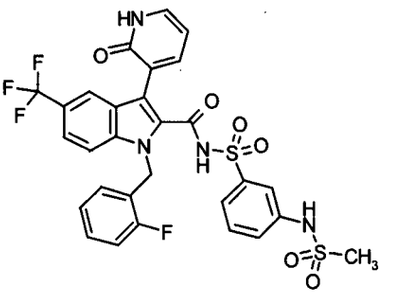


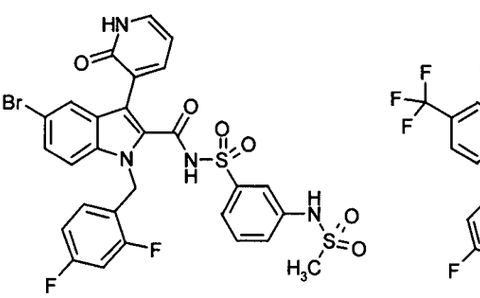


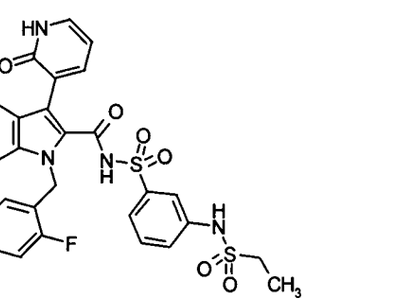


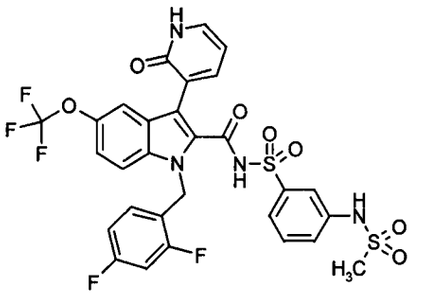


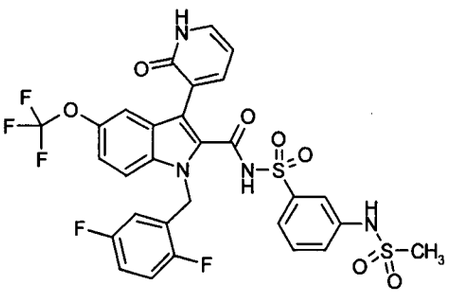


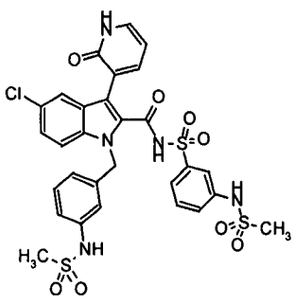


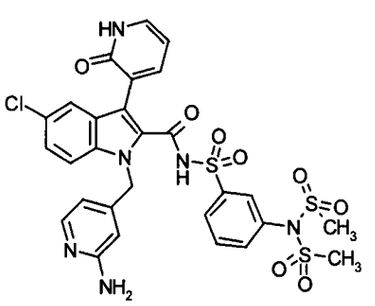


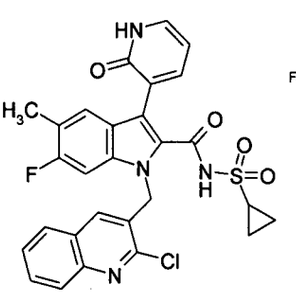


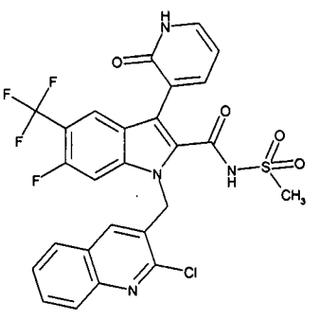


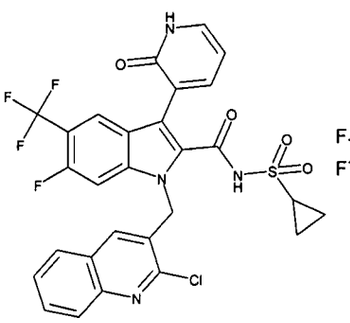


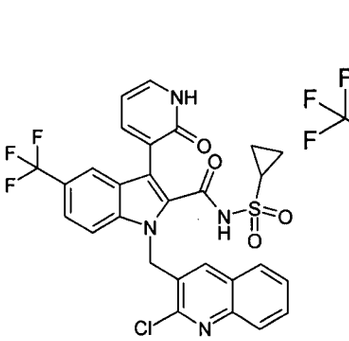


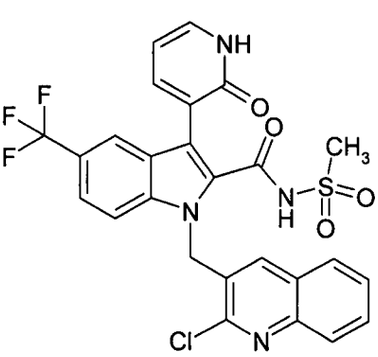


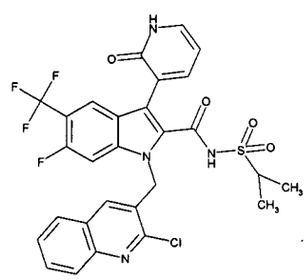


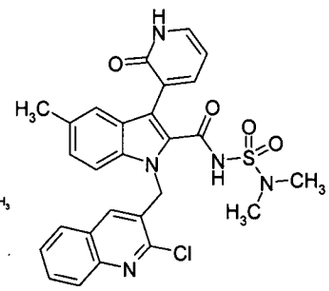


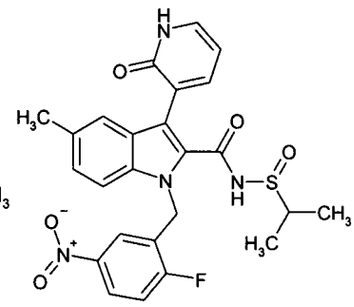


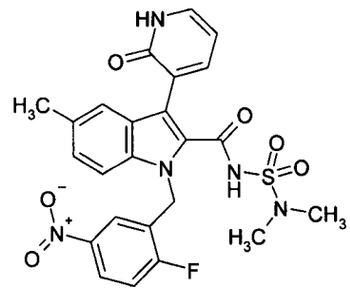


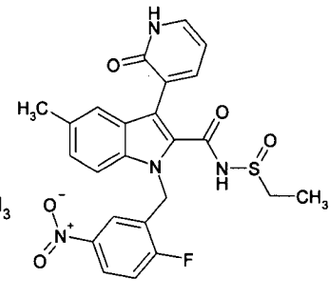


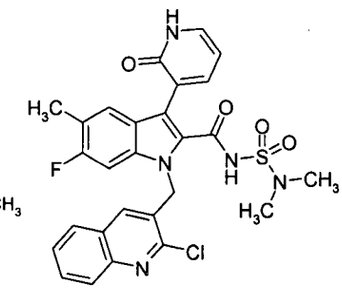


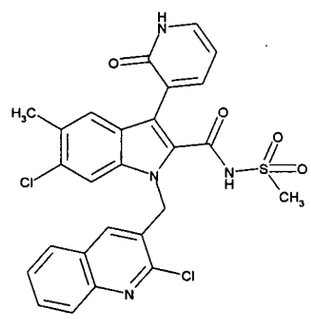


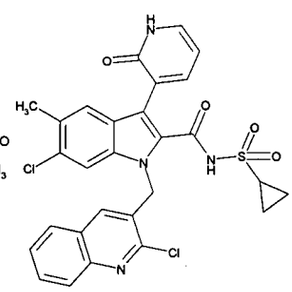


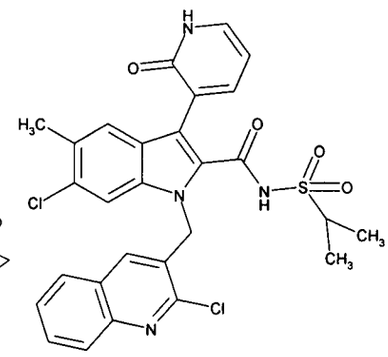


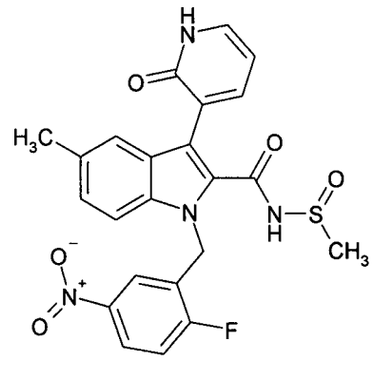


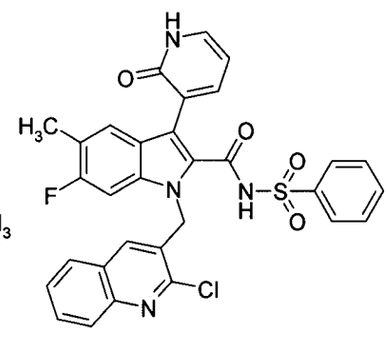


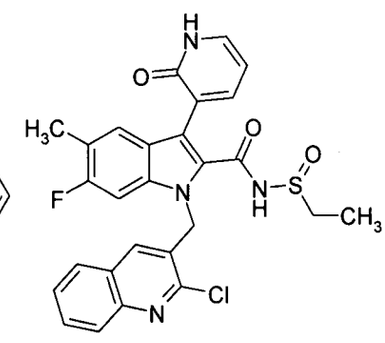


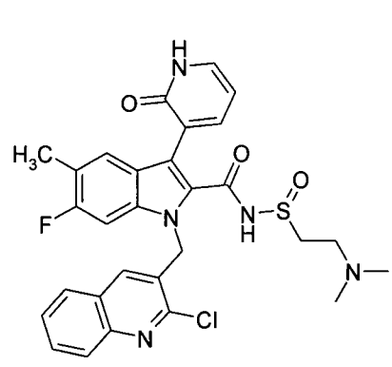


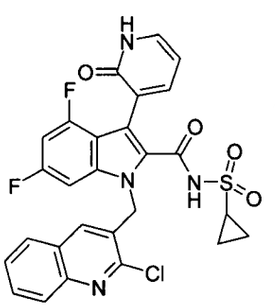


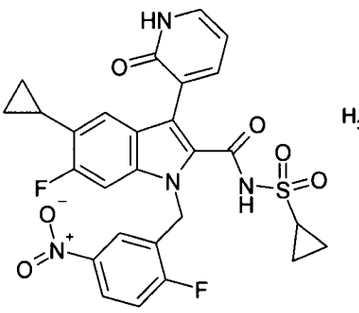


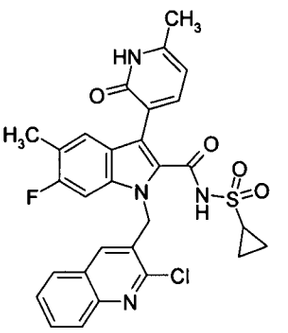


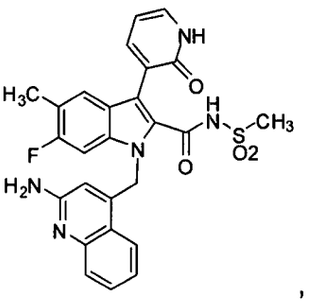


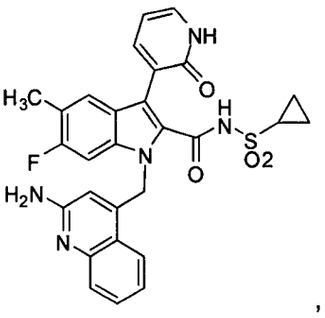


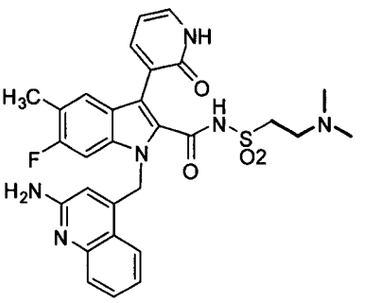


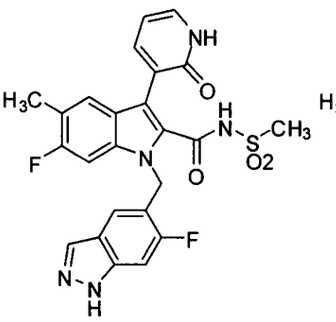


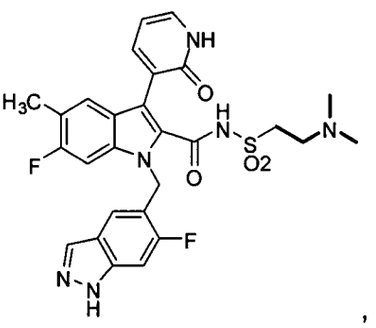


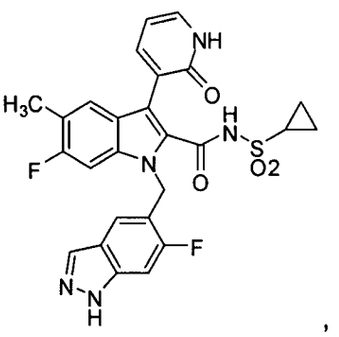


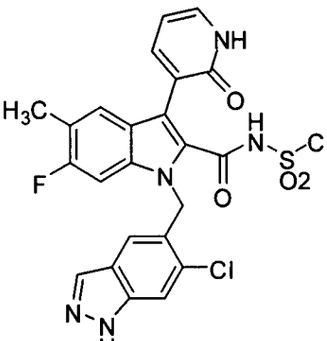


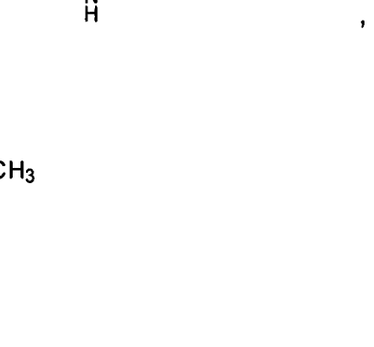


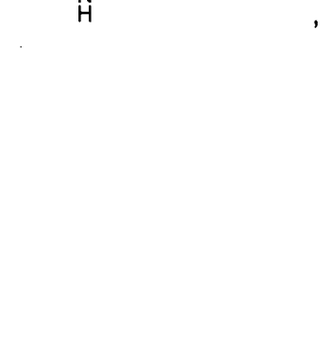


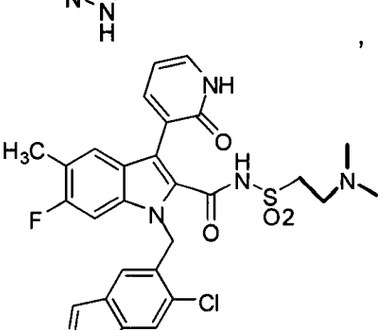


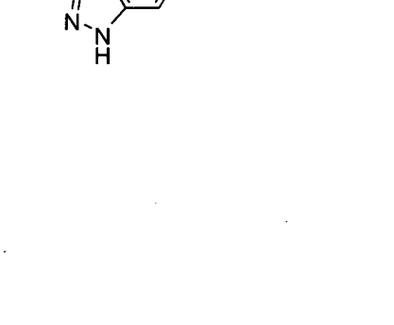


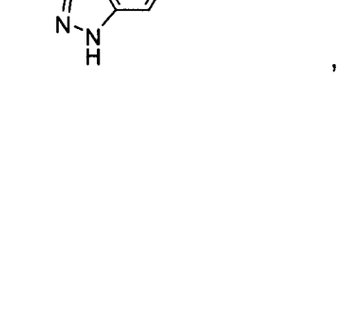


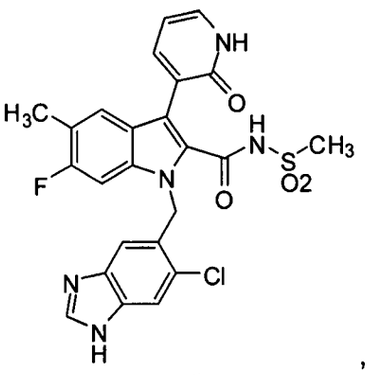
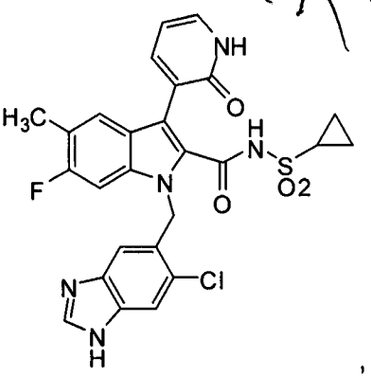
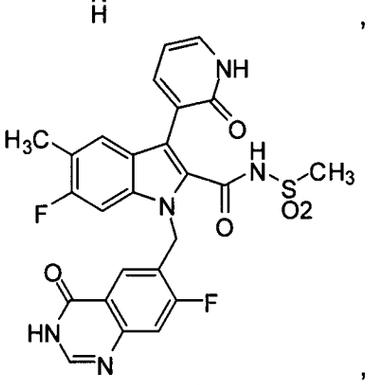
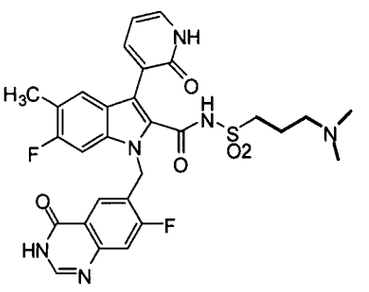
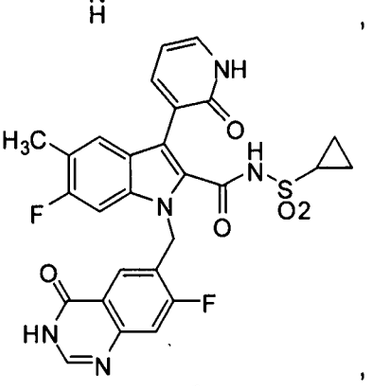
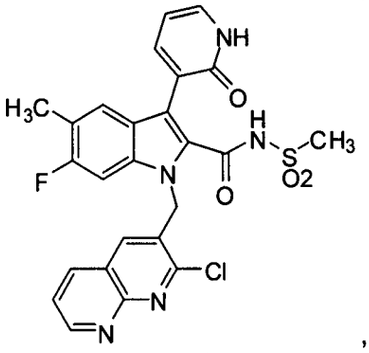
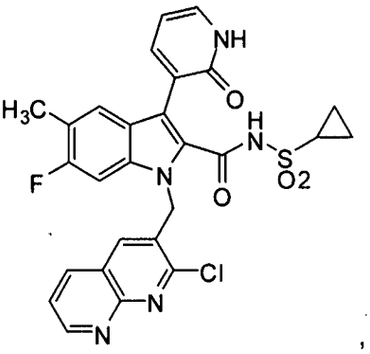
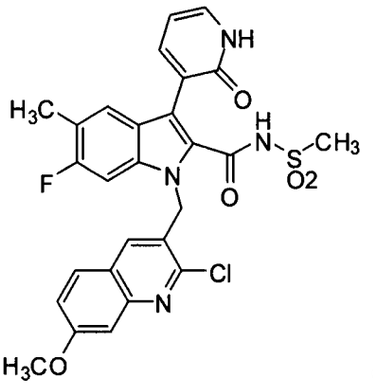
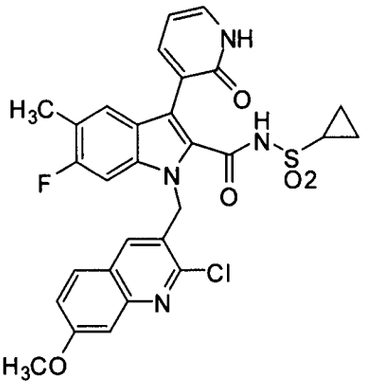











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o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

39. Una composición que comprende por lo menos un compuesto de la reivindicación 1 o una de sus sales, solvatos, ésteres o prodrogas aceptables

desde el punto de vista farmacéutico, y por lo menos un vehículo aceptable desde el punto de vista farmacéutico.

40. Una composición que comprende por lo menos un compuesto de la reivindicación 25 o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico, y por lo menos un vehículo aceptable desde el punto de vista farmacéutico.

41. Una composición que comprende por lo menos un compuesto de la reivindicación 38 o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico, y por lo menos un vehículo aceptable desde el punto de vista farmacéutico.

42. Un método para tratar una infección viral en un paciente, el método comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de la reivindicación 1 o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

43. Un método para tratar una infección viral en un paciente, el método comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de la reivindicación 25 o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

44. Un método para tratar una infección viral en un paciente, el método comprende administrar al paciente una cantidad efectiva de por lo menos un compuesto de la reivindicación 38 o una de sus sales, solvatos, ésteres o prodrogas aceptables desde el punto de vista farmacéutico.

45. El método de la reivindicación 42, que comprende, además, administrar al paciente por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia

con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

46. El método de la reivindicación 43, que comprende, además, administrar al paciente por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

47. El método de la reivindicación 44, que comprende, además, administrar al paciente por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

48. El método de la reivindicación 45, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

49. El método de la reivindicación 74, en el cual el inhibidor de replicación viral es ribavirina.

50. El método de la reivindicación 49, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

51. El método de la reivindicación 50, en el cual el inhibidor de replicación viral es ribavirina.

52. El método de la reivindicación 47, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

53. La composición de la reivindicación 39, que además comprende por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

54. La composición de la reivindicación 40, que además comprende por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

55. La composición de la reivindicación 41, que además comprende por lo menos un agente antiviral adicional, en el cual el agente adicional se selecciona de un inhibidor de polimerasa de VHC, un interferón, un inhibidor de la replicación viral, un nucleósido, un agente antisentido, una vacuna terapéutica, un inhibidor de proteasa viral, un inhibidor de producción de viriones, una terapia con anticuerpos (monoclonal o policlonal), y cualquier agente útil para tratar un trastorno relacionado con la polimerasa dependiente del ARN.

56. La composición de la reivindicación 53, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

57. La composición de la reivindicación 56, en el cual el inhibidor de replicación viral es ribavirina.

58. La composición de la reivindicación 54, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

59. La composición de la reivindicación 58, en el cual el inhibidor de replicación viral es ribavirina.

60. La composición de la reivindicación 55, en el cual el(los) agente(s) adicional(es) se seleccionan de uno o más de un inhibidor de polimerasa de VHC, un inhibidor de proteasa viral, un nucleósido, un interferón, un interferón pegilado o un inhibidor de la replicación viral.

61. La composición de la reivindicación 60, en el cual el inhibidor de replicación viral es ribavirina.

62. El método de la reivindicación 42, en el cual la infección viral es infección por hepatitis C.

63. El método de la reivindicación 43, en el cual la infección viral es infección por hepatitis C.

64. El método de la reivindicación 44, en el cual la infección viral es infección por hepatitis C.

p. de: SCHERING CORPORATION

RESUMEN

La presente invención se refiere a derivados indólicos 2,3 sustituidos, composiciones que comprenden por lo menos un derivado indólico 2,3 sustituido, y métodos de uso de los derivados indólicos 2,3 sustituidos para tratar o prevenir una infección viral o un trastorno relacionado con un virus en un paciente.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/010130

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/42 C07D401/04 C07D401/14 A61K31/404 A61P31/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN 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.
A	WO 2007/084435 A (PTC THERAPEUTICS INC [US]) 26 July 2007 (2007-07-26) the whole document	1-64
A	WO 2006/076529 A (GENELABS TECH INC [US]) 20 July 2006 (2006-07-20) the whole document	1-64
P,A	WO 2008/082484 A (SCHERING CORP [US]) 10 July 2008 (2008-07-10) the whole document	1-64

☐ Further documents are listed in the continuation of Box C.

☒ 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
15 January 2009	22/01/2009

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, Fax: (+31–70) 340–3016	Cortés, José

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/010130

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:

see FURTHER INFORMATION sheet PCT/ISA/210

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 42-52 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.

Continuation of Box II.1

Claims Nos.: -

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/010130

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007084435 A	26-07-2007	NONE	
WO 2006076529 A	20-07-2006	AU 2006204917 A1	20-07-2006
		CA 2593450 A1	20-07-2006
		CN 101103026 A	09-01-2008
		EP 1844042 A1	17-10-2007
		HR 20070342 A2	31-10-2007
		JP 2008526980 T	24-07-2008
		KR 20070098914 A	05-10-2007
		US 2006211698 A1	21-09-2006
WO 2008082484 A	10-07-2008	NONE	

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-035485- -00000-0000

Fecha: 2010-03-25 17:21:38 Dep: 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 804

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☐ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☐ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA		
	Radicación No.	10 035485
	Solicitud internacional	PCT/US2008/010130
	Fecha inicio fase nacional	29/03/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	

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
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	10 035485
	Solicitud internacional	PCT/US2008/010130
	Fecha inicio fase nacional	29/03/2010
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	E 06371

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez 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
Directora de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista de fecha 14 MAYO 2010.
adpa11