CSA045260
Organizacion y Digitalizacion CSA Ltda
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-48050

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: COMPUESTOS HETEROCICLICOS QUE CONTIENEN NITROGENO Y METODOS DE USO DE LOS MISMOS

SOLICITANTE: SCHERING CORPORATION

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

APODERADO: CARLOS R. OLARTE

BOGOTÁ 12 de MaYo de 2009

P2009/0000085

OLARTE RAISBECK

OLARTE RAISBECK MOU

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-048050- -00000-0000
Fecha: 2009-05-12 16:23:23 Dep: 2020 NUECREACION
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 614

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000085**

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

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79.782.747 Btá
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA DJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5)

PCT (86)

Solicitud Internacional No. PCT/US2007/023669 Fecha Noviembre 9, 2007

Publicación Internacional No. WO 2008/060476 Fecha Mayo 22, 2008

(6)

Título (54) **COMPUESTOS HETEROCICLICOS QUE CONTIENEN NITROGENO Y METODOS DE USO DE LOS MISMOS**

Clasificación Internacional (51) C07D 471/04, C07D 491/04, A61K 31/519, A61P 3/00, A61P 9/00

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Noviembre 15, 2006	11/600.216
US	Junio 29, 2007	11/771.538

(9)

Comprobante de pago No. 09-34,092 **Fecha** Mayo 08 de 2009

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-033.682
- [ ] 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:**

( ) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

C.C. 79.782.747 Bta T.P. 74.295

LISTA DE INVENTORES **PCT/US2007/023669**

3

Anandan PALANI
25 Reinhart Way,
Bridgewater NJ 08807
Estados Unidos de América.
Nacionalidad: Estadounidense

Jing SU
1398 Graymill Drive,
Scotch Plains NJ 07076
Estados Unidos de América.
Nacionalidad: Estadounidense

Dong XIAO
199 King George Road,
Warren NJ 07059
Estados Unidos de América.
Nacionalidad: China

Xianhai HUANG
16 Hemlock Circle,
Warren, NJ 07059
Estados Unidos de América.
Nacionalidad: China

Ashwin, U. RAO
806 Evergreen Forest Boulevard,
Avenel, NJ 07001
Estados Unidos de América.
Nacionalidad: India

Xiao CHEN
15 Hillwood Avenue,
Edison, NJ 08820
Estados Unidos de América.
Nacionalidad: Estadounidense

Haiqun TANG
5 Waters Lane,
Belle Mead, NJ 08502
Estados Unidos de América.
Nacionalidad: China

Jun QIN
92 Woodbury Road,
Edison, NJ 08820
Estados Unidos de América.

Nacionalidad: China

Ying R. HUANG
178 River Bend Road,
Berkeley Heights, NJ 07922
Estados Unidos de América.
Nacionalidad: Estadounidense

Robert G ASLANIAN
144 Philip Drive, Rockaway,
New Jersey 07866
Estados Unidos de América.
Nacionalidad: Estadounidense

Brian A. MCKITTRICK
14 Millbrook Road, New Vernon,
New Jersey 07976
Estados Unidos de América.
Nacionalidad: Estadounidense

Sylvia J. DEGRADO
6 King James Court,
Scotch Plains, NJ 07076
Estados Unidos de América.
Nacionalidad: Estadounidense

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-048050- -00000-0000
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 614

RECIBO OFICIAL DE CAJA : 09 - 34,092
FECHA : MAYO 8 DE 2009

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105800295	08/05/2009	4,016,000.00

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

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

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

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

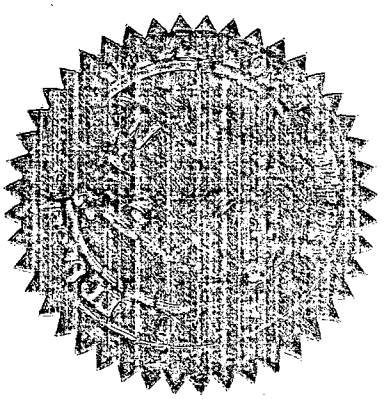
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

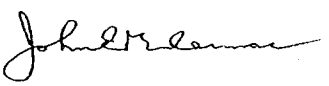
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

4

Power of Attorney

The undersigned,
SCHERING CORPORATION
domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Poder

El suscrito,

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

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

Signature/Firma:

Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

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

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

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):

BLIC (Signature):

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

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22 May 2008 (22.05.2008)

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C07D 471/04 (2006.01) *A61P 3/00* (2006.01)
C07D 491/04 (2006.01) *A61P 9/00* (2006.01)
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11/600,216 15 November 2006 (15.11.2006) US
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(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PALANI, Anandan** [US/US]; 25 Reinhart Way, Bridgewater, NJ 08807 (US). **SU, Jing** [US/US]; 1398 Graymill Drive, Scotch Plains, NJ 07076 (US). **XIAO, Dong** [CN/US]; 199 King George Road, Warren, NJ 07059 (US). **HUANG, Xianhai** [CN/US]; 16 Hemlock Circle, Warren, NJ 07059 (US). **RAO, Ashwin, U.** [IN/US]; 806 Evergreen Forest Boulevard, Avenel, NJ 07001 (US). **CHEN, Xiao** [US/US]; 15 Hillwood Avenue, Edison, NJ 08820 (US). **TANG, Haiqun** [CN/US]; 5 Waters Lane, Belle Mead, NJ 08502 (US). **QIN, Jun** [CN/US]; 92 Woodbury Road, Edison, NJ 08820 (US). **HUANG, Ying; R.** [US/US]; 178 River Bend Road, Berkeley Heights, NJ 07922 (US). **ASLANIAN, Robert, G.** [US/US]; 144 Philip Drive, Rockaway, New Jersey 07866 (US). **MCKITTRICK, Brian, A.** [US/US]; 14 Millbrook Road, New Vernon, New Jersey 07976 (US). **DEGRADO, Sylvia, J.** [US/US]; 6 King James Court, Scotch Plains, NJ 07076 (US).

(74) Agent: **BERGMAN, Jeffrey, P.**; Schering-Plough Corporation, 2000 Galloping Hill Road, Patent Dept. K-6-1, Kenilworth, NJ 07033-0530 (US).

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

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

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:
— *without international search report and to be republished upon receipt of that report*

(54) Title: NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: The present invention provides compounds of Formula (I) and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein: Q is selected from the group consisting of: (a), (b), (c), (d) and (e); and L is selected from the group consisting of: (f), (g), (h), and (i); pharmaceutically compositions comprising one or more compounds of formula (I), and methods of using the compounds of formula (I).

WO 2008/060476 A2

51(5), pp. 1051-1058 discloses one step transformations of (S)-1-benzoyl-3-[(E)-dimethylaminomethylidene]-5-methoxycarbonyl-pyrrolidin-2-one into quinolizinyl- and 2H-2-pyranonyl-substituted alanine derivatives. R. Toplak J. Heterocyclic Chem. (1999), 36(1), pp. 225-235 discloses the synthesis of pyran-2-ones. However, the compounds of the above references differ from those of the present invention.

WO 2004/110368 describes combination therapies for the treatment of hypertension comprising the combination of an anti-obesity agent and an anti-hypertensive agent. However, WO 2004/110368 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

WO 2005/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent. However, WO 2005/000217 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent. However, WO 2004/110375 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

US 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors. However, US 2004/0122033 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent. US 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist. However, the nicotinic acid agonists of US 2004/0229844 are quite different from those of the present invention.

WO2005/077950 describes xanthine derivatives which are agonists of the nicotinic acid receptor HM74A. However, the xanthine derivatives of WO2005/077950 are quite different from the compounds of the present invention.

NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

Field of the Invention

The present invention relates to nicotinic acid receptor agonist compounds useful for treating metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, and non-alcoholic fatty liver disease; pharmaceutical compositions comprising such compounds; pharmaceutical compositions comprising nicotinic acid receptor agonist compounds in combination with other therapeutic agents; and methods of treatment using the compounds and compositions to treat conditions such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis and non-alcoholic fatty liver disease.

Background of the Invention

Nicotinic acid has been used to treat metabolic syndrome and dyslipidemia. However, nicotinic acid has undesirable side effects such as flushing and diarrhea. It is therefore desirable to provide improved nicotinic acid receptor agonists with improved efficacy at treating metabolic syndrome and dyslipidemia, yet without the undesirable side effects. The compounds of the present invention provide such improved nicotinic acid receptor agonists.

M. Ridi, Gazzetta Chim. Ital. (1950) vol. 80, p. 121 and M. Ridi, Gazzetta Chim. Ital. (1952) vol. 82, p. 23 disclose syntheses of barbituric acid derivatives. FR 2563223 discloses nucleoside analogs. T. Paterson et al., J. Chem. Soc., Perkins Trans. I (1972), vol. 8, pp. 1041-1050 discloses the synthesis of 8-substituted pyrido[2,3-d]pyrimidines. S. Rao, Indian J. Chem. (1974), 12(10), pp. 1028-1030 discloses the synthesis of pyrano[2,3-d]pyrimidines. M. Skof, Heterocycles, (1999),

51(5), pp. 1051-1058 discloses one step transformations of (S)-1-benzoyl-3-[(E)-dimethylaminomethylidene]-5-methoxycarbonyl-pyrrolidin-2-one into quinolizinyl- and 2H-2-pyranonyl-substituted alanine derivatives. R. Toplak J. Heterocyclic Chem. (1999), 36(1), pp. 225-235 discloses the synthesis of pyran-2-ones. However, the compounds of the above references differ from those of the present invention.

WO 2004/110368 describes combination therapies for the treatment of hypertension comprising the combination of an anti-obesity agent and an anti-hypertensive agent. However, WO 2004/110368 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

WO 2005/000217 describes combination therapies for the treatment of dyslipidemia comprising the administration of a combination of an anti-obesity agent and an anti-dyslipidemic agent. However, WO 2005/000217 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

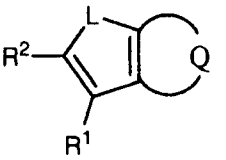
WO 2004/110375 describes combination therapies for the treatment of diabetes comprising the administration of a combination of an anti-obesity agent and an anti-diabetic agent. However, WO 2004/110375 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent.

US 2004/0122033 describes combination therapies for the treatment of obesity comprising the administration of a combination of an appetite suppressant and/or metabolic rate enhancers and/or nutrient absorption inhibitors. However, US 2004/0122033 fails to describe nicotinic acid receptor agonists, or combinations of one or more nicotinic acid receptor agonists with a second therapeutic agent. US 2004/0229844 describes combination therapies for treating atherosclerosis comprising the administration of a combination of nicotinic acid or another nicotinic acid receptor agonist and a DP receptor antagonist. However, the nicotinic acid agonists of US 2004/0229844 are quite different from those of the present invention.

WO2005/077950 describes xanthine derivatives which are agonists of the nicotinic acid receptor HM74A. However, the xanthine derivatives of WO2005/077950 are quite different from the compounds of the present invention.

Summary of the Invention

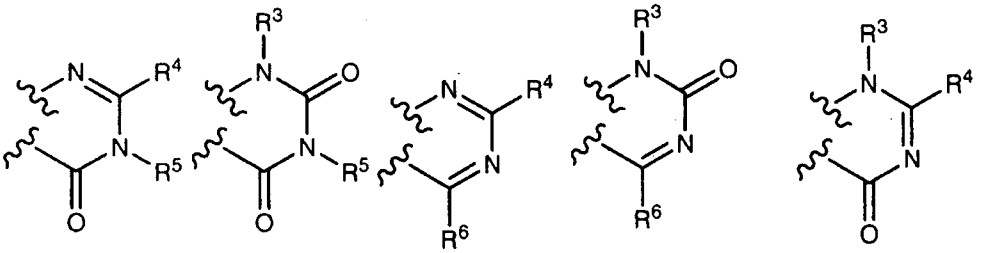
In one embodiment, the present invention is directed to a compound of Formula (I):



(I)

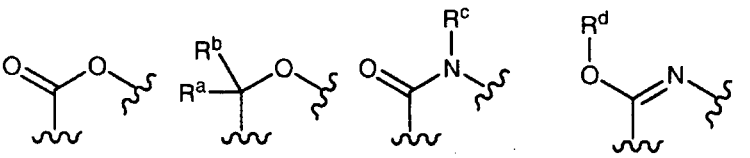
and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein:

Q is selected from the group consisting of:



(a) , (b) , (c) , (d) and (e) ;

L is selected from the group consisting of:



(f) , (g) , (h) , and (i) ;

R^1 is selected from the group consisting of H, alkyl, arylalkyl, -alkylene-S-alkyl, alkenyl, alkynyl, haloalkyl, wherein an alkyl group can be optionally substituted with one or more of the following groups, which can be the same or different: -OH, cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R^{10}, -alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, halogen, -$(CH_2)_n$-$N(R^7)_2$, -alkylene-cycloalkyl, or -alkylene-cycloalkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^1 is unsubstituted or substituted with one or more X groups, said aryl or the aryl portion of said -alkylene-aryl of R^1 is unsubstituted or substituted with one or more Y groups, and said heteroaryl or the heteroaryl portion

of said –alkylene-heteroaryl of R^1 is unsubstituted or substituted with one or more Y groups;

R^2 is selected from the group consisting of H, halogen, alkyl, haloalkyl, alkyl substituted with one or more -OH, -C(O)-alkyl, -C(O)-O-alkyl, -C(O)-OH, -O-R^{10}, -alkylene-O-alkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, and halogen; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring or a 5- or 6-membered heterocyclic ring having 1 or 2 heteroatoms;

R^3 is selected from the group consisting of H, alkyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, alkenyl, aryl, and heteroaryl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^3 is unsubstituted or substituted with one or more X groups, said aryl of R^3 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^3 is unsubstituted or substituted with one or more Y groups;

R^4 is selected from the group consisting of H, halogen, alkyl, haloalkyl, -O-cycloalkyl, -O-alkynyl, -O-R^{10}, -C(O)-O-alkyl, -$S(O)_m$-R^9, -$N(R^7)_2$, -$N(R^7)$-NH-C(O)-alkyl, -$N(R^7)$-NH-C(O)-O-alkyl, -O-N=$C(R^{12})_2$, -$N(R^7)$-N=$C(R^{12})_2$, -C(O)-alkyl, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, -O-$N(R^7)$-C(O)-O-alkyl, -C(O)-$N(R^7)_2$, -CN, -N_3, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -OH, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl -alkylene-C(O)-R^8, -alkylene-C(O)-$N(R^{11})_2$, -alkylene-C(=N-O-alkyl)-aryl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, -alkylene-C(O)-heterocyclyl, and alkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^5 is unsubstituted or substituted with one or more X groups, and the

aryl portion of said -alkylene-C(=N-O-alkyl)-aryl of R^5 is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, -O-R^{10}, halogen, aryl, heteroaryl, and -N(R^7)$_2$,

wherein the aryl of R^6 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^6 is unsubstituted or substituted with one or more Z groups;

each R^7 is independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, -C(O)-alkyl, and -C(O)-aryl,

wherein the cycloalkyl of R^7 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -C(O)-aryl or said aryl of R^7 is unsubstituted or substituted with one or more Y groups;

two R^7 groups, together with the N atom to which they are bonded form a heterocyclyl;

R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl,

wherein the heterocyclyl of R^8 is unsubstituted or substituted with one or more X groups, and said aryl of R^8 is unsubstituted or substituted with one or more Y groups;

R^9 is selected from the group consisting of alkyl, -alkylene-cycloalkyl, alkenyl, -N(R^{11})$_2$, and -alkylene-aryl,

wherein the cycloalkyl portion of said –alkylene-cycloalkyl of R^9 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-aryl of R^9 is unsubstituted or substituted with one or more Y groups, and

with the proviso that when R^9 is -N(R^{11})$_2$, m is 1 or 2;

R^{10} is selected from the group consisting of H, alkyl, cycloalkyl, arylalkyl, haloalkyl, -alkylene-O-alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

wherein an the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl

group; the cycloalkyl portion of said –alkylene-cycloalkyl of R^{10} is unsubstituted or substituted with one or more X groups; the aryl portion of said -alkylene-aryl or -alkenylene-aryl of R^{10} is unsubstituted or substituted with one or more Y groups; and the heteroaryl portion of said -alkylene-heteroaryl of R^{10} is unsubstituted or substituted with one or more Z groups;

R^{11} is selected from the group consisting of H, alkyl, and aryl,

wherein the aryl of R^{11} is unsubstituted or substituted with one or more Y groups; or

two R^{11} groups, together with the N atom to which they are attached, form a heterocyclyl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, and heteroaryl,

wherein the aryl of R^{12} is unsubstituted or substituted with one or more Y groups and said heteroaryl of R^{12} is unsubstituted or substituted with one or more Z groups; or wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group;

R^a and R^b are each independently selected from the group consisting of H, alkyl, aryl, and heteroaryl,

wherein the aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, alkyl, alkylene-aryl, and -C(O)-alkyl,

wherein the aryl portion of said alkylene-aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, alkyl, and alkylene-aryl,

wherein the aryl portion of said alkylene-aryl of R^d is unsubstituted or substituted with one or more Y groups;

each X is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, and -OH;

each Y is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -CN, $-NO_2$, -OH, $-S(O_2)$-alkyl, $-S(O_2)$-aryl,

$-S(O_2)-NH_2$, $-S(O_2)-NH$-alkyl, $-S(O_2)-NH$-aryl, $-S(O_2)-N(alkyl)_2$, $-S(O_2)-N(aryl)_2$, $-S(O_2)-N(alkyl)(aryl)$, and aryl;

each Z is independently selected from the group consisting of alkyl, haloalkyl, halogen, -O-alkyl, -O-haloalkyl, -CN, -OH, aryl, and N-oxide;

n is 0, 1, 2, or 3;

m is 0, 1, or 2; and

with the proviso that when L is (f), and R^2, R^3 and R^5 are each H, then R^1 is not $-CH_3$.

In another embodiment, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, and at least one pharmaceutically acceptable carrier.

In another embodiment, the present invention is directed to a method of treating a disease or disorder in a patient, such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, and non-alcoholic fatty liver disease. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

In another embodiment, the present invention is directed to a method of treating a disease or disorder in a patient, such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis, and non-alcoholic fatty liver disease. The method comprises administering to the patient an effective amount of at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, in combination with at least one additional active ingredient selected from the group consisting of hydroxy-substituted azetidinone compounds, substituted β-lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid

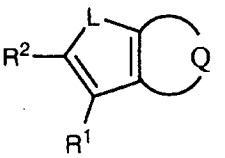
sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols (e.g., Omacor® from Pronova Biocare, Oslo, norway), low-density lipoprotein receptor activators, anti-oxidants, PPAR α agonists, PPAR γ-agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 agonists, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC2 inhibitors, β3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, antidiabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists,

noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α-glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

DETAILED DESCRIPTION OF THE INVENTION

The nicotinic acid receptor agonist compounds of the present invention are useful for treating conditions such as metabolic syndrome, dyslipidemia, cardiovascular diseases, disorders of the peripheral and central nervous system, hematological diseases, cancer, inflammation, respiratory diseases, gastroenterological diseases, diabetes, hepatic steatosis, and non-alcoholic fatty liver disease and other diseases listed herein. One or more compounds of the present invention can be administered alone or in combination with one or more other therapeutic agents as described herein.

The present invention provides compound of Formula (I):



(I)

and pharmaceutically acceptable salts, solvates, estesr, and tautomers thereof, wherein L, Q, R^1 and R^2 are defined above for the compound of formula (I).

In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is $-OH$.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-H$.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

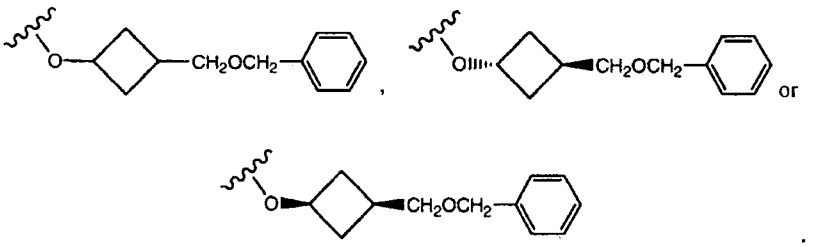
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

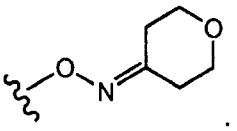
In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

In one embodiment, R^4 is –O-cyclobutyl.

In another embodiment, R^4 is:



In one embodiment, R^4 is:



In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

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

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

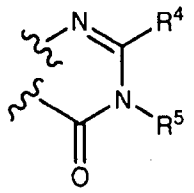
In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

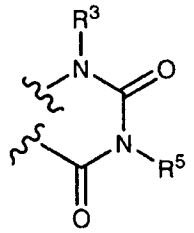
In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, Q is:



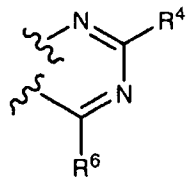
(a)

In another embodiment, Q is:



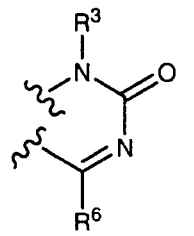
(b)

In another embodiment, Q is:



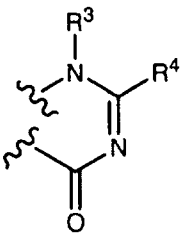
(c)

In still another embodiment, Q is:



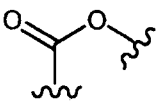
(d)

In yet another embodiment, Q is:



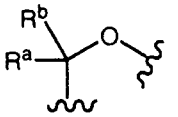
(e)

In one embodiment, L is:



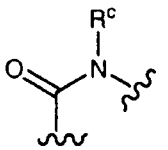
(f)

In another embodiment, L is:



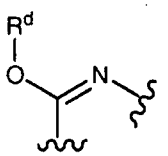
(g)

In another embodiment, L is:



(h)

In still another embodiment, L is:



(i)

In another embodiment of the compounds of Formula (I),

R^1 is selected from the group consisting of -(C_1-C_6)alkyl, -(C_1-C_6)alkenyl, -(C_1-C_6)alkynyl, -(C_1-C_6)haloalkyl, -(C_1-C_6)alkyl substituted with one hydroxyl group, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, -(C_1-

C_6)alkylene-(C_6-C_{10})aryl, -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl, -(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl, -$(CH_2)_n$-N(R^7)$_2$, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, and -(C_1-C_6)alkylene-(C_3-C_7)cycloalkenyl

wherein the -(C_3-C_7)cycloalkyl or the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl is unsubstituted or substituted with one or more X groups, the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl is unsubstituted or substituted with one or more Y groups, and the (C_2-C_{10})heteroaryl portion of said -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl is unsubstituted or substituted with one or more Z groups;

R^2 is H, halogen, unsubstituted aryl, aryl substituted with one or more independently selected Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more independently selected Y groups; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring;

R^3 is selected from the group consisting of H, (C_1-C_6)alkyl, -(C_3-C_6)alkylene-O-(C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-C(O)-O-alkyl, and (C_1-C_6)alkenyl,

wherein the (C_3-C_7)cycloalkyl or the (C_3-C_7)cycloalkyl portion of said -(C_3-C_6)alkylene-(C_3-C_7)cycloalkyl of R^3 is unsubstituted or substituted with one or more X groups;

R^4 is selected from the group consisting of halogen, -O-R^{10}, -C(O)-O-(C_1-C_6)alkyl, -$S(O)_m$-R^9, -N(R^7)$_2$, -O-N=C(R^{12})$_2$, -N(R^7)-NH-C(O)-O-(C_1-C_6)alkyl and -C(O)-(C_1-C_6)alkyl;

R^5 is selected from the group consisting of H, -(C_1-C_6)alkyl, -(C_1-C_6)alkylene-C(O)-R^8, -(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl, (C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl, and (C_2-C_6)alkenyl

wherein the (C_3-C_7)cycloalkyl or the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl of R^5 is unsubstituted or substituted with one or more X groups, and the (C_6-C_{10})aryl portion of said

-(C_1-C_6)alkylene-C(=N-O-(C_1-C_6)alkyl)-(C_6-C_{10})aryl of R^5 is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of –O-R^{10}, halogen, and -N(R^7)$_2$;

each R^7 is independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, and (C_6-C_{10})aryl,

wherein the (C_3-C_7)cycloalkyl of R^7 is unsubstituted or substituted with one or more X groups, and said (C_6-C_{10})aryl of R^7 is unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted (C_6-C_{10})aryl, (C_6-C_{10})aryl substituted with one or more Y groups, -OH, unsubstituted (C_2-C_{10})heterocyclyl, and (C_2-C_{10})heterocyclyl substituted with one or more X groups;

R^9 is selected from the group consisting of (C_1-C_6)alkyl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, (C_2-C_6)alkenyl, and -(C_1-C_6)alkylene-(C_6-C_{10})aryl,

wherein the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl of R^9 is unsubstituted or substituted with one or more X groups, and the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl of R^9 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, (C_1-C_6)alkyl, -(C_1-C_6)alkylene-(C_6-C_{10})aryl, -(C_2-C_6)alkenylene-(C_6-C_{10})aryl, -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, and -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl,

wherein the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl of R^{10} is unsubstituted or substituted with one or more X groups, and the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl or -(C_2-C_6)alkenylene-(C_6-C_{10})aryl of R^{10} is unsubstituted or substituted with one or more Y groups, and the (C_2-C_{10})heteroaryl portion of said -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl of R^{10} is unsubstituted or substituted with one or more Z groups;

each R^{12} is independently a (C_1-C_6)alkyl;

R^a and R^b are each independently a (C_1-C_6)alkyl;

R^c is H;

R^d is selected from the group consisting of H, $(C_1\text{-}C_6)$alkyl, and -$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl,

wherein the $(C_6\text{-}C_{10})$aryl portion of said -$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl of R^d is unsubstituted or substituted with one or more Y groups;

each X is independently selected from the group consisting of F, Cl, Br, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, -O-$(C_1\text{-}C_6)$alkyl, -O-$(C_1\text{-}C_6)$haloalkyl, and –OH;

each Y is independently selected from the group consisting of F, Br, Cl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, -O-$(C_1\text{-}C_6)$alkyl, -O-$(C_1\text{-}C_6)$haloalkyl, -CN, $-NO_2$, -OH, , $-S(O_2)-(C_1\text{-}C_6)$alkyl, $-S(O_2)-(C_6\text{-}C_{10})$aryl, $-S(O_2)-NH_2$, $-S(O_2)-NH-(C_1\text{-}C_6)$alkyl, $-S(O_2)-NH-(C_6\text{-}C_{10})$aryl, $-S(O_2)-N((C_1\text{-}C_6)\text{alkyl})_2$, $-S(O_2)-N((C_6\text{-}C_{10})\text{aryl})_2$, $-S(O_2)-N((C_1\text{-}C_6)\text{alkyl})((C_6\text{-}C_{10})\text{aryl})$, and $(C_6\text{-}C_{10})$aryl; and

each Z is independently selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$haloalkyl, F, Br, and Cl, -O-$(C_1\text{-}C_6)$alkyl, -CN, -OH, $(C_6\text{-}C_{10})$aryl, and N-oxide.

In another embodiment of the compounds of Formula (I),

R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2CH_2CH{=}CH_2$, $-CH_2CH_2CH{=}CHCH_3$, $-CH_2CH_2CH_2CH_2CH{=}CH_2$, $-CH_2CH_2CH_2CH{=}CH_2$, $-CH_2$-OH, -CH(CH_3)-OH, cyclobutyl, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CF_3$, $-CHBrCH_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclobutyl, $-CH_2CH_2$-cyclobutyl, $-CH_2CH_2CH_2$-cyclobutyl, $-CH_2CH_2CH_2CH_2$-cyclobutyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2CH_2CH_2$-cyclopentyl, $-CH_2CH_2CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C{\equiv}CH$, $-CH_2CH_2CH_2C{\equiv}CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), and $-CH_2$-NH(3-methoxyphenyl);

R^2 is selected from the group consisting of H, F, Cl, Br, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring;

R^3 is selected from the group consisting of H, -CH_2-cyclopropyl, -CH_2-C(O)-O-CH_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentyl, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH{=}CH_2$, and -CH_2-O-CH_3;

R^4 is selected from the group consisting of Cl, -O-R^{10}, -C(O)-O-CH_3, -$S(O)_2$-CH_3, -S(O)-CH_3, -S(O)-CH_2CH_3, -S(O)-$CH(CH_3)_2$, -S(O)-$C(CH_3)_3$, -S(O)-CH_2-cyclopropyl, -S(O)-CH_2-phenyl, -S(O)-$CH(CH_3)$-phenyl, -S-CH_2-$CH{=}CH_2$, -$N(R^7)_2$, -O-N=$C(CH_3)_2$, -NH-NH-C(O)-O-CH_3, and -C(O)-CH_3,

wherein the phenyl portion of said -S(O)-CH_2-phenyl, or -S(O)-$CH(CH_3)$-phenyl of R^4 is unsubstituted or substituted with one or more groups Y;

R^5 is selected from the group consisting of H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -CH_2-C(O)-phenyl, -CH_2-C(O)-OH, -CH_2-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, -CH_2-C(O)-piperidyl, -CH_2-cyclopropyl, -CH_2-C(O)-O-CH_3, and -CH_2-$CH{=}CH_3$,

wherein the phenyl portion of said -CH_2-C(O)-phenyl is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of –OR^{10}, Cl, and -$N(R^7)_2$;

each R^7 is independently selected from the group consisting of H, cyclobutyl, unsubstituted phenyl, and phenyl substituted with one or more Y groups;

R^{10} is selected from the group consisting of H, -CH_3, -CH_2-cyclopropyl, -CH_2-$CH{=}CH_3$, -$CH_2C{\equiv}C$-CH_3, -CH_2-phenyl, -$CH(CH_3)$-phenyl, -$CH(CH_2CH_3)$-phenyl, -$CH(CH_2CH_2CH_3)$-phenyl, -$CH(CH(CH_3)_2)$-phenyl, -$CH(CH_2CH{=}CH_2)$-phenyl, -CH_2-pyridyl, -$CH(CH_3)$-thiazolyl, and -CH_2-pyrimidinyl,

wherein the phenyl portion of said -CH_2-phenyl, -$CH(CH_3)$-phenyl, -$CH(CH_2CH_3)$-phenyl, -$CH(CH_2CH_2CH_3)$-phenyl, -$CH(CH(CH_3)_2)$-phenyl,

or -CH($CH_2CH=CH_2$)-phenyl of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of said -CH_2-pyridyl, -CH_2-thiazolyl, or -CH_2-pyrimidinyl of R^{10} is unsubstituted or substituted with one or more groups Z;

R^a and R^b are each $-CH_3$;

R^c is H;

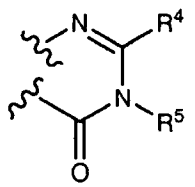
R^d is selected from the group consisting of H, -CH_3, and $-CH_2$-phenyl, wherein the phenyl portion of said $-CH_2$-phenyl of R^d is unsubstituted or substituted with one or more Y groups;

each Y is independently selected from the group consisting of F, Cl, Br, -CH_3, -CF_3, -O-CH_3, -O-CF_3, -CN, -OH, and phenyl; and

each Z is independently selected from the group consisting of $-CH_3$, -CF_3, F, Br, and Cl, -O-CH_3, -CN, -OH, phenyl, and N-oxide.

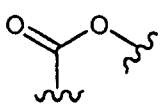
In another embodiment of the compounds of Formula (I),

Q is:



(a) ;

L is:



(f) ;

R^1 is selected from the group consisting of -(C_1-C_6)alkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, unsubstituted (C_6-C_{10})aryl, and (C_6-C_{10})aryl substituted with one or more substituents Y;

R^2 is H or halogen;

R^4 is selected from the group consisting of halogen, -O-R^{10}, -C(O)-O-(C_1-C_6)alkyl, -$S(O)_m$-R^9, -$N(R^7)_2$, -O-N=$C(R^{12})_2$, -N(R^7)-NH-C(O)-O-(C_1-C_6)alkyl, and -C(O)-(C_1-C_6)alkyl;

R^5 is H or (C_1-C_6)alkyl;

each R^7 is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, unsubstituted $(C_6$-$C_{10})$aryl, and $(C_6$-$C_{10})$aryl substituted with one or more Y groups;

R^9 is selected from the group consisting of $(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, and -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl,

wherein the $(C_6$-$C_{10})$aryl of said -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl of R^9 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, -$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl, -$(C_1$-$C_6)$alkylene-$(C_2$-$C_{10})$heteroaryl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, and -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl

wherein the aryl of said -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl or -$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl of R^{10} is unsubstituted or substituted with one or more groups Y, and the $(C_2$-$C_{10})$heteroaryl of said -$(C_1$-$C_6)$alkylene-$(C_2$-$C_{10})$heteroaryl of R^{10} is unsubstituted or substituted with one or more groups Z;

each R^{12} is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, and $(C_2$-$C_{10})$heteroaryl,

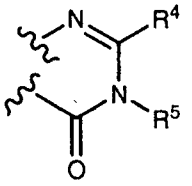
wherein the $(C_6$-$C_{10})$aryl is unsubstituted or substituted with one or more Y group, and said $(C_2$-$C_{10})$heteroaryl is unsubstituted or substituted with one or more Z group;

each Y is independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -CN, -NO_2, -OH, -$S(O_2)$-$(C_1$-$C_6)$alkyl, -$S(O_2)$-$(C_6$-$C_{10})$aryl, -$S(O_2)$-NH_2, -$S(O_2)$-NH-$(C_1$-$C_6)$alkyl, -$S(O_2)$-NH-$(C_6$-$C_{10})$aryl, -$S(O_2)$-$N((C_1$-$C_6)$alkyl$)_2$, -$S(O_2)$-$N((C_6$-$C_{10})$aryl$)_2$, -$S(O_2)$-$N((C_1$-$C_6)$alkyl$)((C_6$-$C_{10})$aryl), and $(C_6$-$C_{10})$aryl; and

each Z is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, halogen, -O-alkyl, -O-$(C_1$-$C_6)$haloalkyl, -CN, -OH, $(C_6$-$C_{10})$aryl, and, and N-oxide.

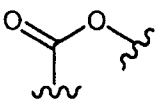
In another embodiment of the compounds of Formula (I),

Q is:



(a) ;

L is:



(f) ;

R^1 is $-CH_2CH_3$, butyl, pentyl, $-CH_2-CH_2-CH_2$-cyclopropyl;

R^2 is H, Br, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups;

R^4 is selected from the group consisting of Cl, $-O-R^{10}$, $-C(O)-O-CH_3$, $-S(O)-CH_3$, $-S(O)-CH_2CH_3$, $-S(O)-CH(CH_3)_2$, $-S(O)-C(CH_3)_3$, $-S(O)-CH_2$-cyclopropyl, $-S-CH_2-CH=CH_2$, $-S(O)-CH_2$-phenyl, $-S(O)-CH(CH_3)$-phenyl, $-N(R^7)_2$, $-O-N=C(CH_3)_2$, $-NH-NH-C(O)-O-CH_3$, and $-C(O)-CH_3$,

wherein the phenyl portion of said $-S(O)-CH_2$-phenyl, or $-S(O)-CH(CH_3)$-phenyl of R^4 is unsubstituted or substituted with one or more groups Y;

R^5 is H or $-CH_2CH_3$;

each R^7 is independently selected from the group consisting of H and cyclobutyl;

R^{10} is selected from the group consisting of H, $-CH_3$, $-CH_2$-cyclopropyl, $-CH_2-CH=CH_2$, $-CH_2C\equiv C-CH_3$, $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl, $-CH(CH(CH_3)_2)$-phenyl, $-CH(CH_2CH_2CH_3)$-phenyl, $-CH(CH_2CH=CH_2)$-phenyl, $-CH_2$-pyridyl, $-CH(CH_3)$-thiazolyl, $-CH_2$-pyrimidinyl,

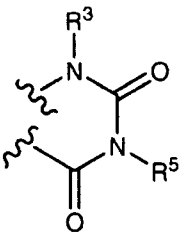
wherein the phenyl portion of said $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl, $-CH(CH(CH_3)_2)$-phenyl, $-CH(CH_2CH=CH_2)$-phenyl, or $-CH(CH_2CH_2CH_3)$-phenyl, of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of said $-CH_2$-pyridyl, $-CH(CH_3)$-thiazolyl, or $-CH_2$-pyrimidinyl of R^{10} is unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, and phenyl; and

each Z is independently selected from the group consisting of $-CH_3$, phenyl, and N-oxide.

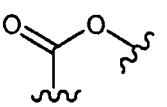
In another embodiment of the compounds of Formula (I),

Q is:



(b) ;

L is:



(f) ;

is selected from the group consisting of $-(C_1-C_6)$alkyl, $-(C_1-C_6)$alkenyl, $-(C_1-C_6)$alkynyl, $-(C_1-C_6)$alkylene-C(O)-O-(C_1-C_6)alkyl, $-(C_3-C_7)$cycloalkyl, $-(C_1-C_6)$alkylene-O-(C_1-C_6)alkyl, $-(C_1-C_6)$alkylene-(C_6-C_{10})aryl, $-(C_1-C_6)$alkylene-(C_2-C_{10})heteroaryl, $-(C_1-C_6)$alkylene-(C_3-C_7)cycloalkyl, $-(C_1-C_6)$alkylene-(C_3-C_7)cycloalkenyl, (C_1-C_6)alkyl substituted with one or more hydroxyl groups, $-(CH_2)_n-N(R^7)_2$, and $-(C_1-C_6)$haloalkyl

wherein the $-(C_3-C_7)$cycloalkyl or the (C_3-C_7)cycloalkyl portion of said $-(C_1-C_6)$alkylene-(C_3-C_7)cycloalkyl is unsubstituted or substituted with one or more X groups, the (C_6-C_{10})aryl portion of said $-(C_1-C_6)$alkylene-(C_6-C_{10})aryl is unsubstituted or substituted with one or more Y groups, and the (C_2-C_{10})heteroaryl portion of said $-(C_1-C_6)$alkylene-(C_2-C_{10})heteroaryl is unsubstituted or substituted with one or more Z groups;

R^2 is H;

R^3 is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_6)$alkylene-C(O)-O-$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, and -$(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl;

R^5 is selected from the group consisting of H, -$(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, -$(C_1$-$C_6)$alkylene-C(O)-R^8, -$(C_1$-$C_6)$alkylene-C(=N-O-$(C_1$-$C_6)$alkyl)-$(C_6$-$C_{10})$aryl, $(C_3$-$C_6)$cycloalkyl, -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl, and -$(C_1$-$C_6)$alkylene-C(O)-O-$(C_1$-$C_6)$alkyl;

each R^7 is independently selected from the group consisting of H and aryl, wherein the aryl of R^7 is unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted $(C_6$-$C_{10})$aryl, $(C_6$-$C_{10})$aryl substituted with one or more Y groups, -OH, unsubstituted $(C_2$-$C_{10})$heterocyclyl and $(C_2$-$C_{10})$heterocyclyl substituted with one or more X groups;

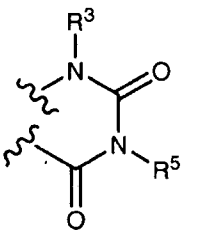
each X is independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -O-$(C_1$-$C_6)$haloalkyl, and –OH;

each Y is independently selected from the group consisting of halogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -CN, -NO_2, -OH, -$S(O_2)$-$(C_1$-$C_6)$alkyl, -$S(O_2)$-$(C_6$-$C_{10})$aryl, -$S(O_2)$-NH_2, -$S(O_2)$-NH-$(C_1$-$C_6)$alkyl, -$S(O_2)$-NH-$(C_6$-$C_{10})$aryl, -$S(O_2)$-N$((C_1$-$C_6)$alkyl$)_2$, -$S(O_2)$-N$((C_6$-$C_{10})$aryl$)_2$, -$S(O_2)$-N$((C_1$-$C_6)$alkyl$)((C_6$-$C_{10})$aryl), and $(C_6$-$C_{10})$aryl; and

each Z is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, F, Br, and Cl, -O-$(C_1$-$C_6)$alkyl, -CN, -OH, $(C_6$-$C_{10})$aryl, and N-oxide.

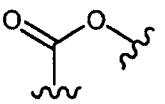
In another embodiment of the compounds of Formula (I),

Q is:



(b) ;

L is:



(f) ;

R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2CF_3$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, $-CH_2OH$, $-CH(CH_3)OH$, $-CH_2N(R^7)_2$, cyclobutyl, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), and $-CHBrCH_3$;

R^2 is H; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring;

R^3 is selected from the group consisting of H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, -cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH=CH_2$, and $-CH_2$-O-CH_3;

R^5 is selected from the group consisting of H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, $-CH_2$-C(O)-R^8, $-CH_2$-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, and $-CH_2CH=CH_2$;

each R^7 is independently H or phenyl,

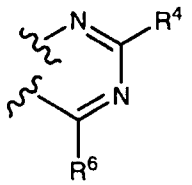
wherein the phenyl of R^7 is unsubstituted or substituted with one or more Y groups;

R^8 is selected from the group consisting of unsubstituted phenyl, phenyl substituted with one or more Y groups, -OH, and piperidyl; and

each Y is independently selected from the group consisting of F, $-CF_3$, $-OCH_3$, -CN, and –OH.

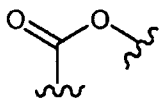
In another embodiment of the compounds of Formula (I),

Q is:



(c) ;

L is:



(f) ;

R^1 is selected from the group consisting of -(C_1-C_6)alkyl, -(C_1-C_6)alkenyl, -(C_1-C_6)alkynyl, -(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl, -(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl, -(C_1-C_6)alkylene-(C_6-C_{10})aryl, -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl, -(C_1-C_6)alkylene-(C_3-C_7)cycloalkenyl, -(C_1-C_6)alkyl substituted with one or more hydroxyl groups, -$(CH_2)_n$-$N(R^7)_2$, and -(C_1-C_6)haloalkyl

wherein the -(C_3-C_7)cycloalkyl or the (C_3-C_7)cycloalkyl portion of said -(C_1-C_6)alkylene-(C_3-C_7)cycloalkyl is unsubstituted or substituted with one or more X groups, the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl is unsubstituted or substituted with one or more Y groups, and the (C_2-C_{10})heteroaryl portion of said -(C_1-C_6)alkylene-(C_2-C_{10})heteroaryl is unsubstituted or substituted with one or more Z groups;

R^2 is H; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring;

R^4 is selected from the group consisting of halogen, -O-R^{10}, -C(O)-O-(C_1-C_6)alkyl, -$S(O)_m$-R^9, -$N(R^7)_2$, -O-N=$C(R^{12})_2$, -$N(R^7)$-NH-C(O)-O-(C_1-C_6)alkyl, and -C(O)-(C_1-C_6)alkyl;

R^6 is selected from the group consisting of –O-R^{10}, halogen, and -$N(R^7)_2$;

each R^7 is independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, unsubstituted $(C_6$-$C_{10})$aryl, and $(C_6$-$C_{10})$aryl substituted with one or more Y groups;

R^9 is selected from the group consisting of $(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkenyl, and -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl,

wherein the $(C_6$-$C_{10})$aryl portion of said -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl of R^9 is unsubstituted or substituted with one or more groups Y;

R^{10} is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, -$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl, -$(C_1$-$C_6)$alkylene-$(C_2$-$C_{10})$heteroaryl, $(C_2$-$C_6)$alkenyl, $(C_2$-$C_6)$alkynyl, and -$(C_1$-$C_6)$alkylene-$(C_3$-$C_6)$cycloalkyl,

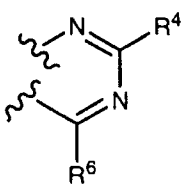
wherein the $(C_6$-$C_{10})$aryl portion of said -$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl or -$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl of R^{10} is unsubstituted or substituted with one or more groups Y, and the $(C_2$-$C_{10})$heteroaryl portion of said -$(C_1$-$C_6)$alkylene-$(C_2$-$C_{10})$heteroaryl of R^{10} is unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Br, Cl, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, -O-$(C_1$-$C_6)$alkyl, -O-$(C_1$-$C_6)$haloalkyl, -CN, -NO_2, -OH, , -$S(O_2)$-$(C_1$-$C_6)$alkyl, -$S(O_2)$-$(C_6$-$C_{10})$aryl, -$S(O_2)$-NH_2, -$S(O_2)$-NH-$(C_1$-$C_6)$alkyl, -$S(O_2)$-NH-$(C_6$-$C_{10})$aryl, -$S(O_2)$-N$((C_1$-$C_6)$alkyl$)_2$, -$S(O_2)$-N$((C_6$-$C_{10})$aryl$)_2$, -$S(O_2)$-N$((C_1$-$C_6)$alkyl$)((C_6$-$C_{10})$aryl), and $(C_6$-$C_{10})$aryl; and

each Z is independently selected from the group consisting of $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$haloalkyl, F, Br, and Cl, -O-$(C_1$-$C_6)$alkyl, -CN, -OH, $(C_6$-$C_{10})$aryl, and N-oxide.

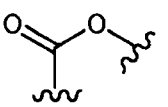
In another embodiment of the compounds of Formula (I),

Q is:



(c) ;

L is:



(f) ;

R^1 is selected from the group consisting of $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2$-OH, $-CH(CH_3)$-OH, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, cyclobutyl, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), $-CHBrCH_3$ and $-CH_2CF_3$;

R^2 is H; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a cyclopentenyl or cyclohexenyl ring

R^4 is selected from the group consisting of Cl, -O-R^{10}, -C(O)-O-CH_3, -S(O)$_2$-CH_3, -S(O)-CH_3, -S(O)-CH_2CH_3, -S(O)-$CH(CH_3)_2$, -S(O)-$C(CH_3)_3$, -S(O)-CH_2-cyclopropyl, -S-CH_2-$CH=CH_2$, -S(O)-CH_2-phenyl, -S(O)-$CH(CH_3)$-phenyl, -N(R^7)$_2$, -O-N=$C(CH_3)_2$, -NH-NH-C(O)-O-CH_3, and -C(O)-CH_3,

wherein the phenyl portion of said -S(O)-CH_2-phenyl, or -S(O)-$CH(CH_3)$-phenyl of R^4 is unsubstituted or substituted with one or more groups Y;

R^6 is selected from the group consisting of -O-R^{10}, -N(R^7)$_2$, and Cl;

each R^7 is independently selected from the group consisting of H, unsubstituted phenyl, phenyl substituted with one or more Y groups, and cyclobutyl;

R^{10} is selected from the group consisting of H, CH_3, $-CH_2$-cyclopropyl, $-CH_2$-C$\equiv$C-CH_3, $-CH_2$-$CH=CH_2$, $-CH_2$-phenyl, $-CH(CH_3)$-phenyl,

-CH(CH_2CH_3)-phenyl, -CH($CH(CH_3)_2$)-phenyl, -CH($CH_2CH_2CH_3$)-phenyl, -CH($CH_2CH{=}CH_2$)-phenyl, -CH_2-pyridyl, -CH(CH_3)-thiazolyl, -CH_2-pyrimidinyl,

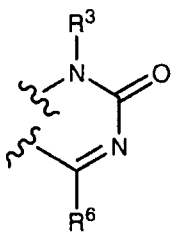
wherein the phenyl portion of said -CH_2-phenyl, -CH(CH_3)-phenyl, -CH(CH_2CH_3)-phenyl, -CH($CH_2CH{=}CH_2$)-phenyl, or -CH($CH_2CH_2CH_3$)-phenyl of R^{10} is unsubstituted or substituted with one or more groups Y, and the pyridyl, thiazolyl, or pyrimidinyl portion of said -CH_2-pyridyl, -CH(CH_3)-thiazolyl, or -CH_2-pyrimidinyl of R^{10} is unsubstituted or substituted with one or more groups Z;

each Y is independently selected from the group consisting of F, Cl, Br, -CH_3, -CF_3, -O-CH_3, -O-CF_3, -CN, -OH, and phenyl; and

each Z is independently selected from the group consisting of -CH_3, F, Br, and Cl, -O-CH_3, -CN, -OH, phenyl, and N-oxide.

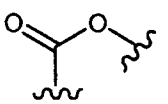
In another embodiment of the compounds of Formula (I),

Q is:



(d) ;

L is:



(f) ;

R^1 is -(C_1-C_6)alkyl;

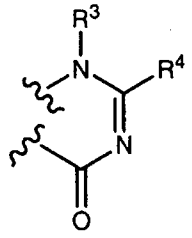
R^2 is H;

R^3 is H or -(C_2-C_6)alkenyl; and

R^6 is -OH or -O-(C_1-C_6)alkylene-(C_1-C_6)cycloalkyl.

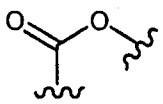
In another embodiment of the compounds of Formula (I),

Q is:



(e) ;

L is:



(f) ;

R^1 is -(C_1-C_6)alkyl or -(C_1-C_6)haloalkyl;

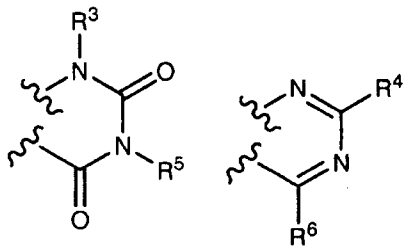
R^2 is H;

R^3 is selected from the group consisting of H, -(C_1-C_6)alkylene-(C_1-C_6)cycloalkyl, -(C_1-C_6)alkylene-C(O)-O-(C_1-C_6)alkyl, -(C_1-C_6)cycloalkyl, (C_1-C_6)alkyl, (C_2-C_6)alkenyl, and -(C_1-C_6)alkylene-O-(C_1-C_6)alkyl; and

R^4 is -O-N=C((C_1-C_6)alkyl)$_2$.

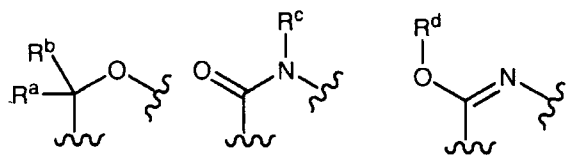
In another embodiment of the compounds of Formula (I),

Q is:



(b) or (c) ;

L is selected from the group consisting of:



(g) , (h) , and (i) ;

R^a and R^b are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_6-C_{10})aryl, and (C_2-C_{10})heteroaryl,

wherein the (C_6-C_{10})aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said (C_2-C_{10})heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, (C_1-C_6)alkyl, -(C_1-C_6)alkylene-(C_6-C_{10})aryl, and -C(O)-(C_1-C_6)alkyl,

wherein the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, (C_1-C_6)alkyl, and -(C_1-C_6)alkylene-(C_6-C_{10})aryl,

wherein the (C_6-C_{10})aryl portion of said -(C_1-C_6)alkylene-(C_6-C_{10})aryl of R^d is unsubstituted or substituted with one or more Y groups;

R^1 is (C_1-C_6)alkyl or or -(C_1-C_6)haloalkyl;

R^2 is H;

R^3 is H;

R^4 is –O-R^{10};

R^5 is H or -(C_1-C_6)alkylene-(C_3-C_6)cycloalkyl;

R^6 is –O-R^{10};

R^{10} is H, (C_1-C_6)alkyl, or -(C_1-C_6)alkylene-(C_6-C_{10})aryl; and

each Y is independently selected from the group consisting of F, Br, Cl, (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, -O-(C_1-C_6)alkyl, -O-(C_1-C_6)haloalkyl, -CN, -NO_2, -OH, , -$S(O_2)$-(C_1-C_6)alkyl, -$S(O_2)$-(C_6-C_{10})aryl, -$S(O_2)$-NH_2, -$S(O_2)$-NH-(C_1-C_6)alkyl, -$S(O_2)$-NH-(C_6-C_{10})aryl, -$S(O_2)$-N((C_1-C_6)alkyl)$_2$, -$S(O_2)$-N((C_6-C_{10})aryl)$_2$, -$S(O_2)$-N((C_1-C_6)alkyl)((C_6-C_{10})aryl), and (C_6-C_{10})aryl; and

each Z is independently selected from the group consisting of (C_1-C_6)alkyl, (C_1-C_6)haloalkyl, F, Br, and Cl, -O-(C_1-C_6)alkyl, -CN, -OH, (C_6-C_{10})aryl, and N-oxide.

In another embodiment of the Formula (I), R^1 is –CH_3, –CH_2CH_3, -$CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_3$, -$CH(CH_3)_2$, -CH_2-C(O)-O-CH_2CH_3, -CH_2CF_3, -CH_2-OH, -$CH(CH_3)$OH, -CH_2-N(R^7)$_2$, -CH_2-NH(3-methoxyphenyl), -$CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH_2CH_2CH_2CH_3$, -$CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH_2CH(CH_3)_2$, -$CH_2CH_2CH{=}CH_2$, -$CH_2CH_2CH{=}CHCH_3$, -$CH_2CH_2CH_2CH_2CH{=}CH_2$, -$CH_2CH_2CH_2CH{=}CH_2$, cyclobutyl, -$CH_2CH_2CH_2$-O-$CH_3$, -$CH_2CF_3$, -$CHBrCH_3$,

$-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$, , $-CH_2$-(2-thiophenyl), $-CH_2CH_2CH_2$-(2-thiophenyl), $-CH_2$-cyclopropyl, $-CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2$-cyclopropyl, $-CH_2CH_2CH_2CH_2$-cyclopropyl, $-CH_2$-cyclopentyl, $-CH_2CH_2$-cyclopentyl, $-CH_2$-cyclohexyl, $-CH_2$-(4-methylcyclohexyl), $-CH_2CH_2$-cyclohexyl, $-CH_2$-cycloheptyl, $-CH_2$-(2-cyclopentenyl, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-phenyl, $-CH_2$-(2-fluorophenyl), $-CH_2$-(3-fluorophenyl), or $-CHBrCH_3$.

In another embodiment of the Formula (I), R^2 is H.

In another embodiment of the Formula (I), R^2 is Br.

In another embodiment, R^1 and R^2 together with the ring carbon atoms to which they are shown attached in Formula (I), form a cyclopentenyl or cyclohexenyl ring.

In another embodiment of the Formula (I), R^3 is H, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, -cyclopropyl, cyclobutyl, cyclopentyl, $-CH_3$, $-CH_2CH_3$, $-CH_2$-CH_2CH_3, $-CH_2CH=CH_2$, or $-CH_2$-O-CH_3.

In another embodiment of the Formula (I), R^4 is Cl, -OH, -O-CH_3, -O-CH_2-cyclopropyl, $-CH_2$-C≡C-CH_3, -O-CH_2-phenyl, -O-CH(CH_3)-phenyl, -O-CH(CH_2CH_3)-phenyl, -O-CH($CH_2CH_2CH_3$)-phenyl, -O-CH($CH(CH_3)_2$)-phenyl, -O-CH($CH_2CH=CH_2$)-phenyl, -O-CH_2-pyridyl, -O-CH_2-thiazolyl, -O-CH(CH_3)-thiazolyl, -O-CH_2-pyrimidinyl, -C(O)-O-CH_3, -S(O_2) -CH_3, -S(O)-CH_3, -S(O)-CH_2CH_3, -S(O)-$CH(CH_3)_2$, -S(O)-$C(CH_3)_3$, -S(O)-CH_2-cyclopropyl, -S(O)-CH_2-phenyl, -S(O)-CH(CH_3)-phenyl, -S(O)-$N(R^{11})_2$, -S(O_2)-$N(R^{11})_2$, -S-CH_2-$CH=CH_2$, -N(H)cyclobutyl, -N(H)phenyl, -NH-NH-C(O)-O-CH_3, -O-CH_2-$CH=CH_2$, -O-N=$C(CH_3)_2$, or -C(O)-CH_3, wherein the phenyl portions of any of these groups can be unsubstituted or substituted with one or more Y groups as defined herein, the cyclobutyl portions of any of these groups may be unsubstituted or substituted with one or more X groups as defined herein, and the pyridyl, thiazolyl, or pyrimidinyl portions of any of these groups can be unsubstituted or substituted with one or more Z groups as defined herein.

In another embodiment of the compound of Formula (I), R^5 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2$-C(O)-phenyl, $-CH_2$-C(O)-OH, $-CH_2$-C(=N-O-CH_3)-phenyl, cyclopropyl, cyclobutyl, cyclopentyl, $-CH_2$-C(O)-piperidyl, $-CH_2$-cyclopropyl, $-CH_2$-C(O)-O-CH_3, or $-CH_2$-$CH=CH_3$, wherein the phenyl of said

$-CH_2$-C(O)-phenyl of R^5 is unsubstituted or substituted with one or more Y groups as defined herein, said cyclopropyl, the cyclopropyl of said $-CH_2$-cyclopropyl, cyclobutyl, cyclopentyl, or the piperidyl of said $-CH_2$-C(O)-piperidyl of R^5 are unsubstituted or substituted with one or more X groups as defined herein.

In another embodiment of the compound of Formula (I), R^6 is -OH, Cl, $-O-CH_3$, $-O-CH_2$-cyclopropyl, $-O-CH_2-CH=CH_3$, $-O-CH_2$-phenyl, $-O-CH(CH_3)$-phenyl, $-O-CH(CH_2CH_3)$-phenyl, $-O-CH(CH_2CH_2CH_3)$-phenyl, $-O-CH(CH(CH_3)_2)$-phenyl, $-O-CH(CH_2CH=CH_2)$-phenyl, $-O-CH_2$-pyridyl, $-O-CH_2$-thiazolyl, $-O-CH_2$-pyrimidinyl, and -N(H)cyclobutyl, -N(H)phenyl, $-NH-NH-C(O)-O-CH_3$, wherein the phenyl of said $-O-CH_2$-phenyl, $-O-CH(CH_3)$-phenyl, $-O-CH(CH_2CH_3)$-phenyl, $-O-CH(CH_2CH_2CH_3)$-phenyl, $-O-CH(CH(CH_3)_2)$-phenyl, or $-O-CH(CH_2CH=CH_2)$-phenyl of R^6 is unsubstituted or substituted with one or more groups Y as defined herein, and the pyridyl, thiazolyl , or pyrimidinyl of said $-O-CH_2$-pyridyl, $-O-CH_2$-thiazolyl, or $-O-CH_2$-pyrimidinyl of R^6 is unsubstituted or substituted with one or more groups Z as defined herein.

In another embodiment of the compound of Formula (I), each R^7 is independently H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, unsubstituted phenyl, phenyl substituted with one or more Y groups, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, $-C(O)-CH_3$, and -C(O)-phenyl. Alternatively, two groups R^7, together with the N atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or pyrrolyl ring.

In another embodiment of the compound of Formula (I), R^8 is $-CH_3$, unsubstituted phenyl, phenyl substituted with one or more Y groups, piperidyl, and -OH.

In another embodiment of the compound of Formula (I), R^9 is $-CH_3$, $-CH_2CH_3$, $-CH(CH_3)_2$, $-C(CH_3)_3$, $-CH_2$-cyclopropyl, $-CH_2-CH=CH_2$ (allyl), $-CH_2$-phenyl, and $-CH(CH_3)$-phenyl.

In another embodiment of the compound of Formula (I), R^{10} is H, $-CH_2C\equiv CCH_3$, $-CH_2$-cyclopropyl, $-CH_2CH=CH_2$, $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl, $-CH(CH(CH_3)_2)$-phenyl, $-CH_2$-pyridyl, $-CH_2$-thiazolyl, $-CH(CH_3)$-thiazolyl, $-CH_2$-pyrimidyl, $-CH(CH_2CH=CH_2)$-phenyl, $-CH(CH_2CH_2CH_3)$-phenyl, wherein the phenyl portion of $-CH_2$-phenyl, $-CH(CH_3)$-phenyl, $-CH(CH_2CH_3)$-phenyl,

-CH(CH(CH_3)$_2$)-phenyl, -CH(CH_2CH=CH_2)-phenyl, and -CH($CH_2CH_2CH_3$)-phenyl of R^{10} are unsubstituted or substituted with one or more Y groups, and the pyridyl, thiazolyl, and pyrimidyl portion of said -CH_2-pyridyl, -CH_2-thiazolyl, -CH(CH_3)-thiazolyl, -CH_2-pyrimidyl are unsubstituted or substituted with one or more Z groups.

In another embodiment of the compound of Formula (I), R^{11} is H, -CH_3, or phenyl, wherein the phenyl is unsubstituted or substituted with one or more Y groups. Alternatively, two groups R^{11}, together with the N atom to which they are attached, form an azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyrrolidinonyl, triazolyl, or pyrrolyl ring.

In another embodiment of the compound of Formula (I), R^{12} is H, -CH_3, -CH_2CH_3, or unsubstituted pyridyl or pyridyl substituted with one or more Z groups.

In another embodiment of the compound of Formula (I), R^a is H or -CH_3.

In another embodiment of the compound of Formula (I), R^b is H or -CH_3.

In another embodiment of the compound of Formula (I), R^a and R^b are both –CH_3.

In another embodiment of the compound of Formula (I), R^c is H or -CH_3.

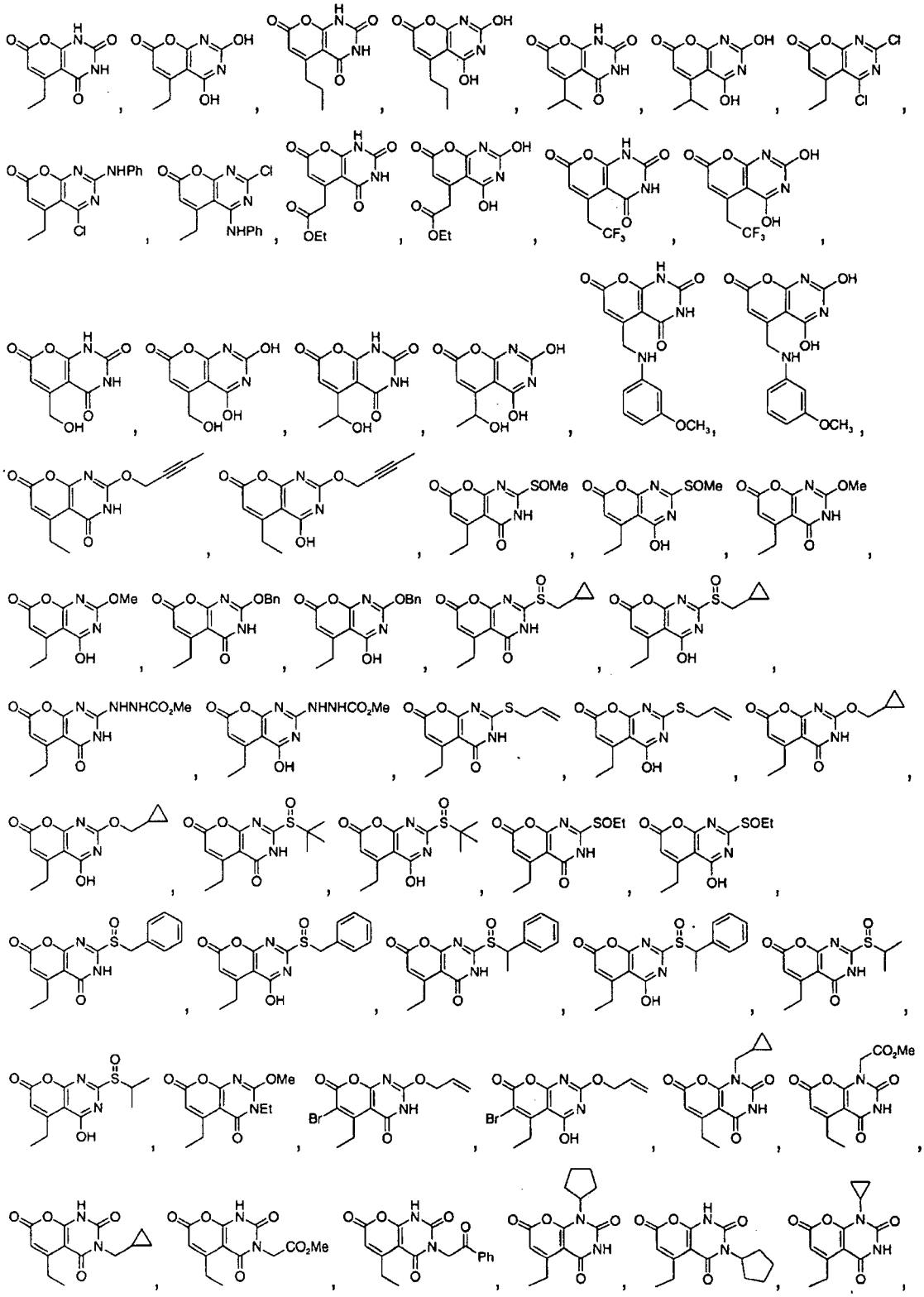
In another embodiment of the compound of Formula (I), R^d is H, -CH_3, or -CH_2-phenyl, wherein the phenyl portion of said –CH_2-phenyl of R^d is unsubstituted or substituted with one or more Y groups as defined herein.

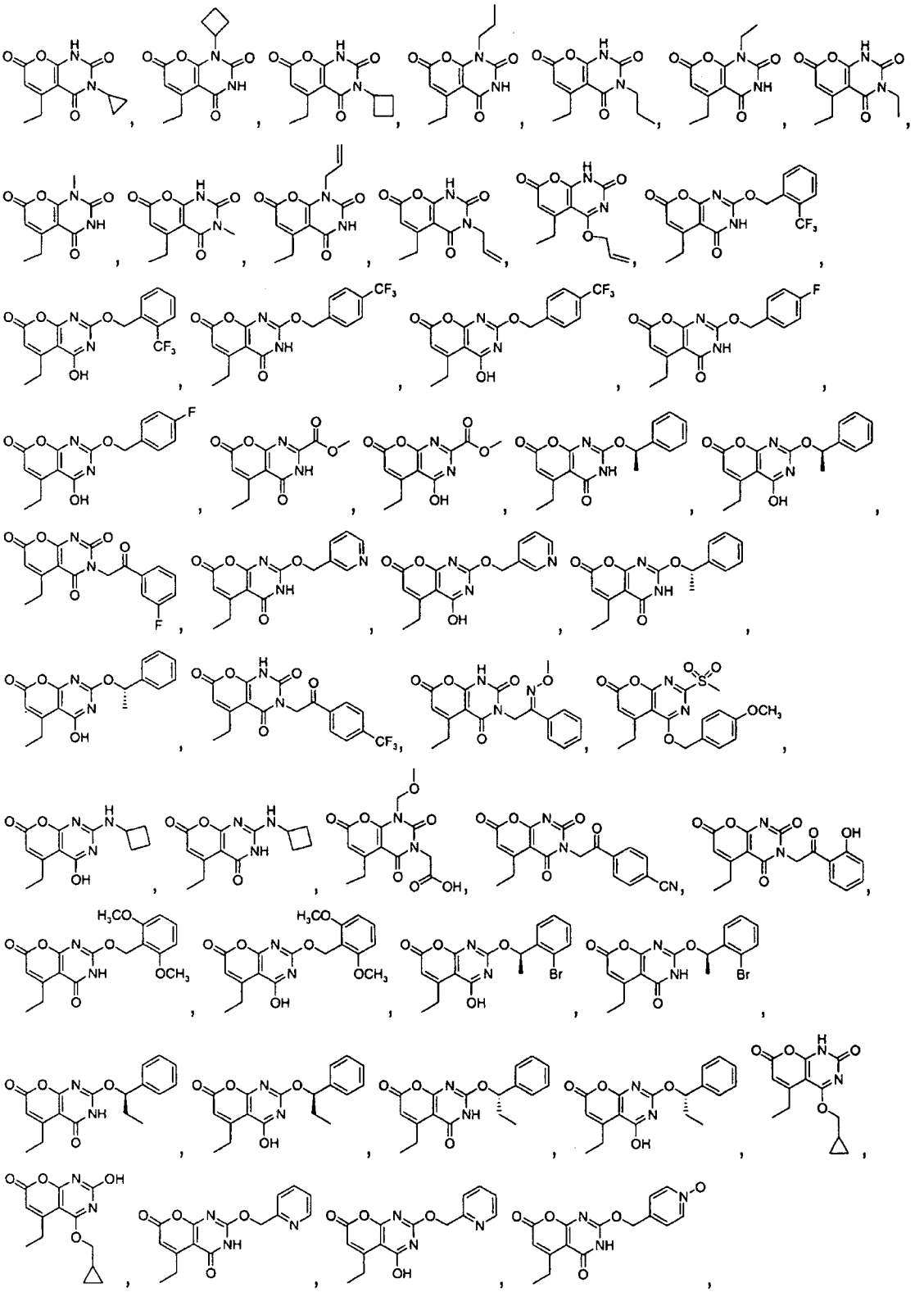
In another embodiment of the compound of Formula (I), each X is independently selected from the group consisting of –CH_3, -CF_3, F, Br, and Cl, -O-CH_3, , -O-CF_3, -CN, -OH, phenyl, and N-oxide;

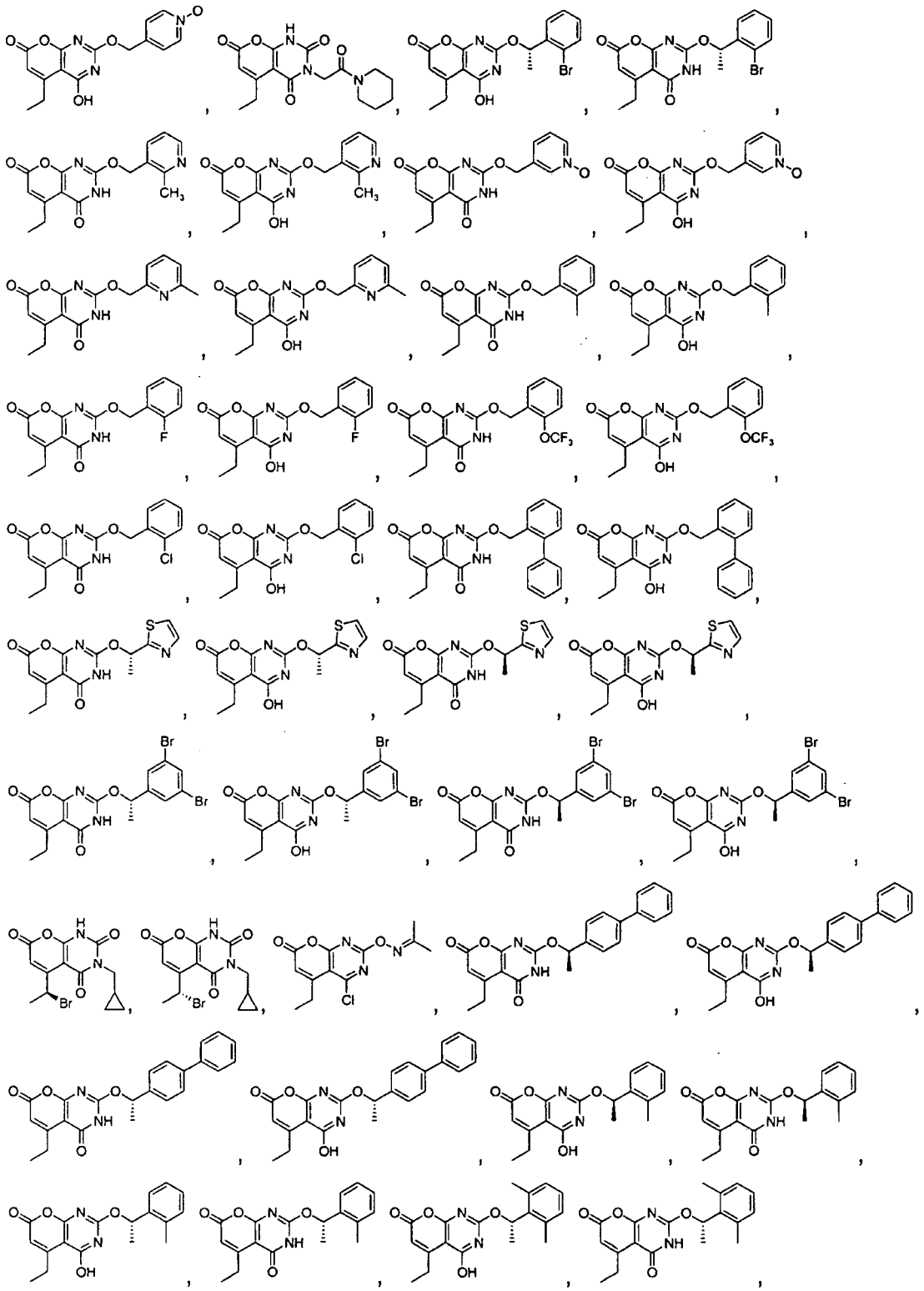
In another embodiment of the compound of Formula (I), each Y is independently selected from the group consisting of F, Cl, Br, -CH_3, -CF_3, -O-CH_3, -O-CF_3, -CN, -OH, and phenyl; and

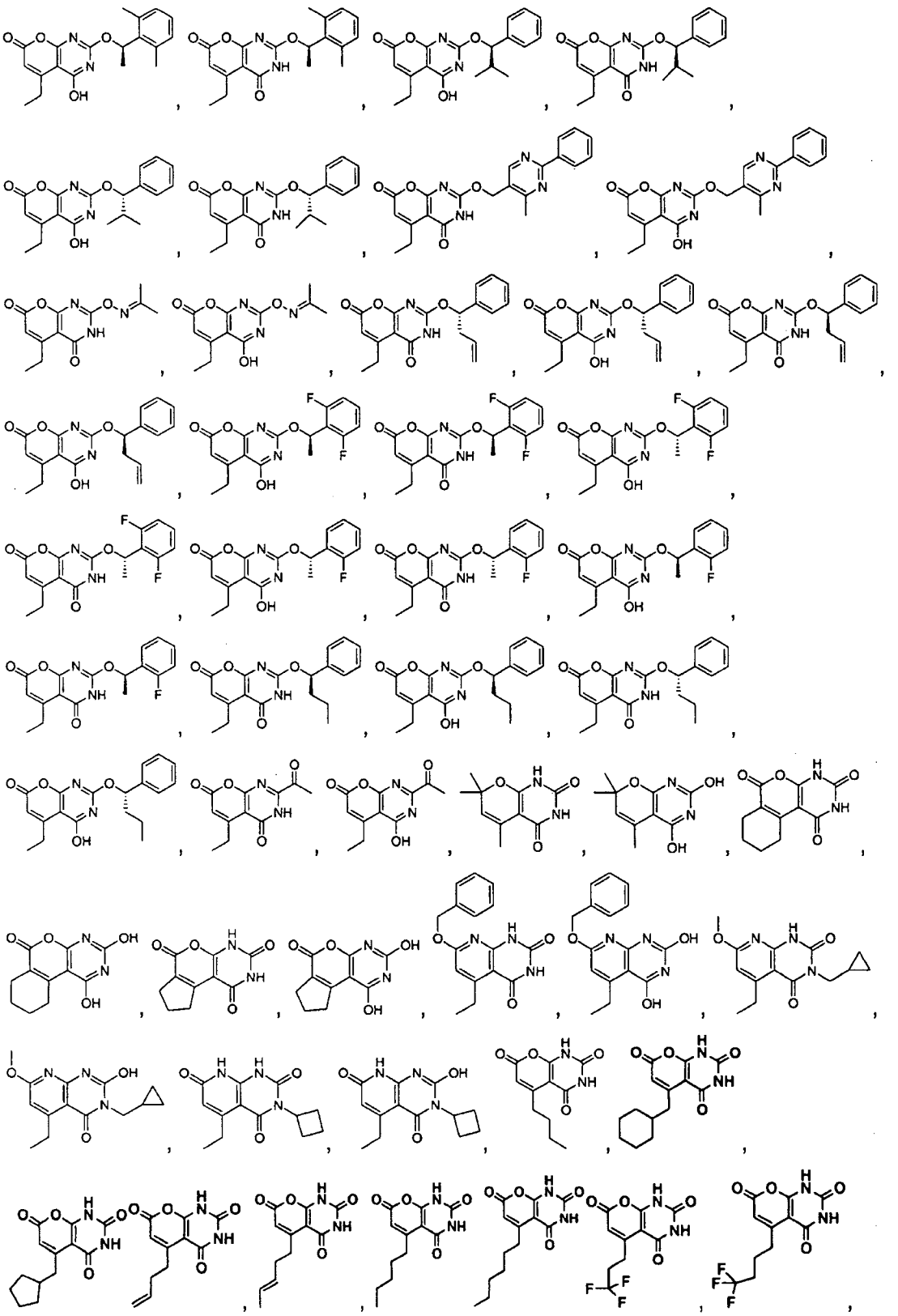
In another embodiment of the compound of Formula (I), each Z is independently selected from the group consisting of –CH_3, -CF_3, F, Br, and Cl, -O-CH_3, -O-CF_3, -CN, -OH, phenyl, and N-oxide.

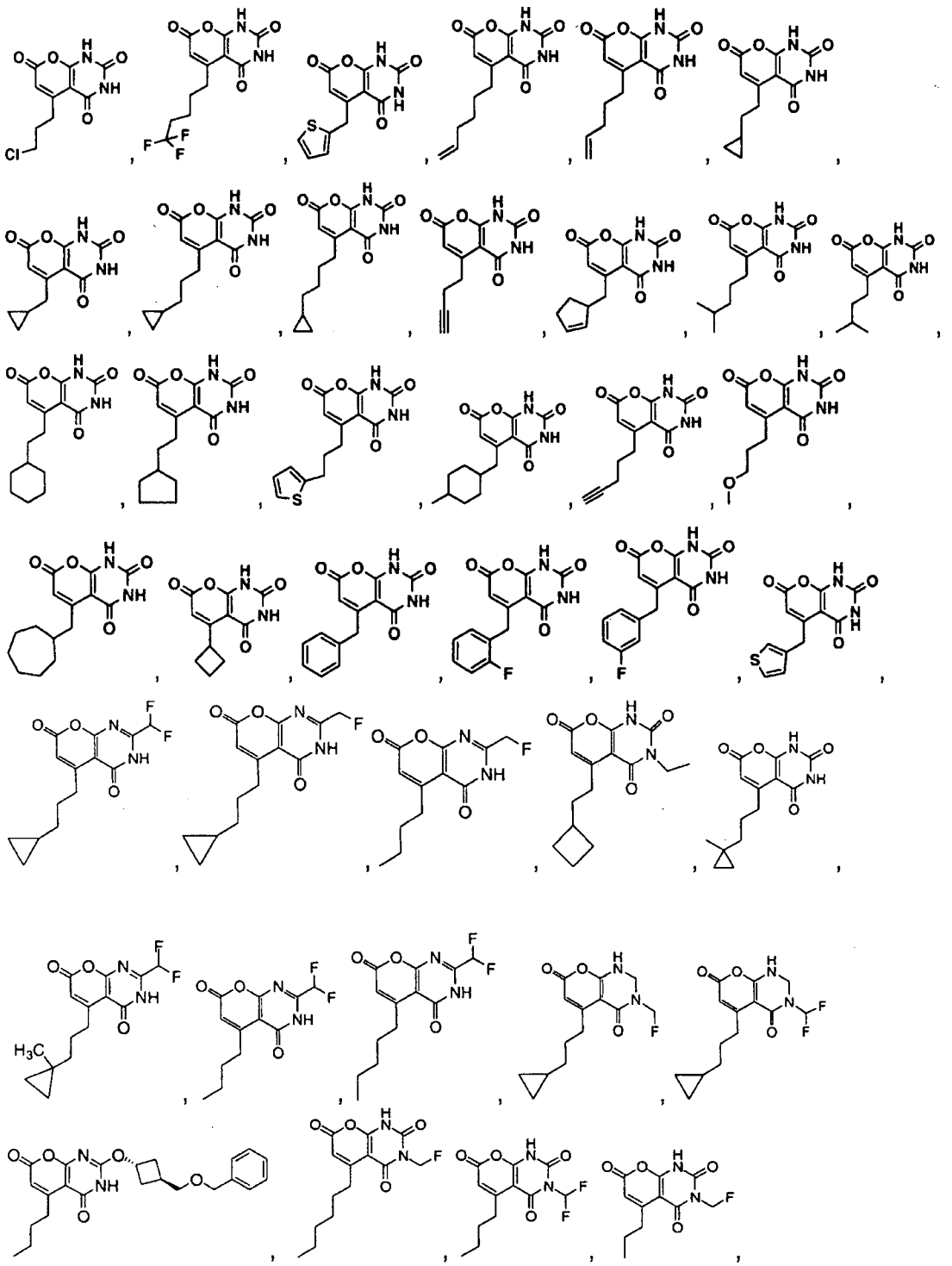
Non-limiting illustrative examples of the compounds of formula (I), include the following compounds:

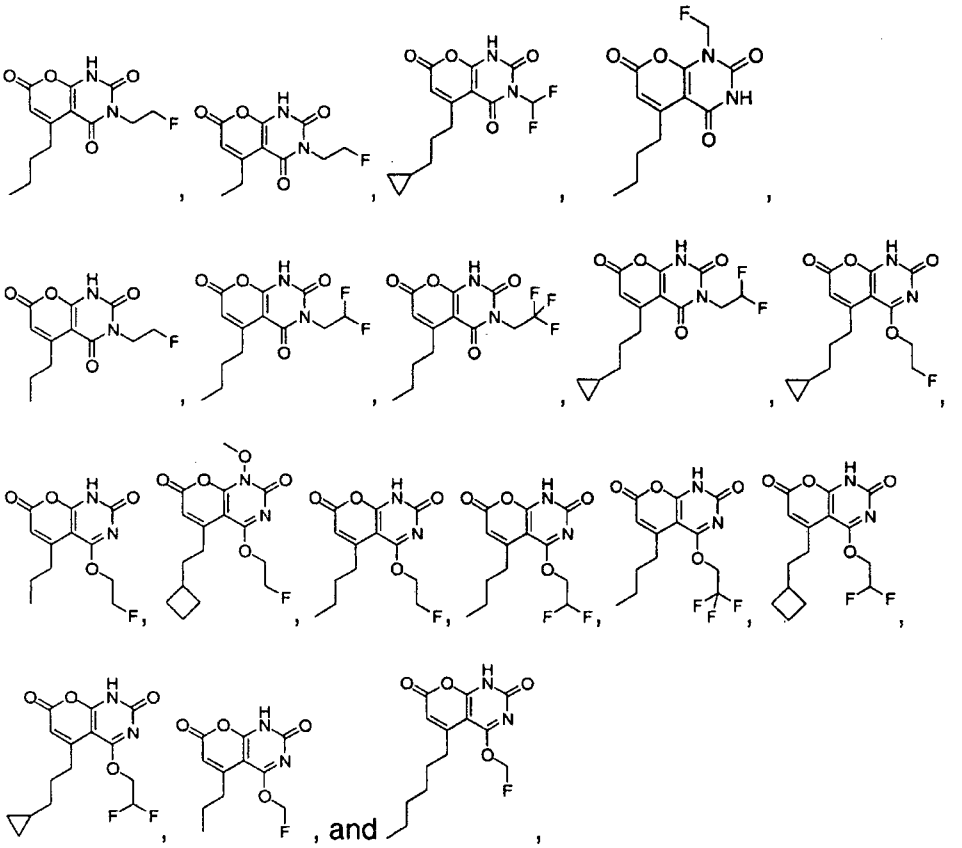






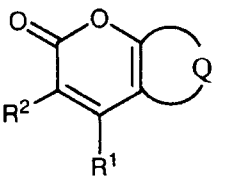






and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

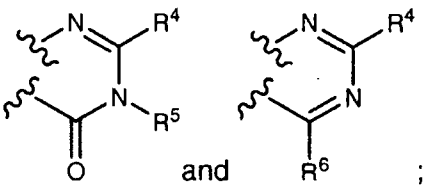
In one embodiment, the compounds of formula (I) have the formula (II):



(II)

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

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

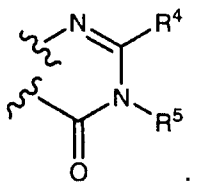
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

The following embodiments refer to the compounds of formula (II), wherein Q is:



In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is –H.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

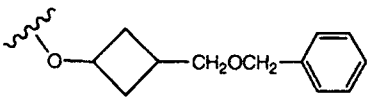
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

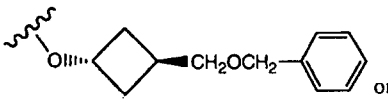
In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

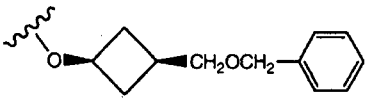
In one embodiment, R^4 is –O-cyclobutyl.

In another embodiment, R^4 is:



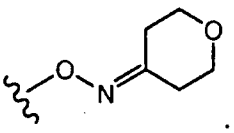
,


or



.

In one embodiment, R^4 is:



.

In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^1 is alkyl and R^5 is –H.

In another embodiment, R^1 is haloalkyl and R^5 is –H.

In another embodiment, R^1 is arylalkyl and R^5 is –H.

In still another embodiment, R^1 is -alkylene-S-alkyl and R^5 is –H.

In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^5 is –H.

In one embodiment, R^1 is alkyl and R^5 is –H.

In another embodiment, R^1 is haloalkyl and R^5 is –H

In another embodiment, R^1 is arylalkyl and R^5 is –H.

In still another embodiment, R^1 is -alkylene-S-alkyl and R^5 is –H.

In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^5 is –H.

In one embodiment, R^1 is alkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is alkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is alkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is alkyl, R^5 is –H and R^4 is $-O-N=C(R^7)_2$.

In one embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is haloalkyl, R^5 is –H and R^4 is $-O-N=C(R^7)_2$.

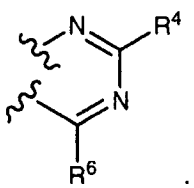
In one embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is –O-alkynyl.

In another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is haloalkyl.

In still another embodiment, R^1 is -alkylene-cycloalkyl, R^5 is –H and R^4 is $-O-N=C(R^7)_2$.

The following embodiments refer to the compounds of formula (II), wherein Q is:



In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is arylalkyl.

In still another embodiment, R^1 is -alkylene-S-alkyl.

In yet another embodiment, R^1 is -alkylene-cycloalkyl.

In another embodiment, R^1 is -alkylene-cyclopropyl, -alkylene-cyclobutyl, -alkylene-cyclopentyl or -alkylene-cyclohexyl.

In a further embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is –H.

In another embodiment, R^4 is -O-cycloalkyl.

In another embodiment, R^4–O-alkynyl.

In still another embodiment, R^4 is -O-alkynylene-cycloalkyl.

In yet another embodiment, R^4 is haloalkyl.

In a further embodiment, R^4 is $-O\text{-}N{=}C(R^7)_2$.

In one embodiment, R^4 is is $-CH_2F$.

In another embodiment, R^4 is $-CH(F)_2$.

In another embodiment, R^4 is $-CF_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

In yet another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclopropyl.

In a further embodiment, R^4 is $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

In one embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

In another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

In still another embodiment, R^4 is $-OCH_2C{\equiv}CCH_2CH_2OH$.

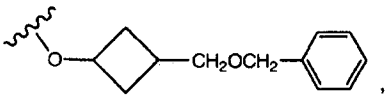
In yet another embodiment, R^4 is $-OCH_2C{\equiv}C(CH_2)_3OH$.

In a further embodiment, R^4 is $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

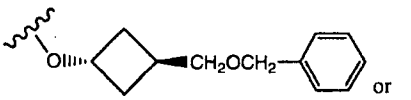
In another embodiment, R^4 is $-OCH_2C{\equiv}C$-cyclohexyl.

In one embodiment, R^4 is $-O$-cyclobutyl.

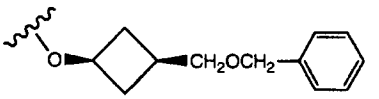
In another embodiment, R^4 is:



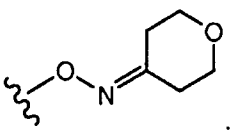
,



or



In one embodiment, R^4 is:



In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

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

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, R^1 is alkyl and R^4 is –O-alkynyl.

In another embodiment, R^1 is alkyl and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is alkyl and R^4 is haloalkyl.

In still another embodiment, R^1 is alkyl and R^4 is $-O-N=C(R^7)_2$.

In one embodiment, R^1 is haloalkyl and R^4 is –O-alkynyl.

In another embodiment, R^1 is haloalkyl and R^4 is -O-alkynylene-cycloalkyl.

In another embodiment, R^1 is haloalkyl and R^4 is haloalkyl.

In still another embodiment, R^1 is haloalkyl and R^4 is $-O-N=C(R^7)_2$.

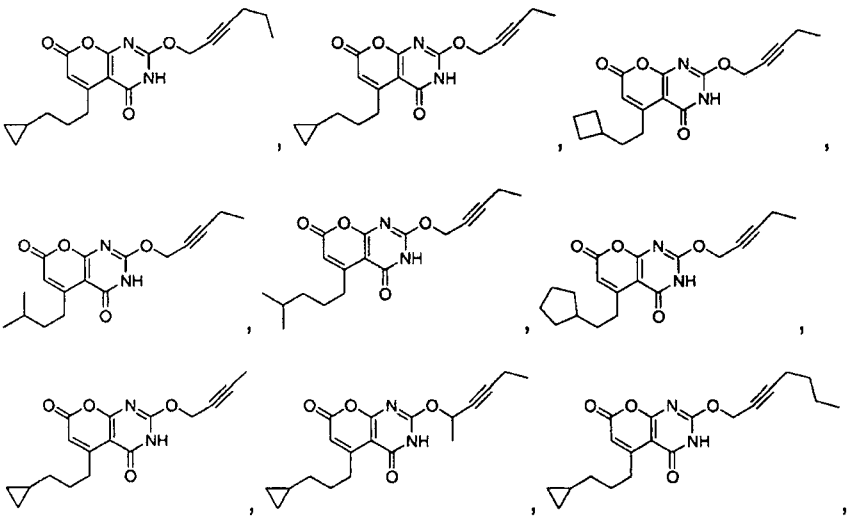
In one embodiment, R^1 is -alkylene-cycloalkyl and R^4 is –O-alkynyl.

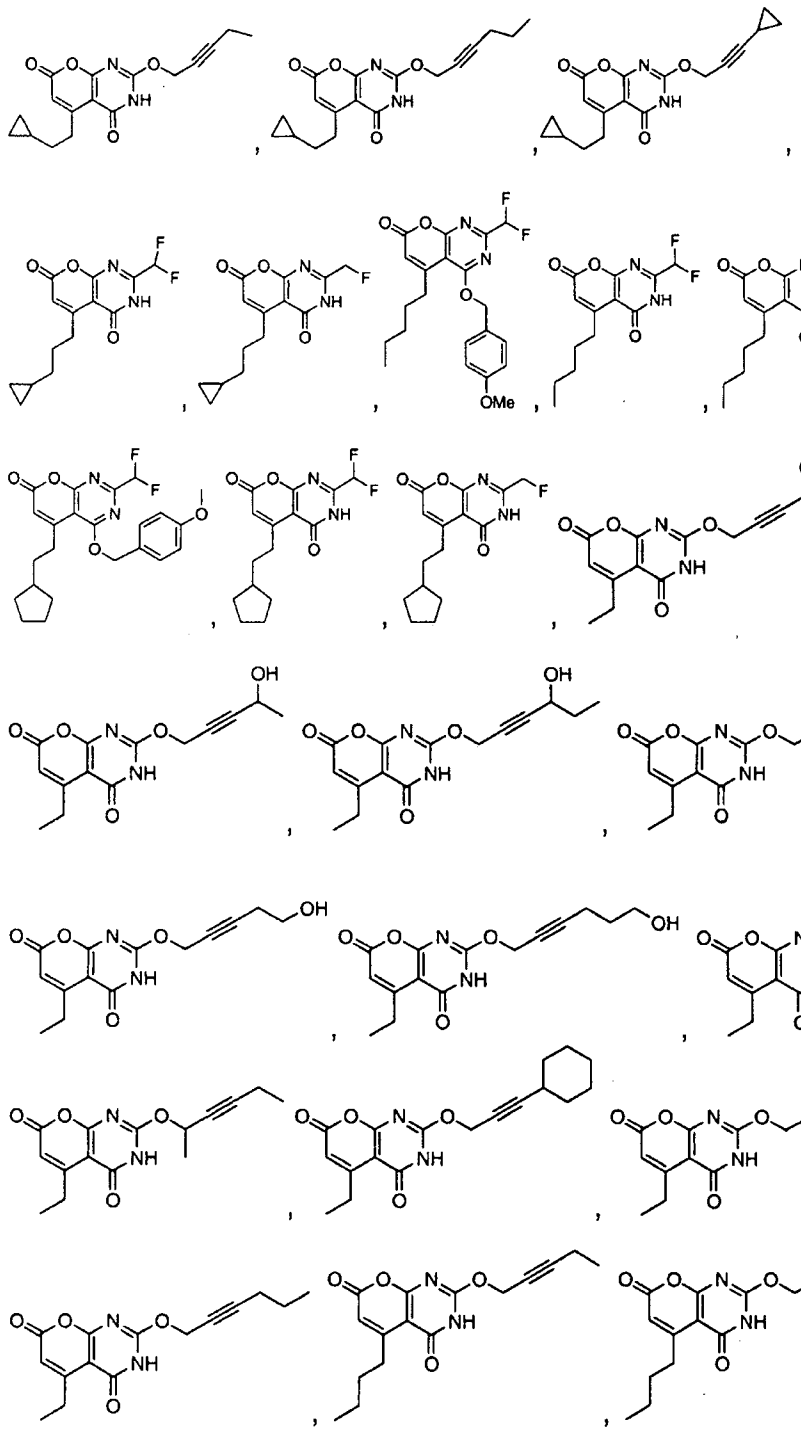
In another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is -O-alkynylene-cycloalkyl.

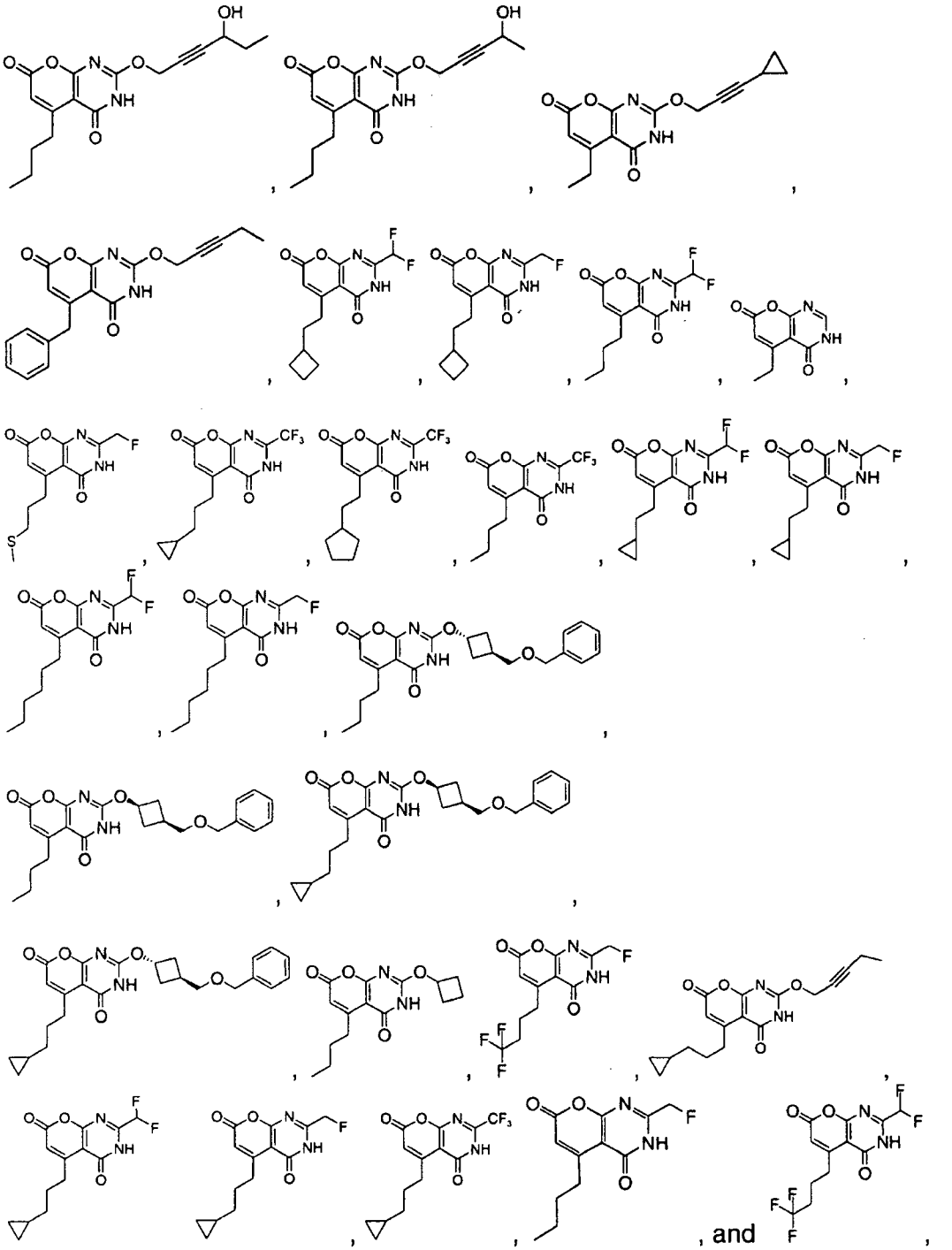
In yet another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is haloalkyl.

In still another embodiment, R^1 is -alkylene-cycloalkyl and R^4 is $-O-N=C(R^7)_2$.

Non-limiting illustrative examples of the compounds of formula (II), include the following compounds:

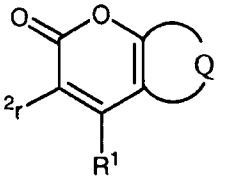






and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

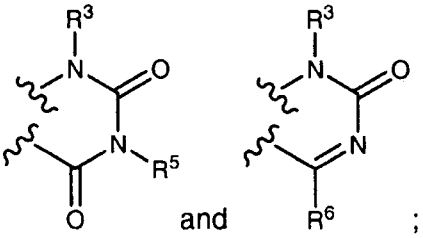
In one embodiment, the compounds of formula (I) have the formula (III):



(III)

and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof, wherein:

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

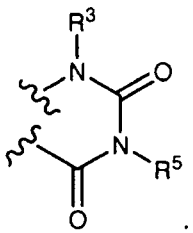
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

The following embodiments refer to the compounds of formula (III), wherein Q is:



In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is -alkylene-S-alkyl.

In still another embodiment, R^1 is -arylalkyl.

In yet another embodiment, R^1 is -alkylene.

In a further embodiment, R^1 is –cycloalkyl.

In one embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is –OH.

In one embodiment, R^5 is –H.

In another embodiment, R^5 is –OH.

In another embodiment, R^5 is alkyl.

In another embodiment, R^5 is haloalkyl.

In still another embodiment, R^5 is -O-alkyl.

In yet another embodiment, R^5 is cycloalkyl.

In a further embodiment, R^5 is heterocyclyl.

In one embodiment, R^5 is -O-arylalkyl.

In another embodiment, R^5 is -alkylene-O-alkyl.

In one embodiment, R^5 is $-OCH_3$.

In another embodiment, R^5 is cyclobutyl.

In another embodiment, R^5 is ethyl.

In still another embodiment, R^5 is *N*-morpholinyl.

In one embodiment, R^5 is –O-benzyl.

In another embodiment, R^5 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^5 is $-OCH_2CH_3$.

In another embodiment, R^5 is $-CH_2F$.

In one embodiment, R^5 is $-CH_2CH_2F$.

In another embodiment, R^5 is –OH.

In one embodiment, R^1 is alkyl, and each of R^2, R^3 and R^5 is -H.

In another embodiment, R^1 is alkyl, R^2 is –H, and one, but not both of R^3 and R^5 is -H.

In another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is alkyl.

In still another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –O-alkyl.

In yet another embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –cycloalkyl.

In one embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –heterocyclyl.

In one embodiment, R^1 is alkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –alkylene-O-alkyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, and each of R^2, R^3 and R^5 is -H.

In another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one, but not both of R^3 and R^5 is -H.

In another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is alkyl.

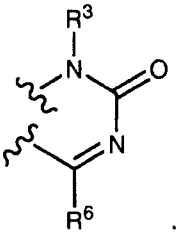
In still another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –O-alkyl.

In yet another embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –cycloalkyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –heterocyclyl.

In one embodiment, R^1 is –alkylene-cycloalkyl, R^2 is –H, and one of R^3 and R^5 is –H and the other is –alkylene-O-alkyl.

The following embodiments refer to the compounds of formula (III), wherein Q is:



In one embodiment, R^6 is alkoxy.

In another embodiment, R^6 is -O-alkylene-O-alkyl.

In another embodiment, R^6 is -O-arylalkyl.

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

In yet another embodiment, R^6 is $-OCH_2$-(4-methoxyphenyl).

In one embodiment, R^6 is $-OCH_2F$.

In another embodiment, R^6 is $-OCH_2CH_2F$.

In another embodiment, R^6 is $-OCH_2CH_3$

In still another embodiment, R^6 is $-OCH_2CH_2OCH_3$.

In one embodiment, R^1 is alkyl.

In another embodiment, R^1 is haloalkyl.

In another embodiment, R^1 is -alkylene-S-alkyl.

In still another embodiment, R^1 is -arylalkyl.

In yet another embodiment, R^1 is -alkylene.

In a further embodiment, R^1 is –cycloalkyl.

In one embodiment, R^1 is -alkylene-cycloalkenyl.

In another embodiment, R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

In one embodiment, R^1 is methyl.

In another embodiment, R^1 is ethyl.

In another embodiment, R^1 is n-propyl.

In still another embodiment, R^1 is n-butyl.

In one embodiment, R^1 is n-pentyl.

In another embodiment, R^1 is n-hexyl.

In yet another embodiment, R^1 is a branched chain alkyl having from 3 to 6 carbon atoms.

In a further embodiment, R^1 is isopropyl.

In one embodiment, R^1 is isobutyl.

In another embodiment, R^1 is isopentyl.

In another embodiment, R^1 is sec-butyl.

In still another embodiment, R^1 is tert-butyl.

In yet another embodiment, R^1 is haloalkyl, having from 1 to 3 F atoms.

In another embodiment, R^1 is $-(CH_2)_3CF_3$.

In one embodiment, R^2 is –H.

In another embodiment, R^2 is –CN.

In another embodiment, R^2 is -NHC(O)-alkyl.

In still another embodiment, R^2 is $-NHC(O)CH_3$.

In one embodiment, R^3 is –H.

In another embodiment, R^3 is –OH.

In another embodiment, R^3 is alkyl.

In another embodiment, R^3 is haloalkyl.

In still another embodiment, R^3 is -O-alkyl.

In yet another embodiment, R^3 is cycloalkyl.

In a further embodiment, R^3 is heterocyclyl.

In one embodiment, R^3 is -O-arylalkyl.

In another embodiment, R^3 is -alkylene-O-alkyl.

In one embodiment, R^3 is $-OCH_3$.

In another embodiment, R^3 is cyclobutyl.

In another embodiment, R^3 is ethyl.

In still another embodiment, R^3 is *N*-morpholinyl.

In one embodiment, R^3 is –O-benzyl.

In another embodiment, R^3 is $-CH_2CH_2OCH_3$.

In yet another embodiment, R^3 is $-OCH_2CH_3$.

In another embodiment, R^3 is $-CH_2F$.

In one embodiment, R^3 is $-CH_2CH_2F$.

In another embodiment, R^3 is –OH.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is alkoxy, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is alkoxy, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-alkylene-O-alkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-arylalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, and each of R^2 and R^3 is -H.

In another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –cycloalkyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and and R^3 is –heterocyclyl.

In one embodiment, R^6 is -O-haloalkyl, R^1 is alkyl, R^2 is –H, and R^3 is –alkylene-O-alkyl.

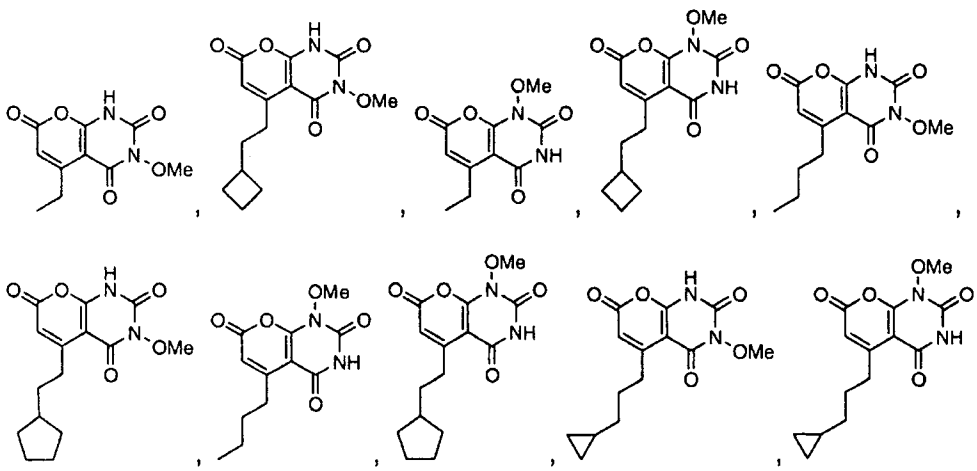
In one embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, and each of R^2 and R^3 is -H.

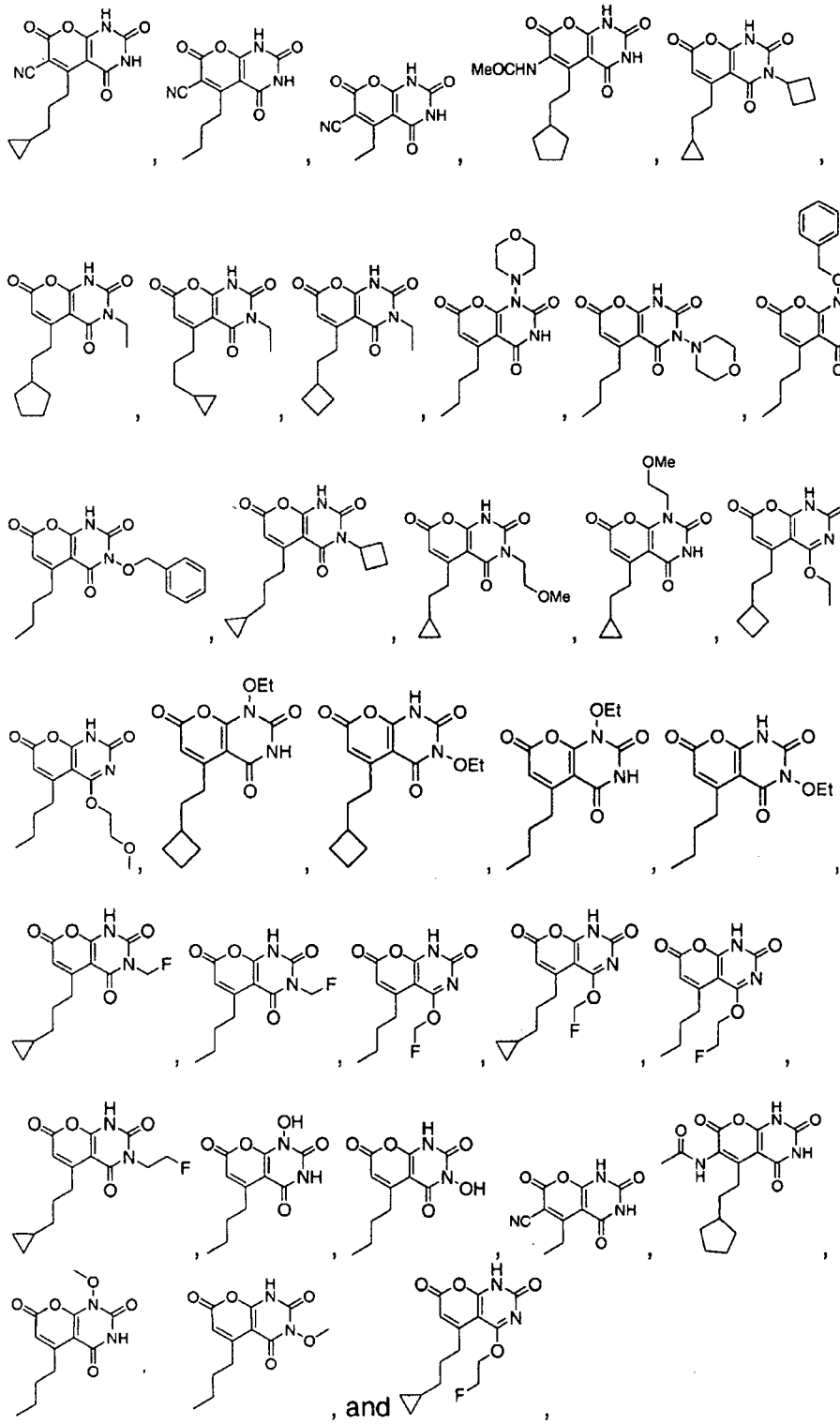
In another embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is alkyl.

In still another embodiment, R^6 is -O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –O-alkyl.

In yet another embodiment, R^6 is –O-haloalkyl, R^1 is –alkylene-cycloalkyl, R^2 is –H, and R^3 is –cycloalkyl.

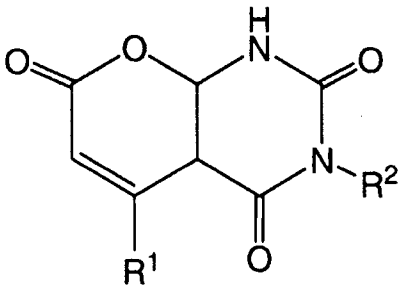
Non-limiting illustrative examples of the compounds of formula (III), include the following compounds:





and pharmaceutically acceptable salts, solvates, esters, or tautomers thereof.

In one embodiment, the compounds of formula (I) are compounds of formula (IV):



(IV)

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

R^1 is haloalkyl; and

R^2 is H or cycloalkyl.

In one embodiment, R^1 is fluoroalkyl.

In another embodiment, R^1 is –alkylene-F.

In another embodiment, R^1 is –alkylene-CF_2.

In still another embodiment, R^1 is $-(CH_2)_2$-CF_2.

In another embodiment, R^1 is $-(CH_2)_3$-CF_2.

In another embodiment, R^1 is $-(CH_2)_4$-CF_2.

In yet another embodiment, R^1 is $-(CH_2)_5$-CF_2.

In still another embodiment, R^1 is $-(CH_2)_3$-F.

In another embodiment, R^1 is $-(CH_2)_4$-F.

In another embodiment, R^1 is $-(CH_2)_5$-F.

In yet another embodiment, R^1 is $-(CH_2)_6$-F.

In one embodiment, R^2 is H.

In another embodiment, R^2 is cyclopropyl.

In another embodiment, R^2 is cyclobutyl.

In still another embodiment, R^2 is cyclopentyl.

In another embodiment, R^2 is cyclohexyl.

In one embodiment, R^1 is fluoroalkyl and R^2 is H.

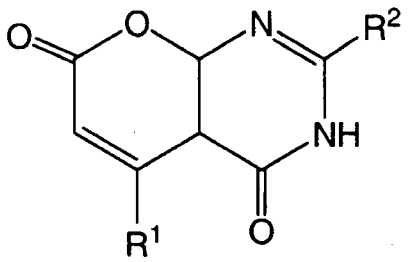
In another embodiment, R^1 is fluoroalkyl and R^2 is cycloalkyl.

In another embodiment, R^1 is –alkylene-CF_2 and R^2 is H.

In another embodiment, R^1 is –alkylene-CF_2 and R^2 is cycloalkyl.

Non-limiting examples of compounds of formula (IV) include compounds **834**, **835** and **837-841** as depicted in the Examples section below, and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

In another embodiment, the compounds of formula (I) are compounds of formula (V):



(V)

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

R^1 and R^2 are each, independently, haloalkyl.

In one embodiment, R^1 is fluoroalkyl.

In another embodiment, R^1 is –alkylene-F.

In another embodiment, R^1 is –alkylene-CF_2.

In still another embodiment, R^1 is $-(CH_2)_2-CF_2$.

In another embodiment, R^1 is $-(CH_2)_3-CF_2$.

In another embodiment, R^1 is $-(CH_2)_4-CF_2$.

In yet another embodiment, R^1 is $-(CH_2)_5-CF_2$.

In still another embodiment, R^1 is $-(CH_2)_3$-F.

In another embodiment, R^1 is $-(CH_2)_4$-F.

In another embodiment, R^1 is $-(CH_2)_5$-F.

In yet another embodiment, R^1 is $-(CH_2)_6$-F.

In one embodiment, R^2 is fluoroalkyl.

In another embodiment, R^2 is -CHF_2.

In one embodiment, R^1 is fluoroalkyl and R^2 is fluroalkyl.

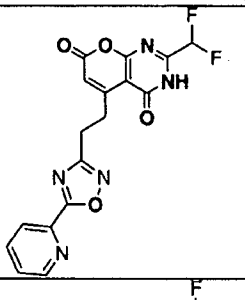
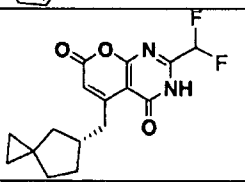
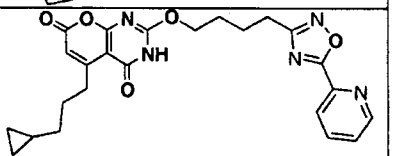
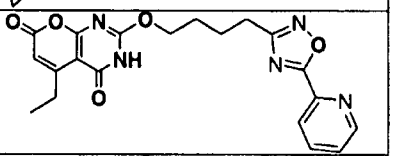
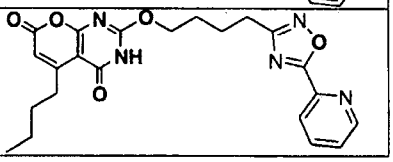
In another embodiment, R^1 is fluoroalkyl and R^2 is $-CHF_2$.

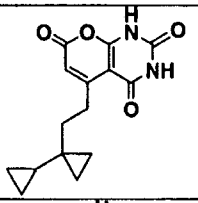
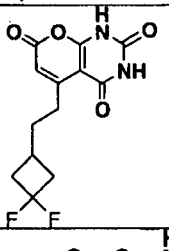
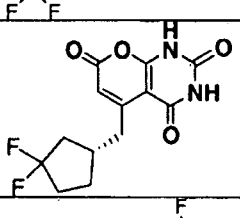
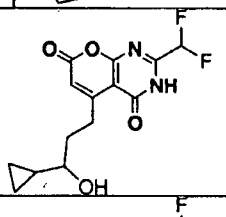
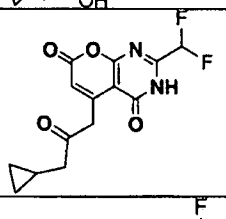
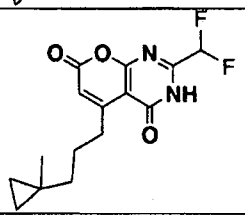
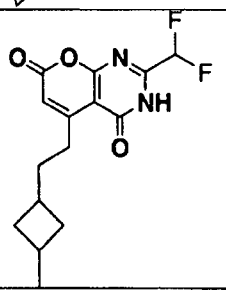
In another embodiment, R^1 is –alkylene-CF_2 and R^2 is fluoroalkyl.

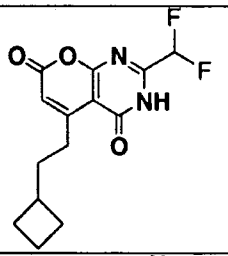
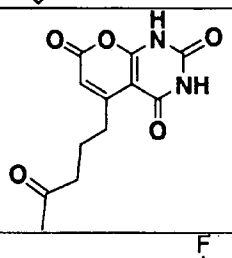
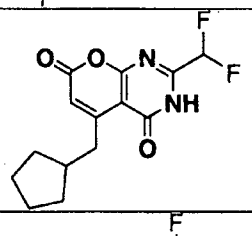
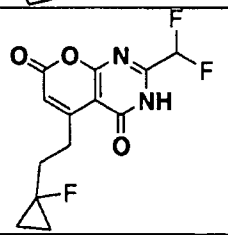
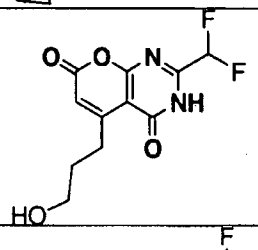
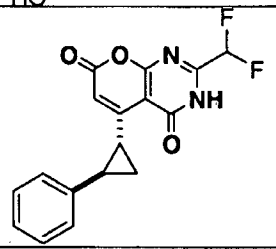
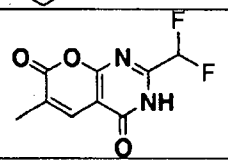
In still another embodiment, R^1 is –alkylene-CF_2 and R^2 is $-CHF_2$.

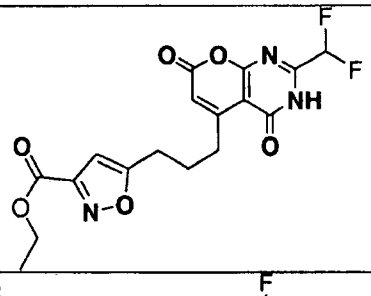
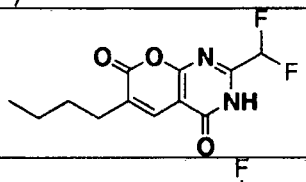
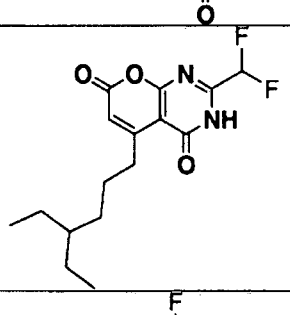
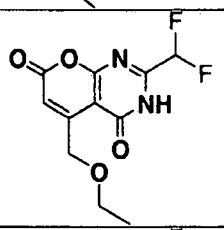
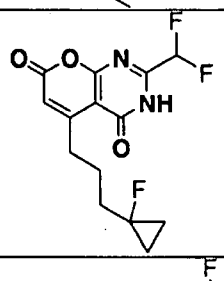
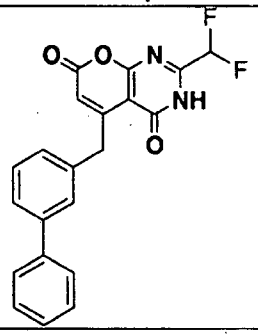
Non-limiting examples of compounds of formula (V) include compounds **836** and **842-844** as depicted in the Examples section below, and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

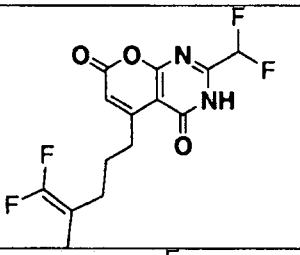
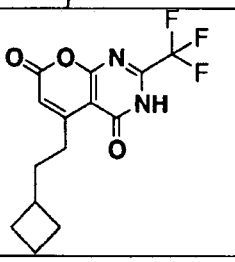
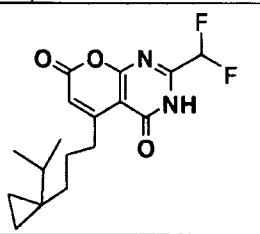
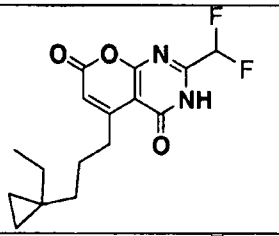
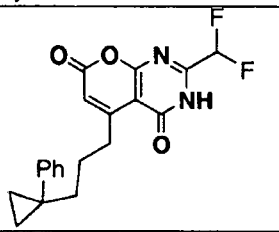
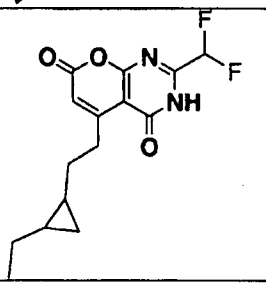
Additional non-limiting examples of compounds of formula (I) include compounds **845-911** as depicted in the following table:

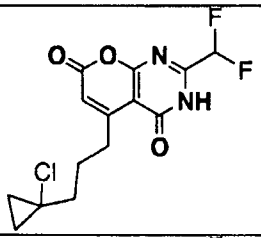
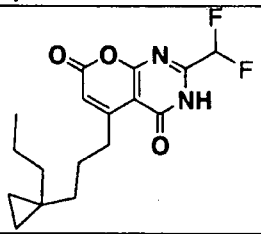
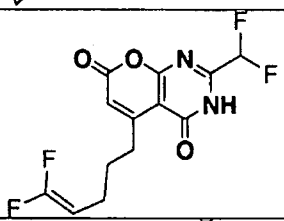
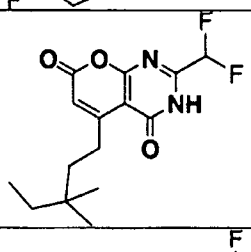
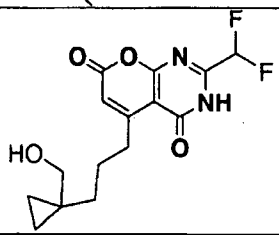
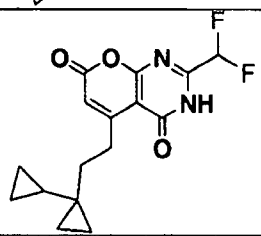
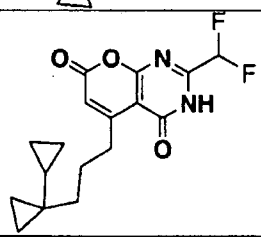
Compound No.	Structure
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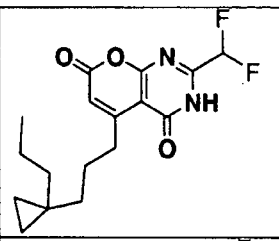
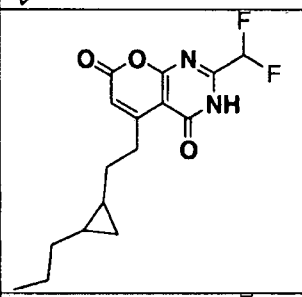
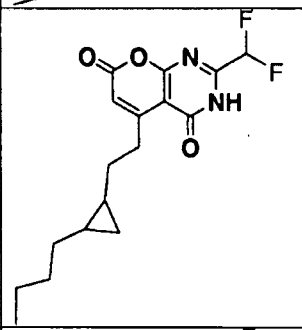
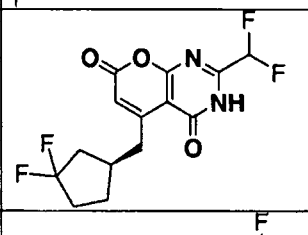
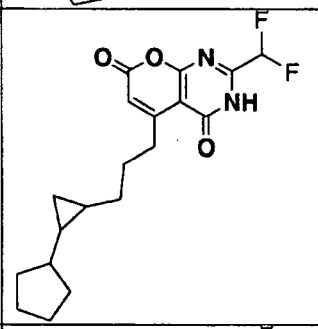
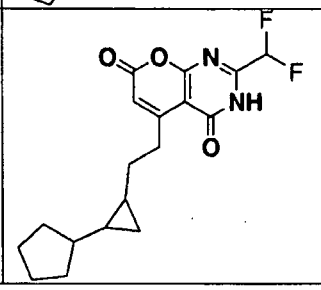
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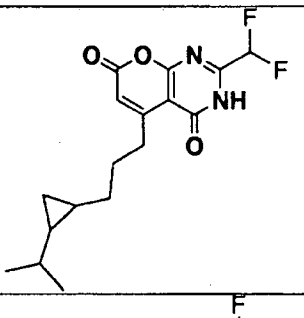
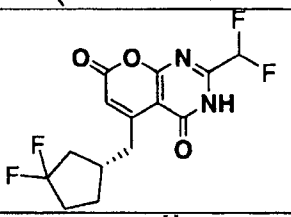
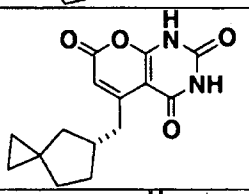
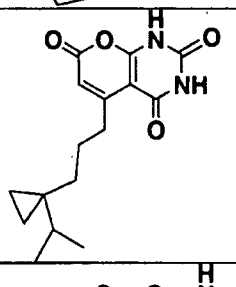
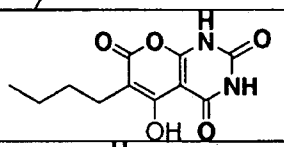
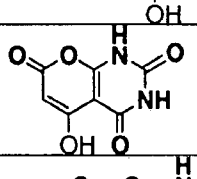
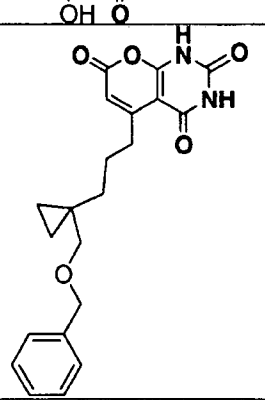
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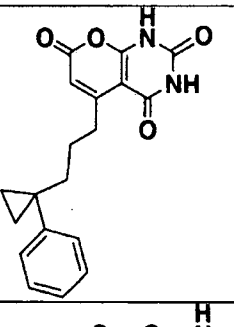
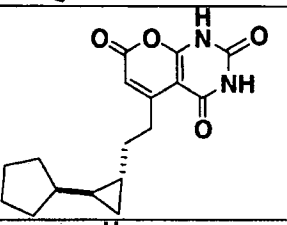
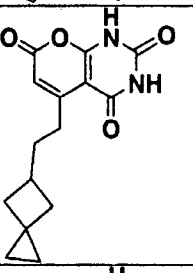
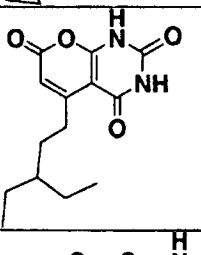
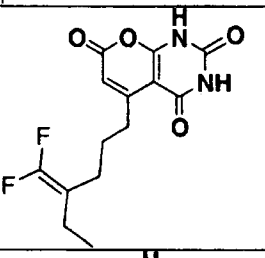
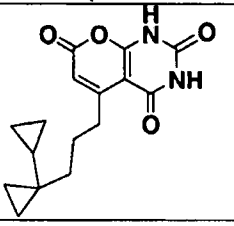
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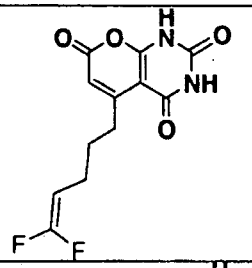
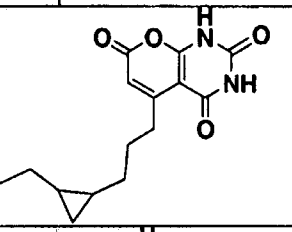
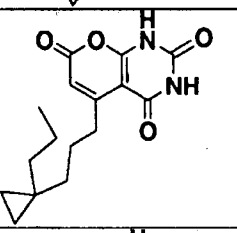
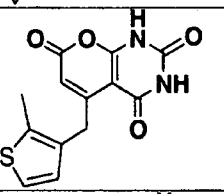
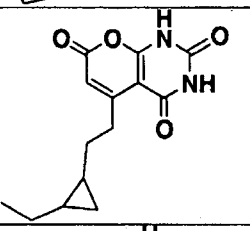
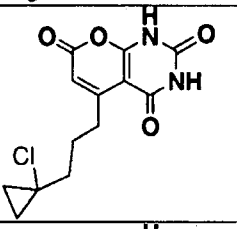
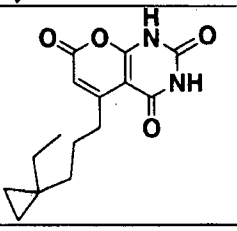
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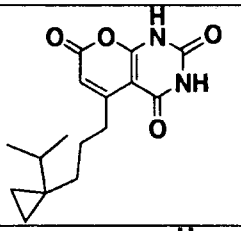
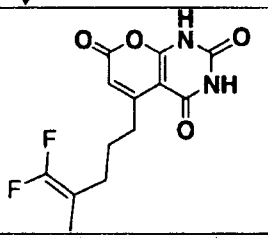
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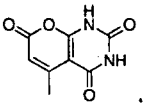
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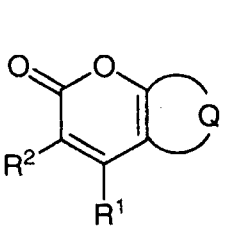
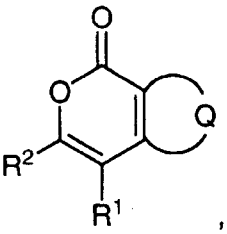
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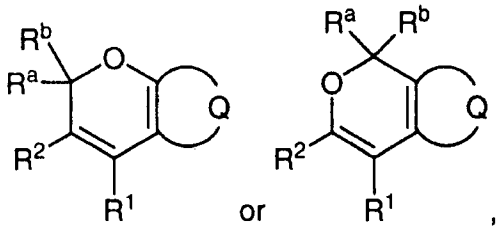
and and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof.

In all embodiments of the present invention, when L is (f), and R^2, R^3 and R^5 are each H, then R^1 is not $-CH_3$. One of skill in the art will recognize that the present invention does not include the following compound, or tautomeric forms thereof:



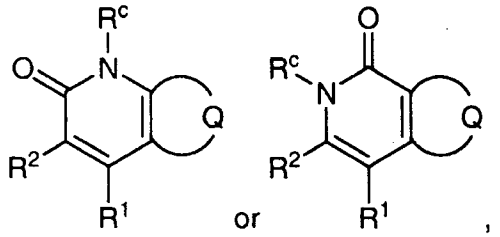
The moiety L of Formula (I) of the present invention can have any chemically stable orientation. That is, when L is (f), the compounds of Formula (I) of the present invention can include the following:

 or  , or salts, solvates, esters, or tautomers thereof. When L is (g), the compounds of Formula (I) of the present invention can include the following:



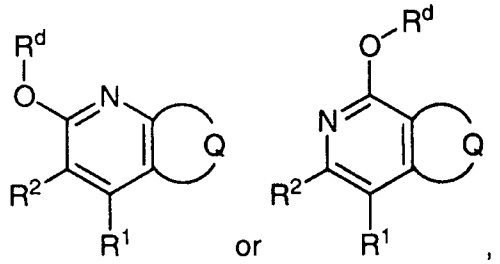
or

, or salts, solvates, esters, or tautomers thereof. When L is (h), the compounds of Formula (I) of the present invention can include the following:



or

, or salts, solvates, esters, or tautomers thereof. When L is (i), the compounds of Formula (I) of the present invention can include the following:



or

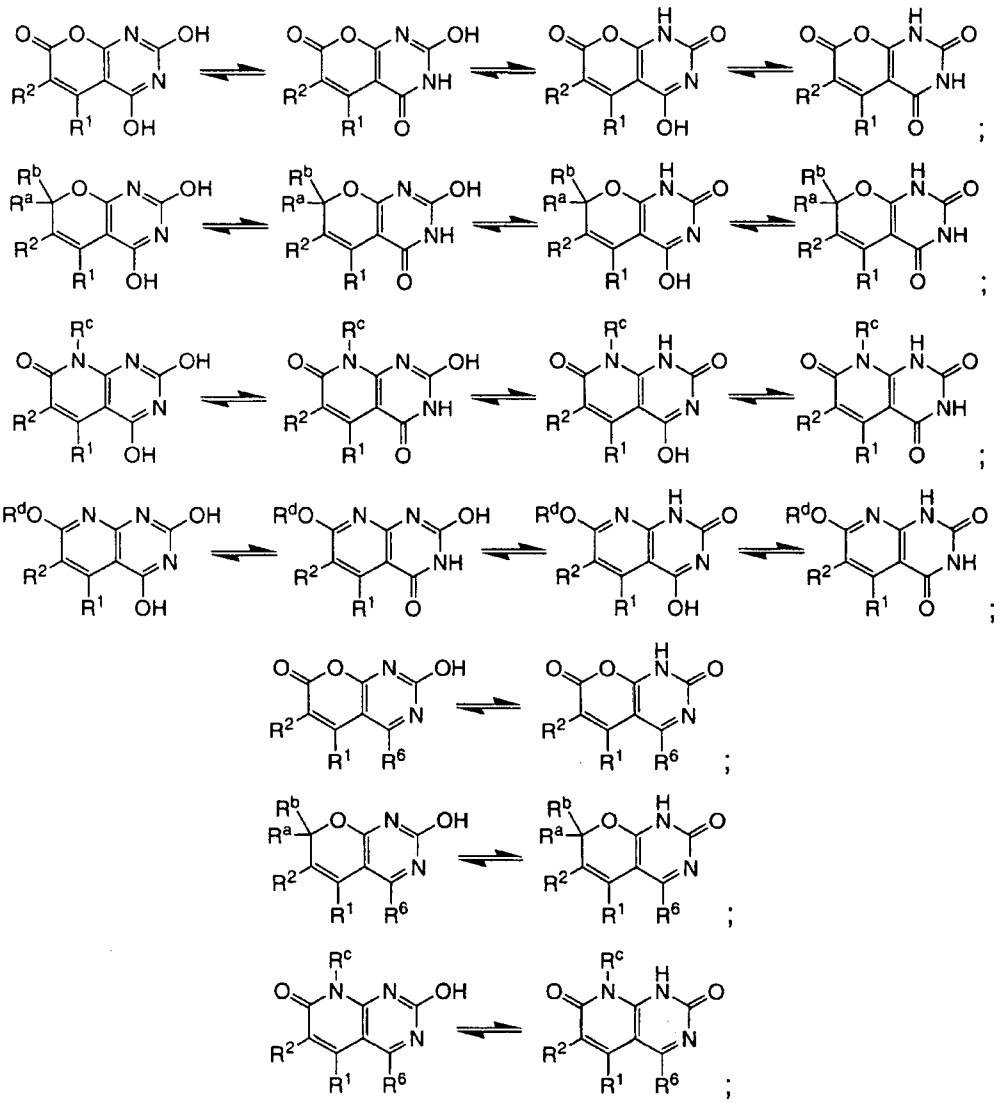
, or salts, solvates, esters, or tautomers thereof.

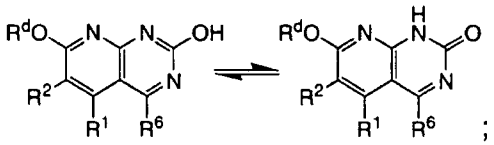
The compounds of Formula (I) can be purified to a degree suitable for use as a pharmaceutically active substance. That is, the compounds of Formula (I) can have a purity of 95 wt% or more (excluding adjuvants such as pharmaceutically acceptable carriers, solvents, etc., which are used in formulating the compound of Formula (I) into a conventional form, such as a pill, capsule, IV solution, etc. suitable for administration into a patient). The purity can be 97 wt% or more, or, 99 wt% or more. A purified compound of Formula (I) includes a single isomer having a purity, as discussed above, of 95 wt% or more, 97 wt% or more, or 99 wt% or more, as discussed above.

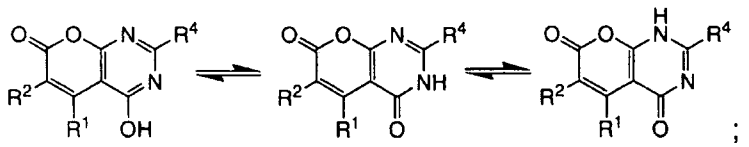
Alternatively, the purified compound of Formula (I) can include a mixture of isomers, each having a structure according to Formula (I), where the amount of impurity (i.e., compounds or other contaminants, exclusive of adjuvants as discussed above) is 5 wt% or less, 3 wt% or less, or 1 wt% or less. For example, the purified

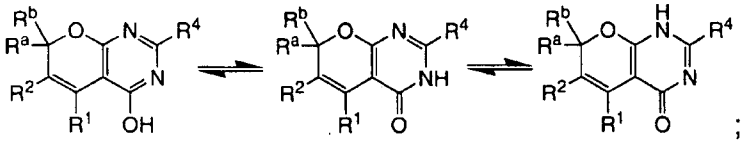
compound of Formula (I) can be an isomeric mixture of compounds of Structure (I), where the ratio of the amounts of the two isomers is approximately 1:1, and the combined amount of the two isomers is 95 wt% or more, 97 wt% or more, or 99 wt% or more.

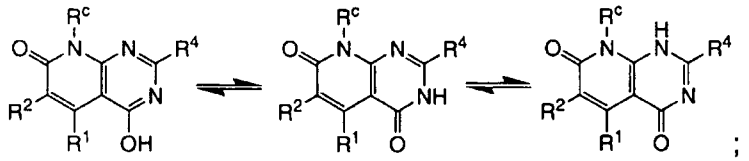
Compounds of Formula (I), and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention. For example, the compounds of the present invention include tautomeric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

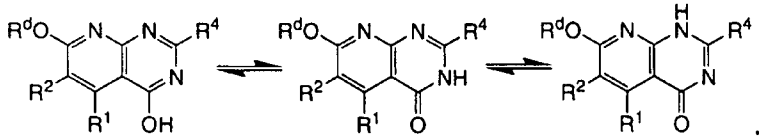



;


;


;


;


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Such tautomeric forms are considered equivalent.

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

"AcOH" means acetic acid.

"Bn" means benzyl.

"BnBr" means benzyl bromide.

"BnOH" means benzyl alcohol.

"CDI" means carbodiimide.

"DCM" means dichloromethane (CH_2Cl_2).

"DIAD" means diisopropyl azodicarboxylate.

"DIEA" means N,N-diisopropylethylamine.

"DMF" means dimethylformamide.

"Et" means ethyl.

"EtO_2" means diethyl ether.

"EtOAc" means ethylacetate.

"HATU" means O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethylammonium hexafluorophosphate.

"HOAc" means acetic acid.

"IBMX" means 3-isobutyl-1-methylxanthine.

"*m*-CPBA" means m-chloroperoxybenzoic acid.

"Me" means methyl.

"MeCN" means acetonitrile.

"MeI" means iodomethane.

"Me_2S" means dimethyl sulfide.

"MeOH" means methanol.

"NaOEt" means sodium ethoxide.

"NaOMe" means sodium methoxide.

"NBS" means *N*-bromosuccinimide.

"NEt_3" means triethylamine.

"NIS" means *N*-iodosuccinimide.

"*t*-Bu" means tertiary-butyl.

"*t*-BuOK" means potassium tertiary-butoxide.

"TFA" means trifluoroacetic acid.

"TfOH" means triflurometh anesulfonic acid.

"THF" means tetrahydrofuran.

"TLC" means thin layer chromatography.

"PMBOH" means 4-methoxybenzyl alcohol.

"PMBCl" means 4-methoxybenzyl chloride.

"Prep TLC" means preparative thin layer chromatography.

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. "Alkyl" 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, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), -$N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

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

"Alkylene" means a difunctional group obtained by removal of a hydrogen atom from an alkyl group that is defined above. Non-limiting examples of alkylene include methylene, ethylene and propylene.

"Alkenylene" means a difunctional group obtained by removal of a hydrogen from an alkenyl group that is defined above. Non-limiting examples of alkenylene include –CH=CH-, $-C(CH_3)=CH-$, and $-CH=CHCH_2-$.

"Alkylene-aryl" (or aryl-alkylene-) means a group in which the aryl and alkylene are as previously described. The bond to the parent moiety is through the alkylene. The alkylene moiety can be bonded to one or more aryl moieties. Alkylene-aryls can comprise a lower alkylene group. Non-limiting examples of suitable alkylene-aryl groups include benzyl, 2-phenethyl, 2,2-diphenylethylene and naphthalenylmethyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl

or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. "Alkynyl" 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 alkyl, aryl and cycloalkyl.

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

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. "Heteroaryl" may also include a heteroaryl as defined above fused to an aryl as defined above. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, 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.

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

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

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like.

"Cycloalkylalkyl" means a cycloalkyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkylalkyls include cyclohexylmethyl, adamantylmethyl and the like.

"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkenyls include cyclopentenyl, cyclohexenyl, cyclohepta-1,3-dienyl, and the like. Non-limiting example of a suitable multicyclic cycloalkenyl is norbornylenyl.

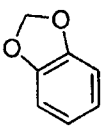
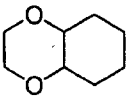
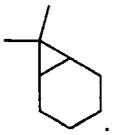
"Cycloalkenylalkyl" means a cycloalkenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable cycloalkenylalkyls include cyclopentenylmethyl, cyclohexenylmethyl and the like.

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

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 is independently replaced with a halogen. In one embodiment, a haloalkyl group is a "fluoroalkyl group."

The term "fluoroalkyl group" as used herein, refers to an alkyl group, wherein one or more of the alkyl group's hydrogen atoms are replaced with a –F atom. In various embodiments, a fluorooalkyl group contains one F atom, two F atoms or three F atoms. Illustrative example of fluoroalkyl groups include, but are not limted to, -CH_2F, -$CH(F)_2$, CH_2CH_2F, -CF_3, and -$(CH_2)_3CF_3$.

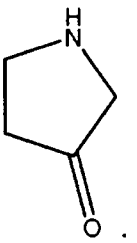
"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- 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  .

"Heteroarylalkyl" means a heteroaryl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heteroaryls include 2-pyridinylmethyl, quinolinylmethyl and the like.

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring

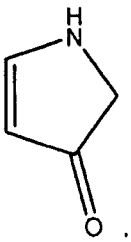
atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like. "Heterocyclyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:



"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

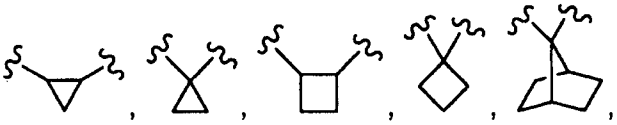
"Heterocyclenyl" means a non-aromatic monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur atom, alone or in combination, and which contains at least one carbon-carbon double bond or carbon-nitrogen double bond. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclenyl rings contain about 5 to about 6 ring atoms. The prefix aza,

oxa or thia before the heterocyclenyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. The heterocyclenyl can be optionally substituted by one or more ring system substituents, wherein "ring system substituent" is as defined above. The nitrogen or sulfur atom of the heterocyclenyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable heterocyclenyl 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. "Heterocyclenyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:

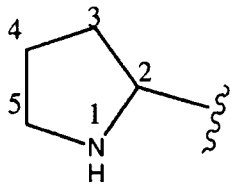


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"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

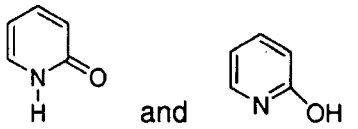
"Cycloalkylene" means a difunctional group obtained by removal of a hydrogen atom from a cycloalkyl group that is defined above. Non-limiting examples of cycloalkylene include  , and  .

It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:



there is no -OH attached directly to carbons marked 2 and 5.

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



are considered equivalent in certain embodiments of this invention.

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

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

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

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

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

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

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

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

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

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

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

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

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

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

"Alkylsulfonyl" means an alkyl-S(O_2)- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-S(O_2)- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the

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

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

The term "purified", "in purified form" or "in isolated and purified form" 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^2, etc.) occurs more than one time in any constituent or in Formula I, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product

which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. 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" means a compound (e.g, a drug precursor) that is transformed *in vivo* to yield a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (e.g., by metabolic or chemical processes), such as, for example, through hydrolysis in blood. A discussion of the use of prodrugs is provided by T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

For example, if a compound of Formula (I) or a pharmaceutically acceptable salt, hydrate or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as, for example, (C_1–C_8)alkyl, (C_2-C_{12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-(C_1-C_2)alkylamino(C_2-C_3)alkyl (such as β-dimethylaminoethyl), carbamoyl-(C_1-C_2)alkyl, N,N-di (C_1-C_2)alkylcarbamoyl-(C1-C2)alkyl and piperidino-, pyrrolidino- or morpholino(C_2-C_3)alkyl, and the like.

Similarly, if a compound of Formula (I) contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as, for example, (C_1-C_6)alkanoyloxymethyl, 1-((C_1-C_6)alkanoyloxy)ethyl, 1-methyl-1-((C_1-C_6)alkanoyloxy)ethyl, (C_1-

C_6)alkoxycarbonyloxymethyl, N-(C_1-C_6)alkoxycarbonylaminomethyl, succinoyl, (C_1-C_6)alkanoyl, α-amino(C_1-C_4)alkanyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1-C_6)alkyl)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate), and the like.

If a compound of Formula (I) incorporates an amine functional group, a prodrug can be formed by the replacement of a hydrogen atom in the amine group with a group such as, for example, R-carbonyl, RO-carbonyl, NRR'-carbonyl where R and R' are each independently (C_1-C_{10})alkyl, (C_3-C_7) cycloalkyl, benzyl, or R-carbonyl is a natural α-aminoacyl or natural α-aminoacyl, —C(OH)C(O)OY^1 wherein Y^1 is H, (C_1-C_6)alkyl or benzyl, —$C(OY^2)Y^3$ wherein Y^2 is (C_1-C_4) alkyl and Y^3 is (C_1-C_6)alkyl, carboxy (C_1-C_6)alkyl, amino(C_1-C_4)alkyl or mono-N—or di-N,N-(C_1-C_6)alkylaminoalkyl, —$C(Y^4)Y^5$ wherein Y^4 is H or methyl and Y^5 is mono-N— or di-N,N-(C_1-C_6)alkylamino morpholino, piperidin-1-yl or pyrrolidin-1-yl, and the like.

One or more compounds of the invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like, and it is intended that the invention embrace both solvated and unsolvated forms. "Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable 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).

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the above-noted diseases and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

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

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

(2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

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

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

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.

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

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

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

It is also possible that the compounds of Formula (I) may exist in different tautomeric forms, and all such forms are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in the invention.

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

3-pyridyl). (For example, if a compound of Formula (I) incorporates a double bond or a fused ring, both the cis- and trans-forms, as well as mixtures, are embraced within the scope of the invention. Also, for example, all keto-enol and imine-enamine forms of the compounds are included in 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, tautomers, 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. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively.

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

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

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

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof according to the invention have pharmacological properties; in particular, the compounds of Formula (I) can be nicotinic acid receptor agonists.

The compounds of Formula (I) of the present invention, or pharmaceutically acceptable salts, solvates, or esters thereof are useful in treating diseases or conditions including dyslipidemia and metabolic syndrome.

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered in any suitable form, e.g., alone, or in combination with a pharmaceutically acceptable carrier, excipient or diluent in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered orally or parenterally, including intravenous, intramuscular, interperitoneal, subcutaneous, rectal, or topical routes of administration, or if so selected, by a combination of one or more of the above-shown methods.

Pharmaceutical compositions comprising at least one compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof can be in a

form suitable for oral administration, e.g., as tablets, troches, capsules, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, syrups, or elixirs. Oral compositions may be prepared by any conventional pharmaceutical method, and may also contain sweetening agents, flavoring agents, coloring agents, and preserving agents.

The amount of compound of Formula (I), or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, administered to a patient can be determined by a physician based on the age, weight, and response of the patient, as well as by the severity of the condition treated. For example, the amount of compound of Formula I, or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, administered to the patient can range from about 0.1 mg/kg body weight per day to about 60 mg/kg/d. In one embodiment, the amount is from about 0.5 mg/kg/d to about 40 mg/kg/d. In another embodiment, the amount is from about 0.5 mg/kg/d to about 10 mg/kg/d. In another embodiment, the amount is from about 1 mg/kg/d to about 5 mg/kg/d. In still another embodiment, the amount is from about 1 mg/kg/d to about 3 mg/kg/d. In a specific embodiment, the amount is about 1 mg/kg/d. In another specific embodiment, the amount is about 3 mg/kg/d. In another specific embodiment, the amount is about 5 mg/kg/d. In another specific embodiment, the amount is about 7 mg/kg/d. In still another specific embodiment, the amount is about 10 mg/kg/d.

The compounds of Formula (I), or pharmaceutically acceptable salts, solvates, or esters thereof, can also be administered in combination with other therapeutic agents. For example one or more compounds of Formula (I) or pharmaceutically acceptable salts, solvates, or esters thereof, can be administered with one or more additional active ingredients selected from the group consisting of anti-flushing agents, hydroxy-substituted azetidinone compounds, substituted β-lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferase inhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, anti-oxidants, PPAR α agonists, PPAR γ-agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis

inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport protein inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1, GLP-1 agonists, GLP-1 mimetics, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, anti-diabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DP receptor antagonists, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α-glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

Non-limiting examples of hydroxy-substituted azetidinone compounds and substituted β-lactam compounds useful in combination with the nicotinic acid receptor

agonists of the present invention are those disclosed in U.S. Patents Nos. 5,767,115, 5,624,920, 5,668,990, 5,656,624 and 5,688,787, 5,756,470, U.S. Patent Application Nos. 2002/0137690 and 2002/0137689 and PCT Patent Application No. WO 2002/066464, each of which is incorporated herein by reference in their entirety. A preferred azetidinone compound is ezetimibe (for example, ZETIA® which is available from Schering-Plough Corporation).

In one embodiment, the additional agent is an anti-flushing agent.

Non-limiting examples of HMG CoA reductase inhibitor compounds useful in combination with the nicotinic acid receptor agonists of the present invention are lovastatin (for example MEVACOR® which is available from Merck & Co.), simvastatin (for example ZOCOR® which is available from Merck & Co.), pravastatin (for example PRAVACHOL® which is available from Bristol Meyers Squibb), atorvastatin, fluvastatin, cerivastatin, CI-981, rivastatin (sodium 7-(4-fluorophenyl)-2,6-diisopropyl-5-methoxymethylpyridin-3-yl)-3,5-dihydroxy-6-heptanoate), rosuvastatin calcium (CRESTOR® from AstraZeneca Pharmaceuticals), pitavastatin (such as NK-104 of Negma Kowa of Japan).

A non-limiting example of a HMG CoA synthetase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, L-659,699 ((E,E)-11-[3'R-(hydroxy-methyl)-4'-oxo-2'R-oxetanyl]-3,5,7R-trimethyl-2,4-undecadienoic acid).

A non-limiting example of a squalene synthesis inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, squalestatin 1.

A non-limiting example of a squalene epoxidase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, NB-598 ((E)-N-ethyl-N-(6,6-dimethyl-2-hepten-4-ynyl)-3-[(3,3'-bithiophen-5-yl)methoxy]benzene-methanamine hydrochloride).

A non-limiting example of a sterol biosynthesis inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention is, for example, DMP-565.

Non-limiting examples of nicotinic acid derivatives (e.g., compounds comprising a pyridine-3-carboxylate structure or a pyrazine-2-carboxylate structure, including acid

forms, salts, esters, zwitterions and tautomers) useful in combination with the nicotinic acid receptor agonists of the present invention are niceritrol, nicofuranose and acipimox (5-methyl pyrazine-2-carboxylic acid 4-oxide).

Non-limiting examples of bile acid sequestrants useful in combination with the nicotinic acid receptor agonists of the present invention are cholestyramine (a styrene-divinylbenzene copolymer containing quaternary ammonium cationic groups capable of binding bile acids, such as QUESTRAN® or QUESTRAN LIGHT® cholestyramine which are available from Bristol-Myers Squibb), colestipol (a copolymer of diethylenetriamine and 1-chloro-2,3-epoxypropane, such as COLESTID® tablets which are available from Pharmacia), colesevelam hydrochloride (such as WelChol® Tablets (poly(allylamine hydrochloride) cross-linked with epichlorohydrin and alkylated with 1-bromodecane and (6-bromohexyl)-trimethylammonium bromide) which are available from Sankyo), water soluble derivatives such as 3,3-ioene, N-(cycloalkyl) alkylamines and poliglusam, insoluble quaternized polystyrenes, saponins and mixtures thereof.

Non-limiting examples of inorganic cholesterol sequestrants useful in combination with the nicotinic acid receptor agonists of the present invention are bismuth salicylate plus montmorillonite clay, aluminum hydroxide and calcium carbonate antacids.

Non-limiting examples of AcylCoA:Cholesterol *O*-acyltransferase ("ACAT") inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention are avasimibe ([[2,4,6-tris(1-methylethyl)phenyl]acetyl]sulfamic acid, 2,6-bis(1-methylethyl)phenyl ester, formerly known as CI-1011), HL-004, lecimibide (DuP-128) and CL-277082 (*N*-(2,4-difluorophenyl)-*N*-[[4-(2,2-dimethylpropyl)phenyl]methyl]-*N*-heptylurea), and the compounds described in P. Chang et al., "Current, New and Future Treatments in Dyslipidaemia and Atherosclerosis", Drugs 2000 Jul; 60(1); 55-93, which is incorporated by reference herein.

Non-limiting examples of cholesteryl ester transfer protein ("CETP") inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention are those disclosed in PCT Patent Application No. WO 00/38721, U.S. Patent Nos. 6,147,090, 6,958,346, 6,924,313 6,906,082, 6,861,561, 6,803,388, 6,794,396, 6,787,570, 6,753,346, 6,723,752, 6,723,753, 6,710,089, 6,699,898, 6,696,472, 6,696,435, 6,683,113, 5,519,001, 5,512,548, 6,410,022, 6,426,365, 6,448,295,

6,387,929, 6,683,099, 6,677,382, 6,677,380, 6,677,379, 6,677,375, 6,677,353, 6,677,341, 6,605,624, 6,586,433, 6,451,830, 6,451,823, 6,462,092, 6,458,849, 6,458,803, 6,455,519, 6,583,183, 6,562,976, 6,555,113, 6,544,974, 6,521,607, 6,489,366, 6,482,862, 6,479,552, 6,476,075, 6,476,057, and 6,897,317, each of which are incorporated herein by reference; compounds described in Yan Xia et al., "Substituted 1,3,5-Triazines As Cholesteral Ester Transfer Protein Inhibitors", Bioorganic & Medicinal Chemistry Letters, vol. 6, No. 7, 1996, pp. 919-922, herein incorporated by reference; natural products described in S. Coval et al., "Wiedendiol-A and-B, Cholesteryl Ester Transfer Protein Inhibitors From The Marine Sponge Xestosponga Wiedenmayeri", Bioorganic & Medicinal Chemistry Letter, vol. 5, No. 6, pp. 605-610, 1995, herein incorporated by reference; the compounds described in Barrett et al. *J. Am. Chem. Soc.,* 188, 7863-63 (1996), herein incorporated by reference; the compounds described in Kuo et al. *J. Am. Chem. Soc.,* 117, 10629-34 (1995), herein incorporated by reference; the compounds described in Pietzonka et al. *Bioorg. Med. Chem. Lett.,* 6, 1951-54 (1996), herein incorporated by reference; the compounds described in Lee et al. *J. Antibiotics,* 49, 693-96 (1996), herein incorporated by reference; the compounds described by Busch et al. *Lipids,* 25, 216-220, (1990), herein incorporated by reference; the compounds described in Morton and Zilversmit *J. Lipid Res.,* 35, 836-47 (1982), herein incorporated by reference; the compounds described in Connolly et al. *Biochem. Biophys. Res. Comm.,* 223, 42-47 (1996), herein incorporated by reference; the compounds described in Bisgaier et al. Lipids, 29, 811-8 (1994), herein incorporated by reference; the compounds described in EP 818448, herein incorporated by reference; the compounds described in JP 10287662, herein incorporated by reference; the compounds described in PCT applications WO 98/35937, WO 9914174, WO 9839299, and WO 9914215, each of which is herein incorporated by reference; the compounds of EP applications EP 796846, EP 801060, 818448, and 818197, each of which is herein incorporated by reference; probucol or derivatives thereof, such as AGI-1067 and other derivatives disclosed in U.S. Patents Nos. 6,121,319 and 6,147,250, herein incorporated by reference; low-density lipoprotein (LDL) receptor activators such as HOE-402, an imidazolidinyl-pyrimidine derivative that directly stimulates LDL receptor activity, described in M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated by

Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, herein incorporated by reference; 4-carboxyamino-2-substituted-1,2,3,4-tetrahydroquinolines, e.g., torcetrapib, described in WO 00/017164, WO 00/017166, WO 00/140190, WO 00/213797, and WO 2005/033082 (each of which is herein incorporated by reference). Torcetrapib can be combined with HMG-CoA reductase inhibitors such as atorvastatin (WO 00/213797, WO 2004/056358, WO 2004/056359, and WO2005/011634).

A non-limiting example of a fish oil containing Omega 3 fatty acids useful in combination with the nicotinic acid receptor agonists of the present invention is 3-PUFA.

Non-limiting examples of GLP-1 mimetics useful in combination with the nicotinic acid receptor agonists of the present invention include exendin-3, exendin-4, Byetta-Exanatide, Liraglutinide, CJC-1131 (ConjuChem), Exanatide-LAR (Amylin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealand Pharmaceuticals), and compounds disclosed in International Publication No. WO 00/07617.

Non-limiting examples of natural water soluble fibers useful in combination with the nicotinic acid receptor agonists of the present invention are psyllium, guar, oat and pectin.

A non-limiting example of a plant stanol and/or fatty acid ester of plant stanols useful in combination with the nicotinic acid receptor agonists of the present invention is the sitostanol ester used in BENECOL® margarine.

A non-limiting example of an anti-oxidant useful in combination with the nicotinic acid receptor agonists of the present invention includes probucol.

Non-limiting examples of PPAR α agonists useful in combination with the nicotinic acid receptor agonists of the present invention include beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil.

Non-limiting examples of lipoprotein synthesis inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include niacin or nicotinic acid.

Non-limiting examples of 5HT (serotonin) transport inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include paroxetine, fluoxetine, fenfluramine, fluvoxamine, sertraline, and imipramine.

Non-limiting examples of NE (norepinephrine) transport inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include GW 320659, despiramine, talsupram, and nomifensine.

Non-limiting examples of CB_1 antagonists/inverse agonists useful in combination with the nicotinic acid receptor agonists of the present invention include rimonabant, SR-147778 (Sanofi Aventis), and the compounds described in US 5,532,237, US 4,973,587, US 5,013,837, US 5,081,122, US 5,112,820, US 5,292,736, US 5,624,941, US 6,028,084, WO 96/33159, WO 98/33765, WO 98/43636, WO 98/43635, WO 01/09120, WO 98/31227, WO 98/41519, WO 98/37061, WO 00/10967, WO 00/10968, WO 97/29079, WO 99/02499, WO 01/58869, WO 02/076949, and EP-658546 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of ghrelin antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in WO 01/87335 and WO 02/08250 (each of the preceding references is herein incorporated by reference). Ghrelin antagonists are also known as GHS (growth hormone secretagogue receptor) antagonists. The pharmaceutical combinations and methods of the present invention therefore comprehend the use GHS antagonists in place of ghrelin antagonists (in combination with the nicotinic acid receptor agonists of the present invention).

Non-limiting examples of H_3 antagonists/inverse agonists useful in combination with the nicotinic acid receptor agonists of the present invention include thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, and GT2394 (Gliatech), those described in WO 02/15905 (herein incorporated by reference); O-[3-(1H-imidazol-4-yl)propanol]carbamates described in Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000) (herein incorporated by reference), piperidine-containing histamine H_3-receptor antagonists described in Lazewska, D. et al., Pharmazie, 56:927-32 (2001) (herein incorporated by reference), benzophenone derivatives and related compounds described in Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)(herein incorporated by reference), substituted N-phenylcarbamates described in Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)(herein incorporated by reference), and proxifan derivatives described in Sasse,

A. et al., J. Med. Chem. 43:3335-43 (2000)(each of the preceding references is herein incorporated by reference).

Non-limiting examples of MCH1R (melanin-concentrating hormone 1 receptor) antagonists and MCH2R (melanin-concentrating hormone 2 receptor) agonists/antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in WO 01/82925, WO 01/87834, WO 02/06245, WO 02/04433, WO 02/51809, and JP 13226269 (each of the preceding references is herein incorporated by reference), and T-226296 (Takeda).

Non-limiting examples of NPY1 antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in US 6,001,836, WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528 (each of the preceding references is herein incorporated by reference); and BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, and GI-264879A.

Non-limiting examples of NPY5 antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in US 6,140,354, US 6,191,160, US 6,258,837, US 6,313,298, US 6,337,332, US 6,329,395, US 6,340,683, US 6,326,375, US 6,335,345, EP-01010691, EP-01044970, WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/27063, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, WO 02/49648, WO 01/14376, WO 04/110375, WO 05/000217 and Norman et al., J. Med. Chem. 43:4288-4312 (2000) (each of the preceding references is herein incorporated by reference); and 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X; FR226928, FR 240662, FR252384; 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104.

Non-limiting examples of NPY2 agonists useful in combination with the nicotinic acid receptor agonists of the present invention include PYY3-36 as described in Batterham, et al., Nature. 418:650-654 (2003), NPY3-36, and other Y2 agonists such as N acetyl [Leu(28,31)] NPY 24-36 (White-Smith and Potter, Neuropeptides 33:526-33 (1999)), TASP-V (Malis et al., Br. J. Pharmacol. 126:989-96 (1999)), cyclo-(28/32)-

Ac-[Lys28-Glu32]-(25-36)-pNPY (Cabrele and Beck-Sickinger J-Pept-Sci. 6:97-122 (2000)) (each of the preceding references is herein incorporated by reference).

Non-limiting examples of NPY4 agonists useful in combination with the nicotinic acid receptor agonists of the present invention include pancreatic peptide (PP) as described in Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91 (Raposinho et al., Neuroendocrinology. 71:2-7(2000) (both references are herein incorporated by reference).

Non-limiting examples of mGluR5 (Metabotropic glutamate subtype 5 receptor) antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and (3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine) (MTEP) and those compounds described in Anderson J. et al., J, Eur J Pharmacol. Jul. 18, 2003;473(1):35-40; Cosford N. et al., Bioorg Med Chem Lett. Feb. 10, 2003;13(3):351-4; and Anderson J. et al., J Pharmacol Exp Ther. December 2002:303(3):1044-51 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of leptins, leptin derivatives, and leptin agonists/modulators useful in combination with the nicotinic acid receptor agonists of the present invention include recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen). Leptin derivatives (e.g., truncated forms of leptin) useful in the present invention include those described in US 5,552,524, US 5,552,523, US 5,552,522, US 5,521,283, WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519, and WO 96/23520 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of opioid antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include nalmefene (Revex™), 3-methoxynaltrexone, naloxone, and naltrexone, as well as opioid antagonists described in WO 00/21509 (herein incorporated by reference).

Non-limiting examples of orexin receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include SB-334867-A, as well as those described in WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838 (each of the preceding references is herein incorporated by reference).

Non-limiting examples of CNTF (specific ciliary neurotrophic factors) useful in combination with the nicotinic acid receptor agonists of the present invention include GI-181771 (Glaxo-SmithKline); SR146131 (Sanofi Aventis); butabindide; PD170,292, PD 149164 (Pfizer).

Non-limiting examples of CNTF derivatives and CNTF agonists/modulators useful in combination with the nicotinic acid receptor agonists of the present invention include axokine (Regeneron) and those described in WO 94/09134, WO 98/22128, and WO 99/43813 (each of which is herein incorporated by reference).

Non-limiting examples of 5HT2c agonists useful in combination with the nicotinic acid receptor agonists of the present invention include BVT933, DPCA37215, WAY161503, and R-1065, as well as those described in US 3,914,250, WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457 (each of which is herein incorporated by reference).

Non-limiting examples of Mc4r agonists useful in combination with the nicotinic acid receptor agonists of the present invention include CHIR86036 (Chiron); ME-10142, and ME-10145 (Melacure), as well as those described in WO 01/991752, WO 01/74844, WO 02/12166, WO 02/11715, and WO 02/12178 (each of which is herein incorporated by reference).

Non-limiting examples of monoamine reuptake inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include sibutramine (Meridia™/Reductil™), as well as those described in WO 01/27068, WO 01/62341, US 4,746,680, US 4,806,570, US 5,436,272, and US 2002/0006964 (each of which is herein incorporated by reference).

Non-limiting examples of serotonin reuptake inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include dexfenfluramine, fluoxetine, and those described in US 6,365,633, WO 01/27060, and WO 01/162341 (each of which is herein incorporated by reference).

A non-limiting example of an acyl-estrogen useful in combination with the nicotinic acid receptor agonists of the present invention includes oleoyl-estrone.

Non-limiting examples of 11β HSD-1 inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include those described in WO 03/065983 and WO 03/104207 (both of which are herein incorporated by reference).

A non-limiting example of a lipase inhibitor useful in combination with the nicotinic acid receptor agonists of the present invention include orlistat.

Anti-diabetic agents useful in combination with the nicotinic acid receptor agonists of the present invention include sulfonylureas, meglitinides, α-amylase inhibitors, α-glucoside hydrolase inhibitors, PPAR-γ agonists, PPARα/γ agonists, biguanides, PTP-1B inhibitors, DP-IV inhibitors, DPP-IV inhibitors, insulin secretagogues, fatty acid oxidation inhibitors, A2 antagonists, c-jun amino-terminal kinase inhibitors, insulin, insulin mimetics, glycogen phosphorylase inhibitors, VPAC2 receptor agonists, glucokinase activators, and non-thiazolidinedione PPAR ligands.

Non-limiting examples of sulfonylureas useful in combination with the nicotinic acid receptor agonists of the present invention include acetohexamide, chlorpropamide, diabinese, glibenclamide, glipizide, glyburide, glimepiride, gliclazide, glipentide, gliquidone, glisolamide, tolazamide, and tolbutamide.

Non-limiting examples of meglitinides useful in combination with the nicotinic acid receptor agonists of the present invention include repaglinide, mitiglinide and nateglinide.

Non-limiting examples of α-amylase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include tendamistat, trestatin, and Al-3688.

Non-limiting examples of α-glucoside hydrolase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include acarbose, adipose, camiglibose, emiglitate, miglitol, voglibose, pradimicin-Q, salbostatin, CDK-711, MDL-25,637, MDL-73,945, and MOR 14.

Non-limiting examples of PPAR-γ agonists useful in combination with the nicotinic acid receptor agonists of the present invention include balaglitazone, ciglitazone, darglitazone, englitazone, isaglitazone (MCC-555), pioglitazone, rosiglitazone, troglitazone, tesaglitazar, netoglitazone, GW-409544, GW-501516, CLX-0921, 5-BTZD, GW-0207, LG-100641, LY-300512, LY-519818, R483 (Roche), and T131 (Tularik).

Non-limiting examples of PPARα/γ agonists useful in combination with the nicotinic acid receptor agonists of the present invention include CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767, and SB 219994.

Non-limiting examples of biguanides useful in combination with the nicotinic acid receptor agonists of the present invention include buformin, metformin, and phenformin.

Non-limiting examples of PTP-1B inhibitors (protein tyrosine phosphatase-1B inhibitors) useful in combination with the nicotinic acid receptor agonists of the present invention include A-401,674, KR 61639, OC-060062, OC-83839, OC-297962, MC52445, and MC52453.

Non-limiting examples of DPP-IV inhibitors (dipeptidyl peptidase IVi inhibitors) useful in combination with the nicotinic acid receptor agonists of the present invention include sitagliptin, saxagliptin, denagliptin, vildagliptin, alogliptin, alogliptin benzoate, Galvus (Novartis), ABT-279 and ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A and BI-B (Boehringer Ingelheim), SYR-322 (Takeda), MP-513 (Mitsubishi), DP-893 (Pfizer) and RO-0730699 (Roche), isoleucine thiazolidide, NVP-DPP728, P32/98, LAF 237, TSL 225, valine pyrrolidide, TMC-2A/2B/2C, CD-26 inhibitors, and SDZ 274-444.

Non-limiting examples of insulin secretagogues useful in combination with the nicotinic acid receptor agonists of the present invention include linogliride and A-4166.

Non-limiting examples of fatty acid oxidation inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include clomoxir and etomoxir.

Non-limiting examples of A2 antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include midaglizole, isaglidole, deriglidole, idazoxan, earoxan, and fluparoxan.

Non-limiting examples of insulin mimetics useful in combination with the nicotinic acid receptor agonists of the present invention include biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente), Lys-Pro insulin, GLP-1 (73-7) (insulintropin), and GLP-1 (7-36)-NH_2).

Non-limiting examples of glycogen phosphorylase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include CP-368,296, CP-316,819, and BAYR3401.

Non-limiting examples of non-thiazolidinedione PPAR ligands useful in combination with the nicotinic acid receptor agonists of the present invention include JT-501 and farglitazar (GW-2570/GI-262579).

Anti-hypertensive agents useful in combination with the nicotinic acid receptor agonists of the present invention include diuretics, β-adrendergic blockers, α-adrenergic blockers, aldosterone inhibitors, alpha 1 blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin antagonists, vasodilators, alpha 2a agonists, and α/β adrenergic blockers.

Non-limiting examples of diuretics useful in combination with the nicotinic acid receptor agonists of the present invention include chlorthalidone, chlorthiazide, dichlorophenamide, hydroflumethiazide, indapamide, hydrochlorothiazide, bumetanide, ethacrynic acid, furosemide, torsemide, amiloride, triamterene, spironolactone, and epirenone.

Non-limiting examples of β-adrendergic blockers useful in combination with the nicotinic acid receptor agonists of the present invention include acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol, and timolol.

Non-limiting examples of alpha 1 blockers useful in combination with the nicotinic acid receptor agonists of the present invention include terazosin, urapidil, prazosin, bunazosin, trimazosin, doxazosin, naftopidil, indoramin, WHIP 164, and XEN010.

Non-limiting examples of calcium channel blockers useful in combination with the nicotinic acid receptor agonists of the present invention include amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cinaldipine, clevidipine, diltiazem, efonidipine, felodipine, gallopamil, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodepine, nisoldipine, nitrendipine, manidipine, pranidipine, and verapamil.

Non-limiting examples of angiotensin converting enzyme inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include alacepril, benazepril, ceronapril, captopril, cilazapril, delapril, enalapril, fosinopril,

imidapril, losinopril, moveltopril, moexipril, quinapril, quinaprilat, ramipril, perindopril, peridropril, quanipril, spirapril, temocapril, trandolapril, and zofenopril.

Non-limiting examples of neutral endopeptidase inhibitors useful in combination with the nicotinic acid receptor agonists of the present invention include omapatrilat, cadoxatril, ecadotril, fosidotril, sampatrilat, AVE7688, and ER4030.

Non-limiting examples of angiotensin II receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include candesartan, eprosartan, irbesartan, losartan, pratosartan, tasosartan, telisartan, valsartan, EXP-3137, FI6828K, RNH6270, losartan monopotassium, and losartan potassium-hydrochlorothiazide.

Non-limiting examples of endothelin antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include tezosentan, A308165, and YM62899.

Non-limiting examples of vasodilators useful in combination with the nicotinic acid receptor agonists of the present invention include hydralazine (apresoline), clonidine (catapres), minoxidil (loniten), and nicotinyl alcohol (roniacol).

Non-limiting examples of alpha 2a agonists useful in combination with the nicotinic acid receptor agonists of the present invention include lofexidine, tiamenidine, moxonidine, rilmenidine, and guanobenz.

Non-limiting examples of α/β adrenergic blockers useful in combination with the nicotinic acid receptor agonists of the present invention include nipradilol, arotinolol, and amosulalol.

DP receptor antagonists useful in combination with the nicotinic acid receptor agonists of the present invention include those described in US 2004/0229844 (herein incorporated by reference).

Non-limiting examples of additional agents that can be combined with the nicotinic acid receptor agonists of the present invention include aspirin, Niaspan, Norvsac® (amlodipine), NSAIDS agents (e.g., Celecoxib (Celebrex®), Diclofenac (Cataflam®, Voltaren®, Arthrotec®,) Diflunisal (Dolobid®), Etodolac (Lodine®), Fenoprofen (Nalfon®), Flurbirofen (Ansaid®), Ibuprofen (Motrin®, ADVIL®, NUPRIN®, Tab-Profen®, Vicoprofen®, Combunox®), Indornethacin (Indocin®, Indo-Lemmon®, Indornethagan®), Ketoprofen (Oruvail®), Ketorolac (Toradol®), Mefenamic acid

(Ponstel®, commercially available from First Horizon Pharmaceutical), flufenamic acid ([N-(3-trifluoromethylphenyl)anthranilic acid]), Meloxicam (Mobic®), Naburnetone (Relafen®), Naproxen (Naprosyn®, ALEVE®, Anaprox®, Naprelan®, Naprapac®), Oxaprozin (Daypro®), Piroxicam (Feldene®), Sulindac (Clinoril®) and Tolmetin (Tolectin®)), antihypertensive agents (Prazosin®, Propranolol, nadolol, timolol, metoprolol, pindolol, labetalol, guanethidine, reserpine, clonidine, methyldopa, guanabenz, captopril, enalapril, lisinopril, losartan, verapamil, diltiazem, nifedipine, hydrochlorothiazide, chlorothalidone, furosemide, triamterene, hydralazine, minoxidil), PGE2 receptor antagonists (e.g., EP2 and EP4).

Non-limiting examples of additional agents that can be combined with the nicotinic acid receptor agonists of the present invention include homocysteinase, orphan GPCR modulator, HRE-based gene therapy, gene therapy, dual PPARα/γ agonists, recombinant FGF-1, VRI-1, CRx-150, VEGF-114 based therapy, CT-500, regadenosan, CK-1827452, JAK2 tyrosine kinase inhibitors, adipose-derived regenerative cells, STARBURST dendrimer-based MRI contrast agents, TBC-11299, HEMOxygenation, heparin, GO-EPO, IDN-6734, ISIS-301012, HIF-alpha gene therapy, α2b adrenoceptor antagonists, KI-0002, adenosine modulators, Ki-23095, PR-5 (Melacure), L-364373, histone deacetylase inhibitors, adenylate cyclase inhibitors (E.g., HI-30435 from Millennium), MITO-0139 (from MitoKor), NV-04 (from Novogen), M-118 (Momenta), hypoxia response element, PI-99 (from progen), NEXVAS (from Resverlogix), CS-207)from Shenzhen Chipscreen Biosciences), estrogen-regulated gene therapy, SLV-327 (from SolvaY), TNX-832 (from Sunol Molecular Corp), SLx-2101 (from Surface Logix), recombinant human annexin (from SurroMed), Chymase inhibitors (e.g, from Toa Eiyo), VM-202 (from ViroMed), liver x receptor modulators (e.g., from Exelixis/Bristol Myers Squibb), Heberkinasa (from Y. M. Biosciences), atorvastatin-amlodipine combination, AGN-195795 (Allergan), angiotensisn (1-7) agonists (e.g., from Arena), Toprol XL/hydrochlorothiazide (from AstraZeneca), Teczem (Aventis), sGC stimulators, calcium channel blockers, CYT-006-AngQb (CytosBiotechnology), renin inhibitors (e.g., from Roche/Speedel), Coxagen (from geneRx+ Inc), MC-4262 (from Medicure), VNP-489 (from Novartis), felodipine (from Pierre Fabre SA), 2-methoxyestradiol (from PR Pharmaceuticals), α1 adrenoreceptor antagonsists (e.g., from Recordati SpA), lercanidipine-enalapril

combination (from Recordati SpA). NO donors 9e.g., from Renopharm), CR-3834 (from Rottapharm Gr), iloprost (from Schering AG), SPP-1100 (from The Speedel Group), angiotensinogen, MC-4232 (from Medicure), ACE inhibitor (from Servier), LCP-Feno/Stat. (from LifeCycle Pharma), APA-01/statin combination (from Phosphagenics Ltd), KH-01502 (from Kos), KS-01019 (from Kos), niacin-lovastatin combination (from Kos/Merck KGaA), MK-0524/extended release niacin/simvastatin combination (from Merck), MK-0524/extended release combination (from Merck), Pro-NAD (from Niadyne Inc), beraprost, perindopril erbumine, barnidipine, irbesartan, valsartan, valsartan-HCTZ conmbination, meclinertant, TAK-536, SR-121463, irbesatran + HCTZ combination, darusentan, PMD-2850, CR-2991, SLV-306, bisoprolol fumarate+ HCTZ combination, NV-04, FG-3019, TRC-4149, AVE-7688, PV-903, diltiazem, QC-BT16, cardiotherpay (from Cytopia), treprostinil sodium, enalapril+diltiazem combination, eprosartan mesylate +HCTZ combination, renin inhibitor (from Vitae), LG-105 inhibitors (from Lexicon(, LG-844 inhibitors (from Lexicon), NO-enhancing PDE inhibitors, hyaluronidase, propranolol hydrochloride, BIO-236, RWJ-351647, metoprolol, YM-222546, bLN-5, olmesartan+azelnidipine combination (from Sanyo), moxonidine + HCTZ combination, NS-304, BIO-123, aldosterone antagonists, clonidine, BIO-003 and CR-3834.

In addition, the nicotinic acid receptor agonists of the present invention can also be used in combination with two or more therapeutic agents. A non-limiting example of two or more therapeutic agents useful in combination with the nicotinic acid receptor agonists of the present invention is the combination of a compound of the present invention with VYTORIN® (a combination of simvastatin and ezetimibe).

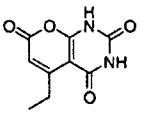
The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

EXAMPLES

In the examples and tables that follow, the exemplary compounds of the invention are referred to by number. In some instances, the compounds of the invention are referred to as "Example X," wherein "X" would be the representative

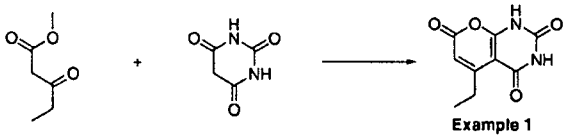
number of that particular compound. In other instances, the compounds of the invention are referred to as "compound X," wherein "X" would be the representative number of that particular compound. In other instances, a compound of the invention may simply be referred to by it's number. It is to be understood that these terms are used interchangeably. For example, the compound labeled "Example 1" can also be referred to as "compound 1" and vice versa.

PREPARATIVE EXAMPLE 1



Example 1

Step A:



Example 1

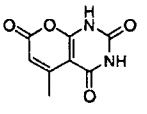
Methyl propionylacetate (12.5 g, 96.1 mmol, 1.23 eq.) and barbituric acid (10 g, 78.1 mmol, 1 eq.) were mixed together and without solvent, the mixture was heated to 195°C in air for 2 hr., at which time all of the liquids had evaporated. The solid was washed with boiling distilled water twice. The remaining solid was recrystallized with 2-methoxyethanol/water to give 4 g of **Example 1** as a yellow solid (20% yield).

^{1}H NMR (CD_3OD): δ 1.20 (t, 3 H, J = 7.3 Hz), 3.00 (q, 2 H, J = 7.3 Hz), 5.80 (s, 1 H)

^{13}C NMR (CD_3OD): δ 12.6, 27.4, 92.0, 104.2, 149.5, 158.4, 161.8, 162.1, 164.1

Mass for $C_9H_9N_2O_4$ $(MH)^+$: 209. Found: 209.

PREPARATIVE EXAMPLE 2



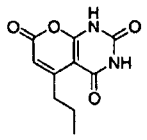
Example 2

Example 2 was prepared by a method analogous to the method used to prepare **Example 1**, except that methyl acetonylacetate was used instead of methyl propionylacetate.

^{1}H NMR (CD_3OD): δ 2.41 (s, 3 H) 5.75 (s, 1 H)

Mass for $C_8H_7N_2O_4$ $(MH)^+$: 195. Found: 195.

PREPARATIVE EXAMPLE 3



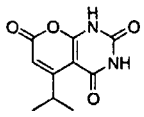
Example 3

Example 3 was prepared by a method analogous to the method used to prepare **Example 1**, except that methyl butanoylacetate was used instead of methyl propionylacetate.

^{1}H NMR (CD_3OD): δ 0.96 (t, 3 H, J = 7.6 Hz), 1.57 (m, 2 H), 2.86 (m, 2 H), 5.75 (s, 1 H)

Mass for $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Found: 223.

PREPARATIVE EXAMPLE 4



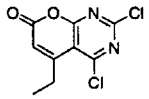
Example 4

Example 4 was prepared by a method analogous to the method used to prepare **Example 1**, except that ethyl isobutylacetate was used instead of methyl propionylacetate, and **Example 4** was purified by HPLC (5% acetonitrile in water to 95% acetonitrile in 10 min).

^{1}H NMR (CD_3OD): δ 1.14 (d, 6 H, J = 6.8 Hz), 4.03 (m, 1 H), 5.86 (s, 1 H)

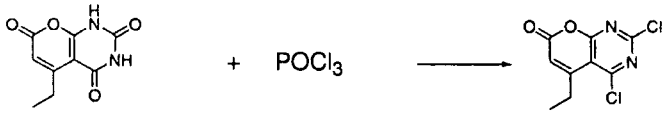
Mass for $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Found: 223.

PREPARATIVE EXAMPLE 5



Example 5

Step A:



Example 1 + $POCl_3$ → Example 5

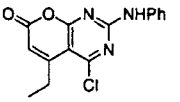
Example 1 (5 g, 24.04 mmol, 1 eq), $POCl_3$ (36.86g, 240 mmol, 10 eq.) and pyridine (0.95g, 12 mmol, 0.5 eq) were mixed and heated to 115°C for 8 hours. After cooling to room temperature, the solvent was removed and the brownish residue was

purified using flash chromatography with 20% EtOAc/hexane as the eluting solvent. The desired product (4 g) was obtained in 68% yield.

^{1}H NMR (CD_3OD): δ 1.29 (t, 3 H, J = 7.2 Hz), 3.12 (m, 2 H), 6.39 (s, 1 H)

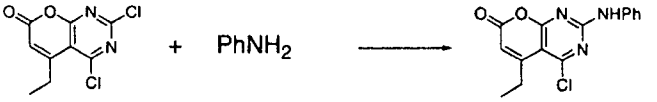
Mass for $C_9H_7Cl_2N_2O_2$ $(MH)^+$: 245. Found: 245.

PREPARATIVE EXAMPLE 6



Example 6

Step A:



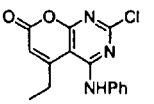
Example 5 + $PhNH_2$ → Example 6

Compound 1 (0.15 g, 0.61 mmol, 1 eq.) and aniline (0.06g, 0.64 mmol, 1.05 eq) were mixed in 3 mL of anhydrous THF and stirred for 12 hours. Solvent was removed and the residue was purified by prep TLC with 25% EtOAc/hexane as the eluting solvent to give desired product as first fraction (7 mg, 4% yield).

^{1}H NMR (CD_3OD): δ 1.27 (t, 3 H, J = 7.2 Hz), 3.05 (m, 2 H), 6.11 (s, 1 H), 7.11 (t, 1 H, J = 7.6 Hz), 7.34 (m, 2 H), 7.48 (br s, 1 H), 7.60 (d, 2 H, J = 8.0 Hz)

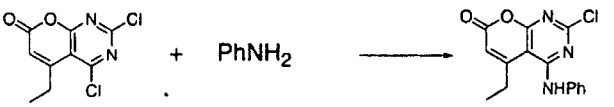
Mass for $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Found: 302.

PREPARATIVE EXAMPLE 7



Example 7

Step A:



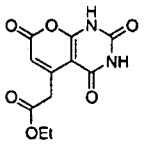
Example 5 Example 7

Example 7 was prepared using the method used to prepare **Example 6**, except that **Example 7** was obtained as the second fraction by prep TLC (8 mg, 4% yield).

^{1}H NMR (CD_3OD): δ 1.43 (t, 3 H, J = 7.2 Hz), 2.96 (m, 2 H), 6.22 (s, 1 H), 7.37 – 7.48 (m, 5H)

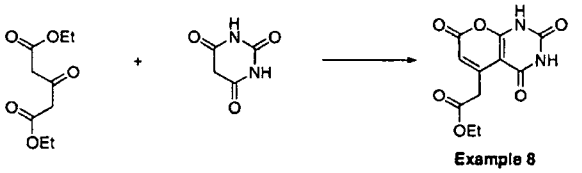
Mass for $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Found: 302.

PREPARATIVE EXAMPLE 8



Example 8

Step A:



Example 8

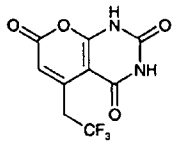
Example 8 was prepared using a method analogous to the method used to prepare **Example 1**, except that diethyl 1,3-acetonedicarboxylate was used instead of methyl propionylacetate.

^{1}H NMR (CD_3OD): δ 1.20 (t, 3 H, J = 7.3 Hz), 3.88 (s, 2 H), 4.10 (q, 2 H, J = 7.3 Hz), 5.81 (s, 1 H)

^{13}C NMR (CD_3OD): δ 13.4, 39.6, 61.2, 92.2, 108.1, 149.7, 153.1, 157.8, 161.7, 162.0, 170.3

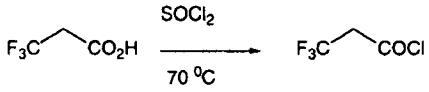
Mass for HRMS for $C_{11}H_{11}N_2O_6$ $(MH)^+$: calcd 267.0617, found 267.0623.

PREPARATIVE EXAMPLE 9



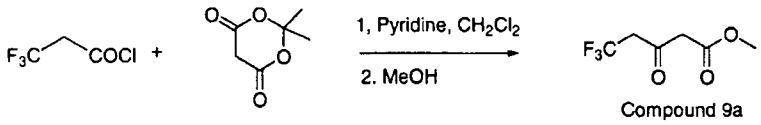
Example 9

Step A:



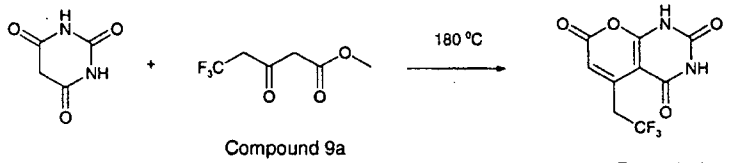
A mixture of 3,3,3,-trifluoropropionic acid (16 g, 125 mmol), thionyl chloride (29.75 g, 250 mmol), and DMF (0.5 mL) was heated to 70°C for 4 hours. The reaction mixture was distilled under reduced pressure to give 3,3,3,-trifluoropropionyl chloride (11.5 g, 72%).

Step B:



Compound 9a

Into a solution of Meldrum's acid (2,2-dimethyl-4,6-dioxo-1,3-dioxane; 9 g, 62 mmol) and pyridine (9.8 g, 68 mmol) in anhydrous CH_2Cl_2 (10 mL), which cooled to 0°C, was added 3,3,3,-trifluoropropionyl chloride (10 g, 68 mmol). The resulting reaction mixture was stirred under N_2 at 0°C for 1 hour then at room temperature for 2 hours. The reaction mixture was then concentrated under reduced pressure. The resulting paste was mixed with MeOH (20 mL), and heated to 80°C for 5 hours. The solvent was removed and the resulting mixture was distilled under reduced pressure to give **Compound 9a** (6.2 g, 54%).



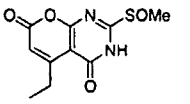
Compound 9a

Example 9

A mixture of **Compound 9a** (2.2 g, 12 mmol) and barbituric acid was heated to 180°C for 1 hour to provide a black solid. After cooling to room temperature, the black solid was dissolved into hot water (70 mL). The resulting mixture was extracted with ethyl acetate (4 x 50 mL). The organic solution was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by reverse phase HPLC

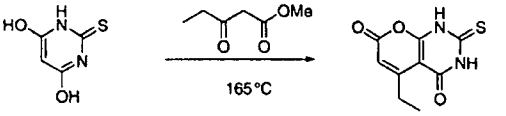
eluting with formic acid (0.1%)/acetonitrile to give **Example 9** (0.17 g, 5 %). Electrospray MS $[M+1]^+$ 263.

PREPARATIVE EXAMPLE 10



Example 10

Step A:



Compound 10a

A mixture of 4,6-dihydroxy-2-mercapto-pyrimidine (20.0 g, 138.7 mmol) and methyl propionylacetate (21.8 mL, 173.4 mmol) was heated at 165°C until the ester was completely reacted. The reaction mixture was cooled down and poured into water (75 mL) and then filtered through a sintered funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to yield **Compound 10a** (11.6 g, 37%).

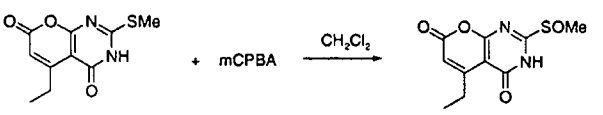
Step B:



Compound 10a Compound 10b

MeI (2.23 mL, 35.72 mmol) was added to a suspension of **Compound 10a** (4.0 g, 17.86 mmol) in DMF (40 mL) at room temperature. The reaction mixture was stirred at room temperature overnight. The reaction mixture was then poured into water (250 mL) and filtered through a sintered funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 10b** (4.1 g, 96%).

Step C:

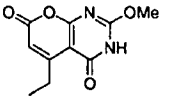


Compound 10b Example 10

m-CPBA (3.1 g, 70%, 12.6 mmol) was added to a suspension of **Compound 10b** (2.0 g, 8.4 mmol) in CH_2Cl_2 (150 mL) at room temperature. The solvent was removed from the suspension after 3 hours and the crude product was purified using

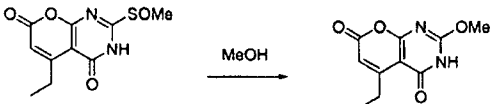
silica gel flash column chromatography, eluting first with hexane/EtOAc (v/v = 1/1) then CH_2Cl_2/MeOH (v/v = 2/1) to give **Example 10** (2.0 g, 94%). Electrospray MS $[M+1]^+$ 255.1.

PREPARATIVE EXAMPLE 11



Example 11

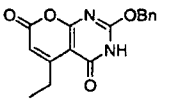
Step A:



Example 10 Example 11

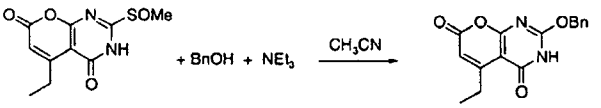
Example 10 (0.35 g, 1.37 mmol) in MeOH (40 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified using silica gel flash column chromatography eluting with CH_2Cl_2/MeOH (v/v = 50/1) to give **Example 11** (0.23 g, 76%). Electrospray MS $[M+1]^+$ 223.1.

PREPARATIVE EXAMPLE 12



Example 12

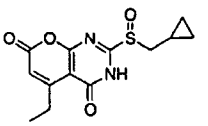
Step A:



Example 10 Example 12

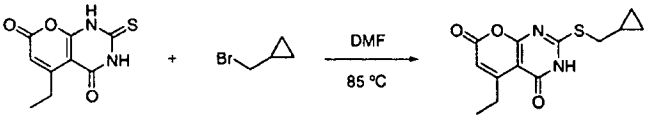
BnOH (2.46 mL, 23.76 mmol) was added to a solution of **Example 10** (0.404 g, 1.58 mmol) and NEt_3 (0.22 mL, 1.58 mmol) in CH_3CN (12.0 mL) at room temperature. The reaction mixture was heated at 85°C overnight. After cooling to room temperature, HOAc (0.09 mL, 1.58 mmol) was added and the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with CH_2Cl_2/MeOH (v/v = 50/1) to give **Example 12** (0.20 g, 42%). Electrospray MS $[M+1]^+$ 299.1.

PREPARATIVE EXAMPLE 13



Example 13

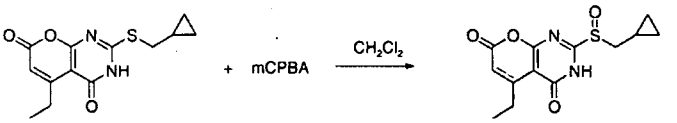
Step A:



Compound 10a Compound 13a

Cyclopropyl methyl bromide (1.30 mL, 13.4 mmol) was added to a suspension of **Compound 10a** (0.5 g, 2.24 mmol) in DMF (5.0 mL) at room temperature. The reaction mixture was stirred at 85°C for two days. The reaction mixture was cooled down and poured into water (75 mL) and then filtered through a sintered funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to give **Compound 13a** (0.55 g, 88%).

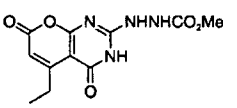
Step B:



Compound 13a Example 13

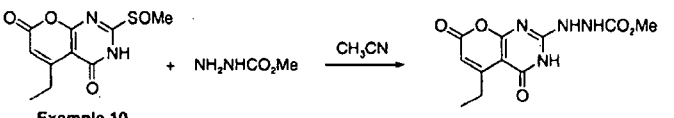
m-CPBA (0.33 g, 70%, 1.35 mmol) was added to a suspension of **Compound 13a** (0.25 g, 0.9 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed after 3 hours, and the crude product was purified using silica gel flash column chromatography eluting with EtOAc/CH_2Cl_2/MeOH (v/v = 4/1/2) to give **Example 13** (0.15 g, 57%). Electrospray MS $[M+1]^+$ 295.1.

PREPARATIVE EXAMPLE 14



Example 14

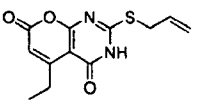
Step A:



Example 10 Example 14

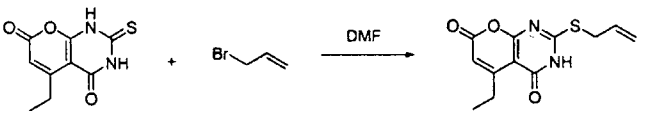
A mixture of **Example 10** (0.205 g, 0.804 mmol) and NH_2NHCO_2Me (0.145 g, 1.608 mmol) in MeCN (4.0 mL) was heated at reflux for 3 hours. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was washed with water (3 x 25 mL) with filtration. The solid was dried under vacuum to give **Example 14** (0.2 g, 89%). Electrospray MS $[M+1]^+$ 281.1.

PREPARATIVE EXAMPLE 15



Example 15

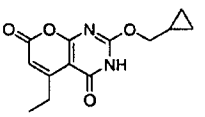
Step A:



Compound 10a Example 15

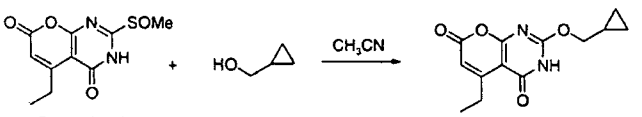
Allyl bromide (1.74 mL, 20.1 mmol) was added to a suspension of **Compound 10a** (1.5 g, 6.7 mmol) in DMF (15.0 mL) at room temperature. The reaction mixture was stirred at 45°C overnight. The reaction mixture was cooled down and poured into water (200 mL) and then filtered through a sintered funnel. The solid residue was washed with water (2 x 40 mL) and dried under vacuum to give **Example 15** (1.55 g, 92%). Electrospray MS $[M+1]^+$ 265.1.

PREPARATIVE EXAMPLE 16



Example 16

Step A:

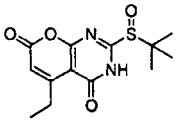


Example 10 Example 16

Cyclopropyl carbinol (0.79 mL, 9.8 mmol) was added to a solution of **Example 10** (0.050 g, 0.196 mmol) in CH_3CN (0.8 mL) at room temperature. The reaction mixture was heated at 85°C overnight. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified using silica gel

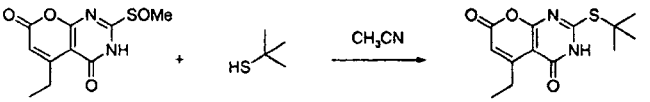
flash column chromatography eluting with hexane/EtOAc (v/v = 1/1) to give **Example 16** (0.027 g, 52%). Electrospray MS $[M+1]^+$ 263.1.

PREPARATIVE EXAMPLE 17



Example 17

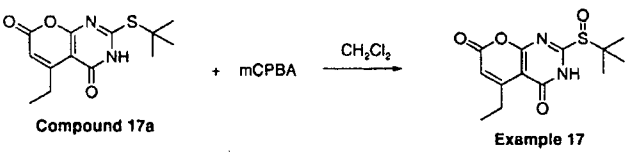
Step A:



Example 10 Compound 17a

A mixture of **Example 10** (0.10 g, 0.392 mmol) and *t*-BuSH (0.66 mL, 5.88 mmol) in 1,4-dioxane (2.0 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with hexane/EtOAc (v/v = 1/1) to give **Compound 17a** (0.045 g, 41%).

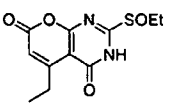
Step B:



Compound 17a Example 17

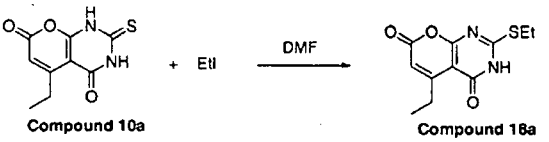
m-CPBA (0.049 g, 70%, 0.20 mmol) was added to a suspension of **Compound 17a** (0.040 g, 0.143 mmol) in CH_2Cl_2 (2.5 mL) at room temperature. Solvent was removed after 3 hours and the crude product was purified using silica gel flash column chromatography eluting first with hexane/EtOAc (v/v = 1/1) then with CH_2Cl_2/MeOH (v/v = 5/1) to give **Example 17** (0.030 g, 71%). Electrospray MS $[M+1]^+$ 297.1.

PREPARATIVE EXAMPLE 18



Example 18

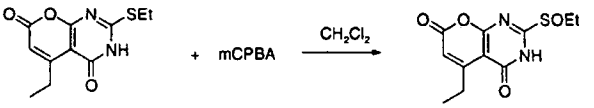
Step A:



Compound 10a Compound 18a

EtI (2.1 g, 13.4 mmol) was added to a suspension of **Compound 10a** (1.5 g, 6.7 mmol) in DMF (20 mL). After stirring at room temperature overnight, the reaction mixture was poured into water (50 mL) and filtered through a Buchner funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 18a** (1.3 g, 76%).

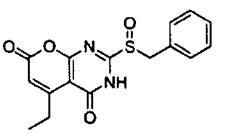
Step B



Compound 18a Example 18

m-CPBA (74 mg, 70%, 3 mmol) was added to a suspension of **Compound 18a** (0.5g, 2 mmol) in CH_2Cl_2 (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH_2Cl_2 (v/v/v = 0.1/4.9/95) to give **Example 18** (0.4 g, 74%). Electrospray MS $[M+1]^+$ 269.

PREPARATIVE EXAMPLE 19



Example 19

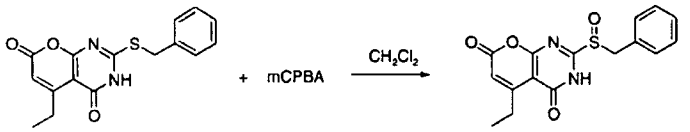
Step A:



Compound 10a Compound 19a

Benzyl bromide (1.54 g, 9 mmol) was added to a suspension of **Compound 10a** (1g, 4.5 mmol) in DMF (20 mL). After stirring at room temperature overnight, the reaction mixture was poured into water (50 mL) and filtered through a Buchner funnel. The solid residue was washed with water (2 x 50 mL) and dried under vacuum to give **Compound 19a** (1.3 g, 92%).

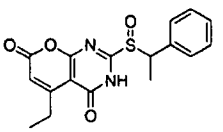
Step B:



Compound 19a Example 19

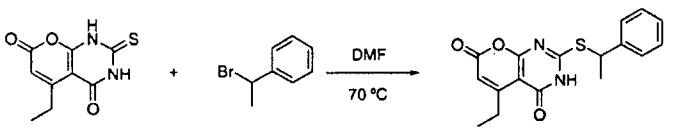
m-CPBA (72 mg, 70%, 3 mmol) was added to a suspension of **Compound 19a** (0.5g, 2 mmol) in CH_2Cl_2 (50 mL) at room temperature. After stirring at room temperature 3 hours, the solvent was removed, and the crude product was purified using silica gel flash column chromatography eluting with AcOH/MeOH/CH_2Cl_2 (v/v/v = 0.1/2.9/97) to give **Example 19** (0.5 g, 76%). Electrospray MS $[M+1]^+$ 331.

PREPARATIVE EXAMPLE 20



Example 20

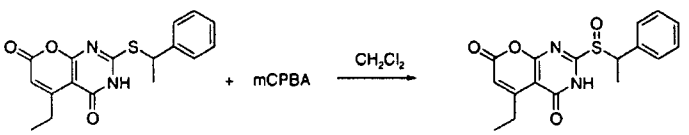
Step A:



Compound 10a Compound 20a

(1-Bromoethyl)benzene (3.4 g, 18 mmol) was added to a suspension of **Compound 10a** (1 g, 4.5 mmol) in DMF (20.0 mL) at room temperature. The reaction mixture was stirred at 70°C for one day. The reaction mixture was cooled down and poured into water (50 mL) and then filtered through a Buchner funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to **Compound 20a** (1.3 g, 87%). Electrospray MS $[M+1]^+$ 329.

Step B:

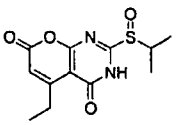


Compound 20a Example 20

m-CPBA (0.3 g, 70%, 1.2 mmol) was added to a suspension of **Compound 20a** (0.33 g, 1 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed

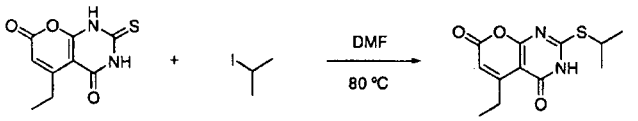
after 3 hours and the crude product was purified using silica gel flash column chromatography eluting with 5 % EtOH in EtOAc/hexanes (v/v = 1:1) to give **Example 20** (0.1 g, 50%). Electrospray MS $[M+1]^+$ 345.

PREPARATIVE EXAMPLE 21



Example 21

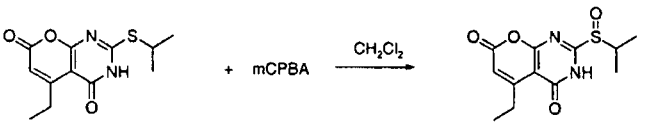
Step A:



Compound 10a Compound 21a

2-Iodopropane (1.53 g, 9 mmol) was added to a suspension of **Compound 10a** (1 g, 4.5 mmol) in DMF (20 mL). The reaction mixture was stirred at 80°C for one day. The reaction mixture was cooled down and poured into water (50 mL) and then filtered through a Buchner funnel. The solid residue was washed with water (2 x 20 mL) and dried under vacuum to give **Compound 21a** (1.05 g, 88%).

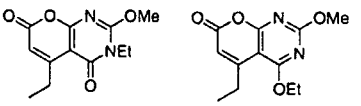
Step B



Compound 21a Example 21

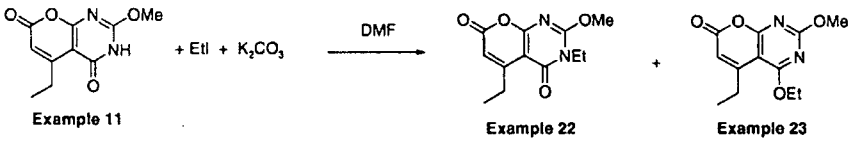
m-CPBA (0.74 g, 70%, 3 mmol) was added to a suspension of **Compound 21a** (0.53 g, 2 mmol) in CH_2Cl_2 (30 mL) at room temperature. Solvent was removed after 3 hours, the crude product was purified using a silica gel flash column chromatography eluting with 0.1% AcOH in MeOH/CH_2Cl_2 (v/v = 2:98) to give **Example 21** (0.45 g, 80%). Electrospray MS $[M+1]^+$ 283.

PREPARATIVE EXAMPLES 22 and 23



Example 22 Example 23

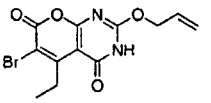
Step A:



Example 11 Example 22 Example 23

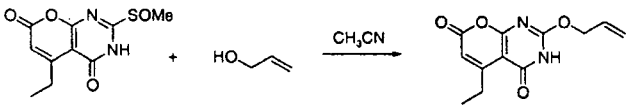
K_2CO_3 (36.7 mg, 0.266 mmol) was added to a mixture of **Example 11** (29.6 mg, 0.133 mmol) and EtI (0.064 mL, 0.8 mmol) in DMF (1.0 mL) at room temperature. The reaction was stirred over night before it was diluted with by the addition of EtOAc (50 mL) and water (10 mL). The organic phase was washed with water (3x15 mL), brine (15 mL), and dried over $MgSO_4$. After filtration and concentration, the crude product was purified using preparative TLC with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/1) as eluent to give **Example 22** (7.0 mg, 21%) and **Example 23** (20 mg, 60%). Electrospray MS $[M+1]^+$ 251.1.

PREPARATIVE EXAMPLE 24



Example 24

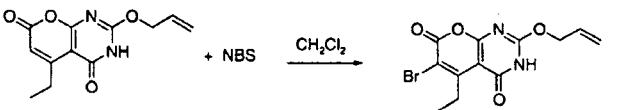
Step A:



Example 10 Compound 24a

Example 10 (0.216 g, 0.847 mmol) in allyl alcohol (3.0 mL) was heated at reflux overnight. After cooling to room temperature, the solvent was removed under reduced pressure and the crude product was purified using silica gel flash column chromatography eluting with EtOAc/MeOH (v/v = 5/1) to give **Compound 24a** (0.1 g, 48%).

Step B:

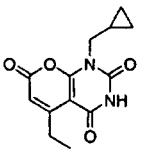


Compound 24a Example 24

NBS (36 mg, 0.202 mmol) was added to a solution of **Compound 24a** (0.040 g, 0.161 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. Solvent was removed over 1 hour and the crude product was purified using silica gel flash column chromatography

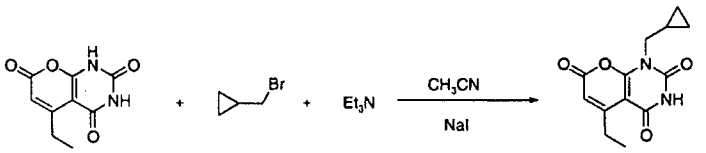
eluting with hexane/EA (v/v = 1/1) to give **Example 24** (0.025 g, 48%). Electrospray MS $[M+1]^+$ 327.1.

PREPARATIVE EXAMPLE 25



Example 25

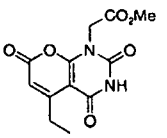
Step A:



Example 1 Example 25

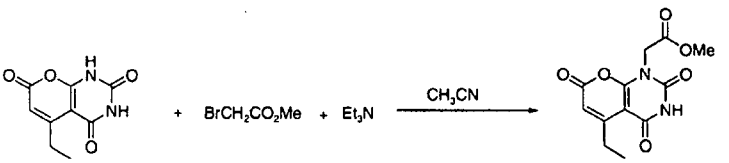
Example 1 (0.5 g, 2.4 mmol) was taken up in CH_3CN (10 mL). Triethylamine (0.33 mL, 2.4 mmol) was added to the suspension followed by cyclopropyl methyl bromide (0.26 mL, 2.64 mmol) and NaI (0.36 g, 2.4 mmol). The reaction mixture was heated to reflux overnight. After cooling to room temperature, the solvent was evaporated in vacuo. The crude product was purified by crystallization from EtOAc/hexanes to give **Example 25** (0.25 g, 40%).

PREPARATIVE EXAMPLE 26



Example 26

Step A:

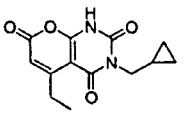


Example 1 Example 26

Example 1 (0.1 g, 0.48 mmol) was taken up in CH_3CN (3.0 mL). Triethylamine (0.067 mL, 0.48 mmol) was added to the suspension followed by methyl bromoacetate

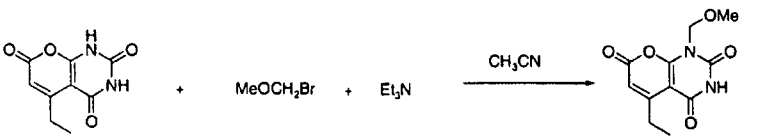
(0.046 mL, 0.48 mmol). The reaction mixture was allowed to stir overnight at room temperature. The solvent was removed under reduced pressure and the crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 26** (0.06 g, 45%).

PREPARATIVE EXAMPLE 27



Example 27

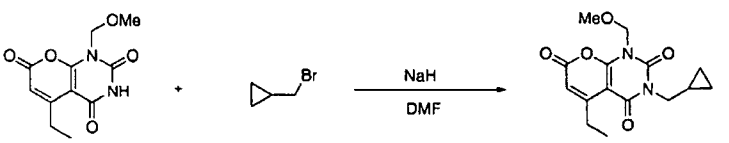
Step A:



Example 1 Compound 27a

Example 1 (1.0 g, 4.8 mmol) was taken up in CH_3CN (20 mL). Triethylamine (0.67 mL, 4.8 mmol) was added to the suspension followed by bromomethyl methyl ether (0.44 mL, 4.8 mmol). The reaction mixture was allowed to stir at room temperature for 10 min after which it was concentrated. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 27a** (0.6 g, 50%).

Step B:

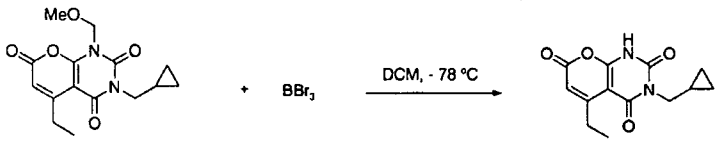


Compound 27a Compound 27b

Sodium hydride (0.058 g, 1.46 mmol) was added to a mixture of **Compound 27a** (0.335 g, 1.33 mmol) in 8 mL DMF at 0°C followed by cyclopropyl methyl bromide (0.142 mL, 1.46 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (10 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product.

The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 27b** (0.175 g, 43%).

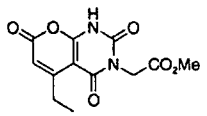
Step C:



Compound 27b Example 27

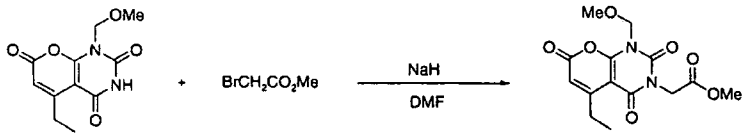
Boron tribromide (2.85 mL, 2.85 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 27b** (0.175 g, 0.57 mmol) in CH_2Cl_2 (8.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 27** (0.1 g, 67%).

PREPARATIVE EXAMPLE 28



Example 28

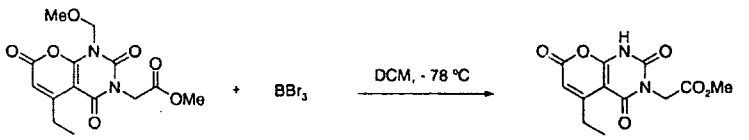
Step A:



Compound 27a Compound 28a

Sodium hydride (0.016 g, 0.396 mmol) was added to a mixture of **Compound 27a** (0.100 g, 0.396 mmol) in 2 mL DMF at 0°C followed by methyl bromoacetate (0.041 mL, 0.44 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (5 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 28a** (0.07 g, 54%).

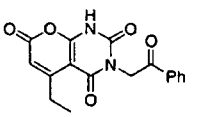
Step B:



Compound 28a Example 28

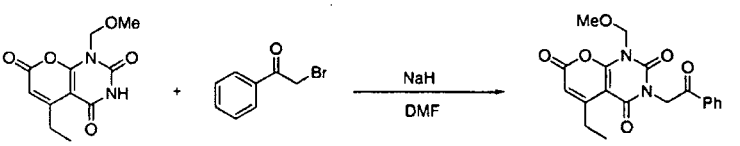
Boron tribromide (1.1 mL, 1.1 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 28a** (0.07 g, 0.22 mmol) in CH_2Cl_2 (3.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 28** (0.02 g, 33%).

PREPARATIVE EXAMPLE 29



Example 29

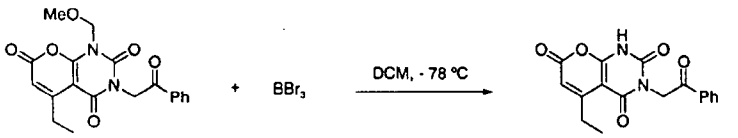
Step A:



Compound 27a Compound 29a

Sodium hydride (0.080 g, 1.98 mmol) was added to a mixture of **Compound 27a** (0.500 g, 1.98 mmol) in 8 mL DMF at 0°C followed by 2-bromoacetophenone (0.434 g, 1.98 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (5 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 29a** (0.37 g, 50%).

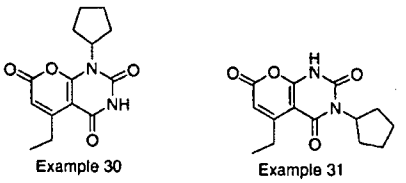
Step B:



Compound 29a Example 29

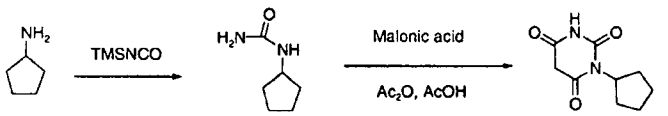
Boron tribromide (4.7 mL, 4.7 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 29a** (0.350 g, 0.95 mmol) in CH_2Cl_2 (10.0 mL) at -78°C. The reaction was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 15 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Example 29** (0.175 g, 56%).

PREPARATIVE EXAMPLE 30 and 31



Example 30 Example 31

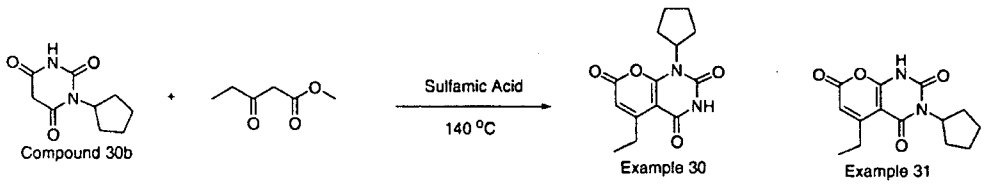
Step A:



Compound 30a Compound 30b

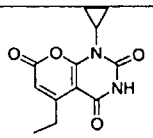
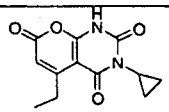
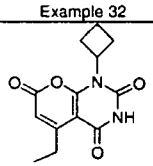
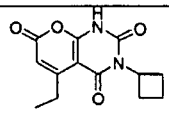
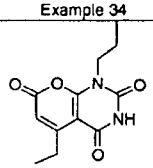
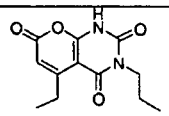
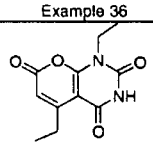
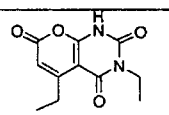
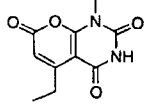
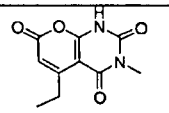
To a CH_2Cl_2 solution of cyclopentylamine was added trimethylsilyl isocyanate. The reaction mixture was stirred overnight. To this was added 200 ml of CH_3OH, and the mixture was stirred for another 2 hrs. The reaction mixture was concentrated and was titrated using diethyl ether to give an off-white precipitate. The precipitate was filtered through a Buchner funnel to give cyclopentyl urea **Compound 30a** as a white crystalline solid compound (13.0 g, 86%). To this urea **Compound 30a** (5.0 g, 38.7 mmol) in acetic acid (11 mL), was added malonic acid (4.0g, 38.7 mmol) followed by acetic anhydride (18 mL) and the reaction was stirred at 70°C for 12 hrs. The reaction mixture was concentrated, cooled in an ice bath and titrated using 4/1 EtO_2/EtOAc. A pale yellow crystalline solid precipitated out. The precipitate was filtered and washed 2-3 times using cold diethyl ether to obtain a pale yellow solid **Compound 30b** (2.5 g, 33%).

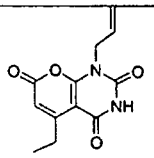
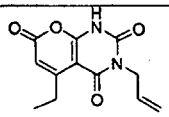
Step B:



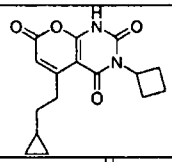
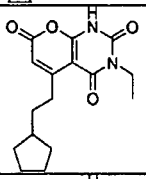
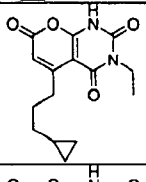
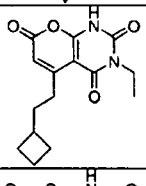
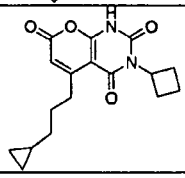
Compound 30b (0.75 g, 1.0 equiv., 3.82 mmol) was condensed with methyl propional acetate (0.48mL, 3.82 mmol) in the presence of sulfamic acid and heated to 140°C for 6 hrs, forming a dark brown solid. The reaction mixture was diluted with EtOAc, washed with H_2O, dried using Na_2SO_4 and concentrated to give a crude mixture. Prep TLC purification of the crude mixture in 95/5 CH_2Cl_2/CH_3OH yielded both the N_1 and N_3 isomers, **Example 30** LCMS: (M+1) 277.1 and **Example 31** LCMS: (M+1). 277.1

A similar two-step procedure was used to synthesize **Examples 32-43**.

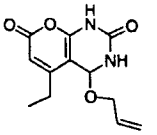
substituents	N-1 products	LCMS: (M+1) of N-1 products	N-3 products	LCMS: (M+1) of N-3 products
cyclopropyl	 Example 32	249.1	 Example 33	249.1
cyclobutyl	 Example 34	263.1	 Example 35	263.1
Pr	 Example 36	251.1	 Example 37	251.1
Et	 Example 38	237.1	 Example 39	237.1
Me	 Example 40		 Example 41	223.0

substituents	N-1 products	LCMS: (M+1) of N-1 products	N-3 products	LCMS: (M+1) of N-3 products
allyl	 Example 42	249.1	 Example 43	249.1

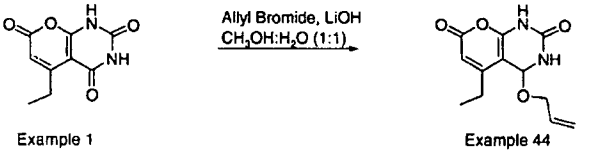
Using the procedure set forth above for making the compound of Example 30, and substituting the appropriate reagents and intermediates, compounds **780-785** were prepared:

Compound No.	Structure	Electrospray LCMS [M+1]+
780		303.1
781		305.2
782		291.2
783		291.2
784		317.2

PREPARATIVE EXAMPLE 44



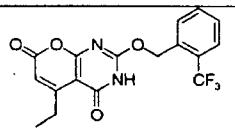
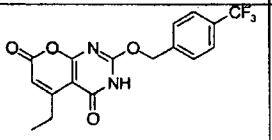
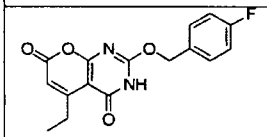
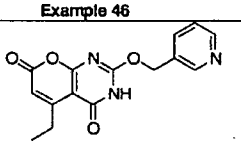
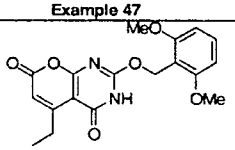
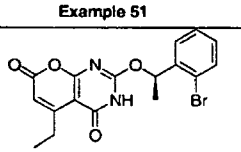
Example 44

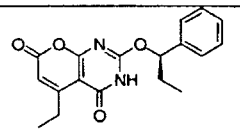
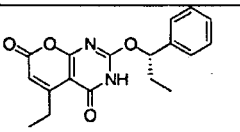
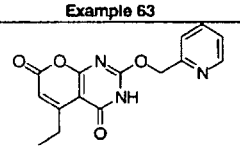
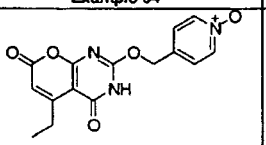
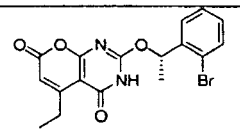
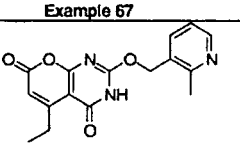
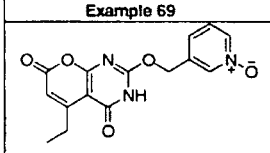
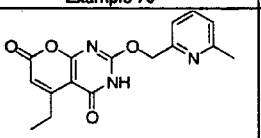
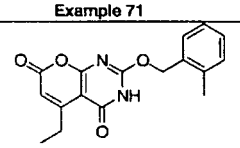
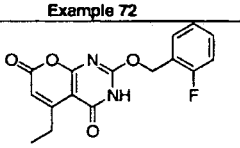
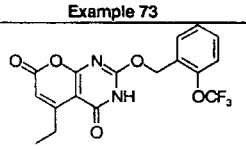
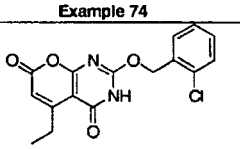
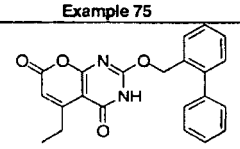
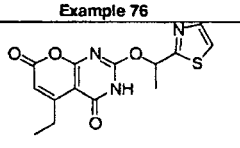
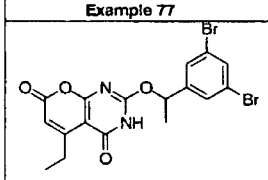


Example 1 Example 44

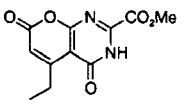
To **Example 1** (0.456 g, 2.2 mmol) in MeOH:H_2O (1:1) was added allyl bromide followed by LiOH, and the reaction mixture was heated to 82°C for 8 hours. The progress of the reaction was monitored by TLC which indicated presence of some starting material. The reaction mixture was then heated for another 6 hours. An orange-red precipitate was produced, which was filtered from the solution using diethyl ether. The filtrate was purified using prep TLC 95/5 CH_2Cl_2/CH_3OH to give **Example 44** LCMS: (M+1).249.0

The following **Examples 45-47, 51, 61-64, 66-67, 69-79** were prepared by a procedure similar to that used for the preparation of **Example 12**, using **Example 10** and the appropriate corresponding alcohol.

PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$
 Example 45	367.1	 Example 46	367.1
 Example 47	317.1	 Example 51	300.1
 Example 61	359.1	 Example 62	391.1

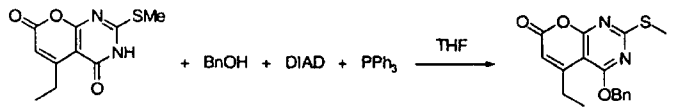
PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$
 Example 63	327.1	 Example 64	327.1
 Example 66	300.1	 Example 67	316.1
 Example 69	391.2	 Example 70	314.1
 Example 71	316.1	 Example 72	314.1
 Example 73	313.1	 Example 74	317.1
 Example 75	383.1	 Example 76	333.1
 Example 77	375.1	 Example 78	320.1
 Example 79	469.1		

PREPARATIVE EXAMPLE 48



Example 48

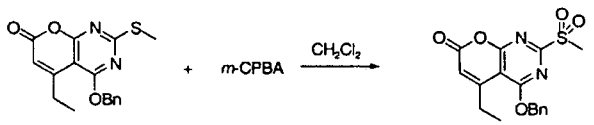
Step A:



Compound 10b Compound 48a

DIAD (0.488 mL, 2.52 mmol) was added dropwise to a solution of **Compound 10b** (0.5 g, 2.10 mmol), BnOH (0.261 mL, 2.52 mmol) and PPh_3 (0.661 g, 2.52 mmol) in THF (6.0 mL) at room temperature. The resulting reaction mixture was stirred for 5 hours before it was worked up by silica gel flash column chromatography using a solid sample loading method, eluting with hexane/EtOAc (v/v = 5/1) to give **Compound 48a** (0.25 g, 36%).

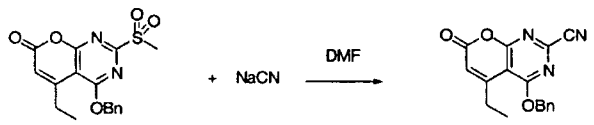
Step B:



Compound 48a Compound 48b

m-CPBA (0.384 g, 1.55 mmol, 60-70%) was added at room temperature to a solution of **Compound 48a** (0.17 g, 0.518 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred for 5 hours before it was quenched with addition of Me_2S (76 uL, 1.55 mmol). The mixture was then diluted with EtOAc and washed with $NaHCO_3$ solution. The organic phase was washed with water, brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure, and the crude product was purified by silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) to give **Compound 48b** (0.15 g, 80%).

Step C:

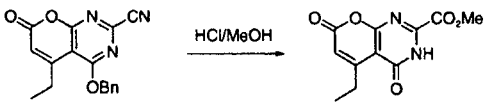


Compound 48b Compound 48c

NaCN (14.0 mg, 0.286 mmol) was added to a solution of **Compound 48b** (85.8 mg, 0.238 mmol) in DMF (1.5 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 hours before it was worked up by dilution with EtOAc and water. The organic phase was washed with water (2x), brine, and dried ($MgSO_4$). Solvent was removed under reduced pressure, and the crude product was purified by

silica gel flash column chromatography, eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 5/1/1) to give **Compound 48c** (37 mg, 50%).

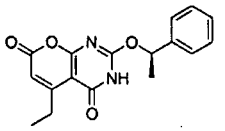
Step D:



Compound 48c Example 48

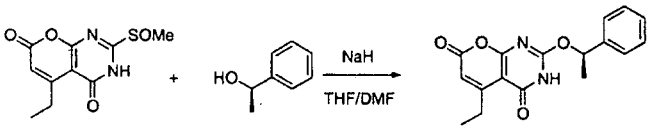
A solution of **Compound 48c** (10 mg, 0.0326 mmol) in 4.0 M HCl in dioxane (0.7 mL) and MeOH (0.7 mL) in a sealed tube was heated at 70°C for 7 hours. The mixture was cooled to room temperature and solvent was removed under reduced pressure to give crude product. The crude product was purified with preparative thin layer silica gel chromatography eluting with hexane/CH_2Cl_2/MeOH (v/v/v = 6/4/1) to give **Example 48** (5 mg, 61%). Electrospray MS $[M+1]^+$ 251.1.

PREPARATIVE EXAMPLE 49



Example 49

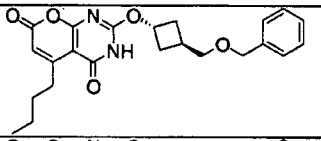
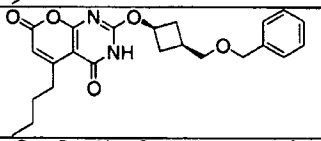
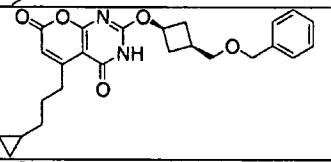
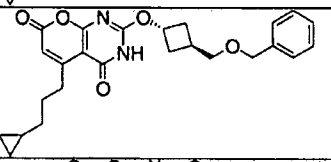
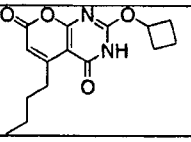
Step A:



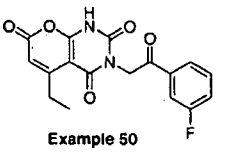
Example 10 Example 49

(R)-Phenethanol (0.24 mL, 2.0 mmol) was added dropwise to a suspension of NaH (87.4 mg, 2.0 mmol, 55% in mineral oil) in THF (3.0 mL) at room temperature. The mixture was stirred for 2 hours until the solution was clear. The alkoxide thus formed was then added dropwise to a solution of the **Compound 10** (0.27 g, 1.0 mmol) in DMF (3.0 mL) at room temperature. The reaction mixture was stirred for 2 hours before it was quenched by the addition of HOAc (0.11 mL, 2.0 mmol). The reaction mixture was taken up in EtOAc/CH_2Cl_2 (8/2), washed with diluted HCl (0.1 M), water and brine, then dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was purified using silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) to give **Compound 49** (0.25 g, 80%). Electrospray MS $[M+1]^+$ 313.1.

Using the method set forth above and substituting the appropriate reagents and intermediates, compounds **791-795** were prepared:

Compound No.	Structure	Electrospray LCMS [M+1]+
791		411.2
792		411.2
793		437.2
794		437.2
795		291.2

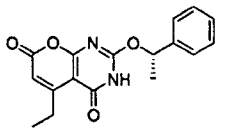
PREPARATIVE EXAMPLE 50



Example 50

Example 50 was prepared by a procedure similar to that used to prepare **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 345.1.

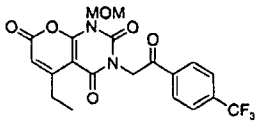
PREPARATIVE EXAMPLE 52



Example 52

Example 52 was prepared by a procedure similar to that used to prepare **Example 49**, using **Example 10** and (S)-phenethanol. Electrospray MS $[M+1]^+$ 313.1.

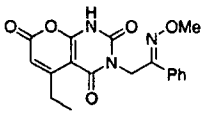
PREPARATIVE EXAMPLE 53



Example 53

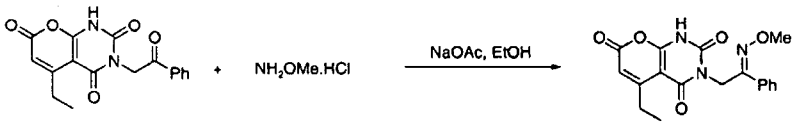
Example 53 prepared by a procedure similar to that used in Step A of the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 439.1.

PREPARATIVE EXAMPLE 54



Example 54

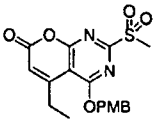
Step A:



Example 29 Example 54

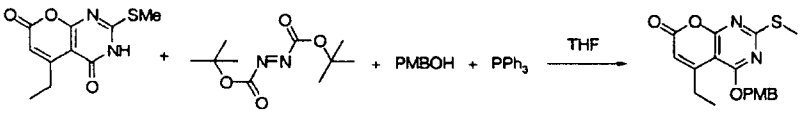
Example 29 (0.05 g, 0.153 mmol) was taken up in ethanol (3.0 mL). Methoxylamine hydrochloride (0.051 g, 0.61 mmol) was added to the mixture followed by sodium acetate (0.038 g, 0.46 mmol). The reaction mixture was stirred at 60°C overnight. After being cooled to room temperature, the solvent was removed under reduced pressure, diluted with CH_2Cl_2 (5 mL) and water (5 mL). The product was extracted from CH_2Cl_2 (2 x 5 mL), dried over $MgSO_4$, concentrated. The crude product was dissolved in minimum CH_2Cl_2, diluted with hexanes and filtered to give **Example 54**. Electrospray MS $[M+1]^+$ 356.1.

PREPARATIVE EXAMPLE 55



Example 55

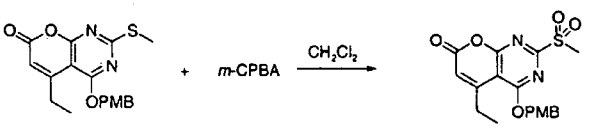
Step A:



Compound 10b Compound 55a

Di-t-butyl diazodicarboxylate (2.32 g, 10.08 mmol) was added to a solution of **Compound 10b** (2.0 g, 8.4 mmol), 4-methoxybenzyl alcohol (1.39 g, 10.08 mmol) and PPh_3 (2.64 g, 10.08 mmol) in THF (20.0 mL) at room temperature. The resulting reaction mixture was stirred for 4 hours before it was worked up by direct silica gel flash column chromatography using a solid sample loading method, eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 9/1/1) to give **Compound 55a** (1.6 g, 53%).

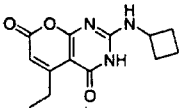
Step B:



Compound 55a Example 55

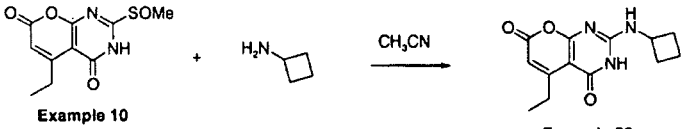
m-CPBA (0.47 g, 1.92 mmol, 60-70%)was added at room temperature to a solution of **Compound 55a** (0.287 g, 0.80 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred for 5 hours before it was quenched by the addition of Me_2S (124 µL, 1.92 mmol). The mixture was then diluted with EtOAc and washed with $NaHCO_3$ solution. The organic phase was washed with water, brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure, crude product was purified with silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) to give **Example 55** (0.15 g, 80%). Electrospray MS $[M+1]^+$ 391.1.

PREPARATIVE EXAMPLE 56



Example 56

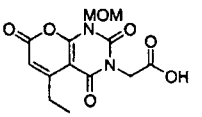
Step A:



Example 10 Example 56

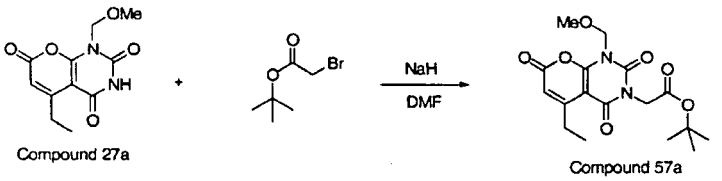
Cyclobutylamine (0.14 g, 2 mmol) was added to a suspension of **Example 10** (0.25 g, 1 mmol) in CH_3CN (15 mL). The reaction mixture was stirred at room temperature for 16 hours. Solvent was removed and the crude product was purified using silica gel flash column chromatography eluting with 10% NH_4OH in $MeOH/CH_2Cl_2$ (v/v = 3:97) to give **Example 56** (0.045 g, 17%). Electrospray MS $[M+1]^+$ 262.1

PREPARATIVE EXAMPLE 57



Example 57

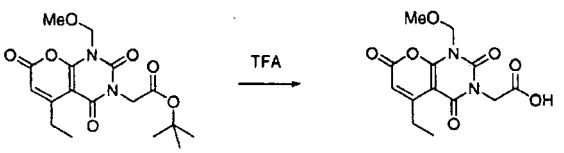
Step A:



Compound 27a Compound 57a

A mixture of **Compound 27a** (2 g, 7.9 mmol) in DMF (100 mL), t-butyl bromoacetate (1.7 g, 8.7 mmol), and diisopropyl ethyl amine (1.1 g, 8.7 mmol) was stirred at 40°C for 4 hours, then at room temperature for 16 hours. The reaction mixture was mixed with water (200 mL), and then extracted with ethyl acetate (100 mL x 3). The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel flash column chromatography eluting with $MeOH/CH_2Cl_2$ (v/v = 2:98) to give **Compound 57a** (1.8 g, 62%). Electrospray MS $[M+1]^+$ 367.2.

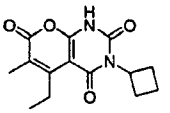
Step B:



Compound 57a Example 57

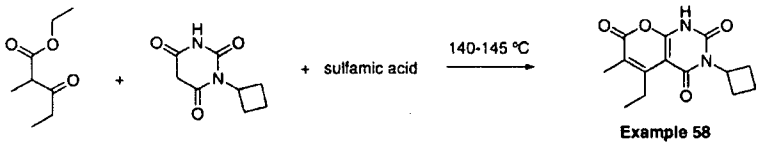
A mixture of **Compound 57a** (0.95g, 2.6 mmol) in CH_2Cl_2 (5 mL) and trifluoroacetic acid (1.5g, 13 mmol) was stirred at room temperature for 4 hours. Removal of solvent and excess trifluoroacetic acid gave **Example 57** (0.8g, 100%). Electrospray MS $[M+1]^+$ 311.2

PREPARATIVE EXAMPLE 58



Example 58

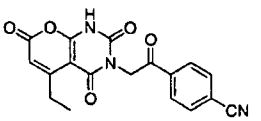
Step A:



Example 58

To a mixture of mono-cyclobutylbarbituric acid (300 mg, 1.6 mmol) and 2-Methyl-3-oxo-pentanoic acid ethyl ester (1.041g, 6.59 mmol) was added sulfamic acid (77 mg, 0.8 mmol). The mixture was heated at 140-145°C for 48h. The residue was loaded onto preparative silica gel plates and eluted with 5% MeOH/CH_2Cl_2 to afford **Example 58** (42 mg, 9%). LCMS: M+1: 277.1

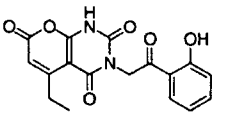
PREPARATIVE EXAMPLE 59



Example 59

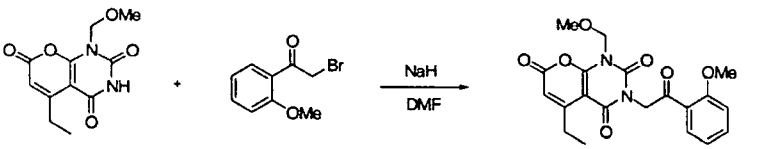
EXAMPLE 59 was prepared using a two step procedure similar to that used for the preparation of **Example 29**, using **Compound 27a** and the appropriate corresponding bromide. Electrospray MS $[M+1]^+$ 252.1.

PREPARATIVE EXAMPLE 60



Compound 60

Step A:

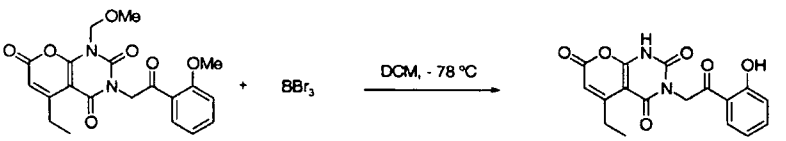


Compound 27a

Compound 60a

Sodium hydride (0.035 g, 0.869 mmol) was added to a mixture of **Compound 27a** (0.200 g, 0.79 mmol) in 3 mL DMF at 0°C followed by 2-methoxyphenacyl bromide (0.2 g, 0.87 mmol). The suspension was allowed to stir at room temperature overnight before being diluted with EtOAc (10 mL) and quenched by the addition of water (5 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 60a**.

Step B:

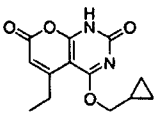


Compound 60a

Compound 60

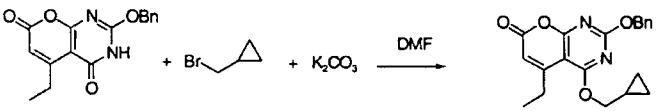
Boron tribromide (1.3 mL, 1.31 mmol, 1.0 M solution in DCM) was added to a solution of **Compound 60a** (0.105 g, 0.262 mmol) in CH_2Cl_2 (5.0 mL) at -78°C. The reaction mixture was allowed to stir for 2 h before being quenched with water (5.0 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated to give the crude product. The crude mixture was purified by column chromatography eluting with EtOAc/hexanes (2/3: v/v) to yield **Compound 60**. Electrospray MS $[M+1]^+$ 343.1.

PREPARATIVE EXAMPLE 65



Example 65

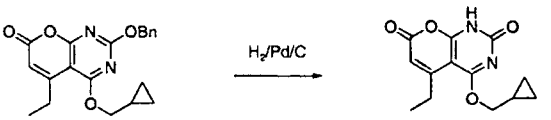
Step A:



Compound 12 Compound 65a

K_2CO_3 (64.7 mg, 0.47 mmol) was added to a mixture of **Example 12** (70 mg, 0.235 mmol) and cyclopropyl methyl bromide (0.068 mL, 0.705 mmol) in DMF (2.0 mL) at room temperature. The reaction mixture was stirred overnight before it was diluted by the addition of EtOAc (50 mL) and water (10 mL). The organic phase was washed with water (3x15 mL), brine (15 mL), and dried over $MgSO_4$. After filtration and concentration, the crude product was purified using preparative TLC with hexane/CH_2Cl_2/EtOAc (v/v/v = 7/3/1) as eluent to give **Compound 65a** (26 mg, 31%).

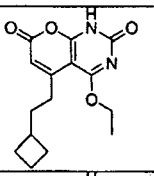
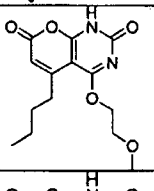
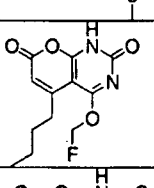
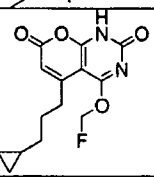
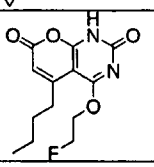
Step B:



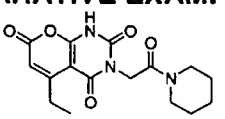
Compound 65a Example 65

Compound 65a (26 mg, 0.074 mmol) in EtOH (5.0 mL) was treated at room temperature with Pd/C (7.8 mg, 10 wt%) and was hydrogenated with a H_2 balloon for 30 minutes. The reaction mixture was filtered through a short pad of Celite and the residue was washed with EtOH (15 mL). Solvent was removed under reduced pressure and the crude product was purified using preparative TLC with hexane/CH_2Cl_2/MeOH (v/v/v = 3/7/1) as eluent to give **Example 65** (6 mg, 30%). Electrospray MS $[M+1]^+$ 263.1.

Using the method set forth above and substituting the appropriate reagents and intermediates, compounds **786-790** were prepared:

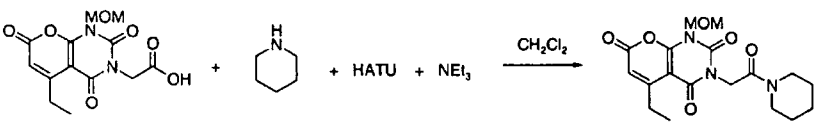
Compound No.	Structure	Electrospray LCMS [M+1]+
786		291.2
787		295.2
788		269.1
789		295.2
790		283.2

PREPARATIVE EXAMPLE 68



Example 68

Step A:

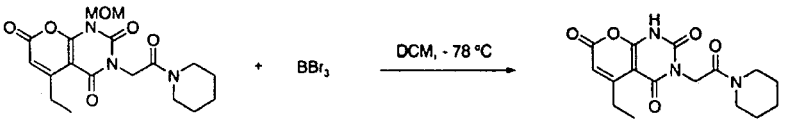


Example 57 Compound 68a

The mixture of **Example 57** (0.1g, 0.32 mmol) in CH_2Cl_2 (5 mL), piperidine (0.027 g, 0.32 mmol), HATU (0.24g, 0.64 mmol), and triethylamine (0,098 g, 0.96 mmol) was stirred at room temperature for 2 hours. The reaction mixture was mixed with water (20 mL), and then extracted with CH_2Cl_2 (10 mL x 2). The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel

flash column chromatography eluting with EtOAc/hexanes (v/v = 1:1) to give **Compound 68a** (0.065 g, 54%). Electrospray MS $[M+1]^+$ 378.2.

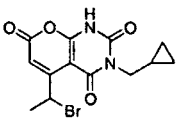
Step B:



Compound 68a Example 68

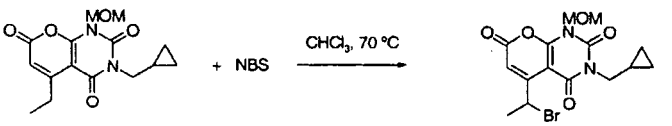
1M BBr_3 solution in CH_2Cl_2 (0.75 mL, 0.75 mmol) was added to a solution of **Compound 68a** (0.056 g, 0.15 mmol) at -78°C. After the reaction mixture was stirred at -78°C for 2 hours, water (5 mL) was added. The organic solution was dried (Na_2SO_4) and concentrated. The crude product was purified using silica gel flash column chromatography eluting with 10% NH_4OH in $MeOH/CH_2Cl_2$ (v/v = 3:97) to give **Example 68** (0.01 g, 20%). Electrospray MS $[M+1]^+$ 334.2.

PREPARATIVE EXAMPLE 80



Example 80

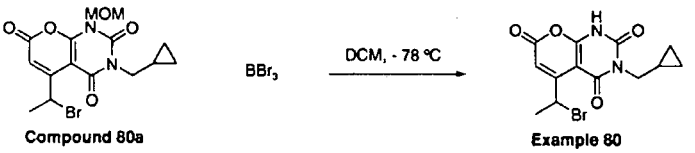
Step A:



Compound 27b Compound 80a

Compound 27a (0.1 g, 0.33 mmol) was taken up in CH_2Cl_2 at room temperature. NBS was then added and the reaction was stirred for 4 hours. After no progress in the reaction was observed, a mixture of NBS (0.061 g, 0.34 mmol) in chloroform (4 mL) was added. The reaction mixture was heated for 12 hrs at 70°C. Both the TLC (30/70 EtOAc/ Hexane) and mass spectrogram indicated that the reaction was complete. The reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 and washed with H_2O. The organic phase was dried with Na_2SO_4 and solvent was removed to give the crude product. Preparative silica gel chromatography purification in EtOAc/Hexane (v/v = 30/70) yielded **Compound 80a** (0.075 g, 60 %).

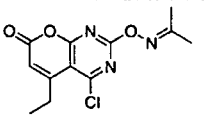
Step B:



Compound 80a Example 80

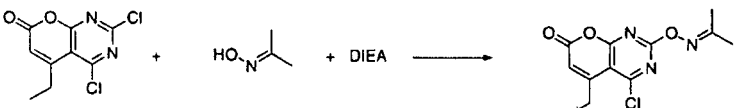
Compound 80a (0.070g, 0.18 mmol) was taken up in CH_2Cl_2 and the mixture was cooled to -78°C. 1M BBr_3 (0.909 mL, 0.9 mmol) was added. The reaction mixture was stirred for 4 hours. Upon completion of the reaction, the mixture was diluted with CH_2Cl_2, washed with H_2O, dried with Na_2SO_4, and then solvent was removed to give crude product. The crude product was purified by preparative silica gel chromatography using 30/70 EtOAc/ Hexane, to give **Example 80.** Electrospray MS $[M+1]^+$ 341.2.

PREPARATIVE EXAMPLE 81



Example 81

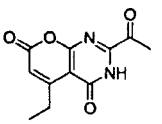
Step A:



Example 5 Example 81

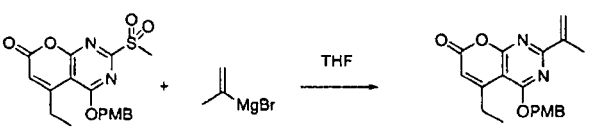
To a mixture of **Example 5** (84 mg, 0.34 mmol) and acetone oxime (27.5 mg, 0.37 mmol) was added DIEA (0.09 ml, 0.52 mmol) and the mixture was stirred for 3 days. The mixture was concentrated and was subjected to silica gel column chromatography to give **Example 81** (30 mg, 31%). LCMS: M+1: 282.1

PREPARATIVE EXAMPLE 92



Example 92

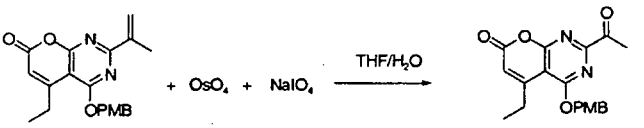
Step A:



Example 55 Compound 92a

Isopropenyl magnesium bromide (0.95 mL, 0.475 mmol, 0.5 M in THF) was added dropwise to a solution of **Example 55** (0.133 g, 0.341 mmol) in THF (4.0 mL) at 0°C. The mixture was stirred at 0°C for 2 hours before it was quenched with HCl (0.2 M). The mixture was taken up in EtOAc and washed with water and brine. The organic phase was dried over $MgSO_4$. Solvent was removed under reduced pressure and the crude product was purified with silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 4/1/1) to give **Compound 92a** (59 mg, 49%).

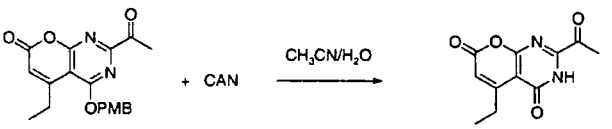
Step B:



Compound 92a Compound 92b

$NaIO_4$ (70.1 mg, 0.328 mmol) was added to a solution of **Compound 92a** (46.2 mg, 0.131 mmol) and OsO_4 (22.2 µL, 4 wt% in water) in THF (5.0 mL) and water (5.0 mL) at room temperature. The reaction mixture was stirred overnight before it was quenched by the addition of Me_2S (20 µL, 0.328 mmol). The mixture was diluted with EtOAc and washed with HCl (0.5 M), water and brine. The organic phase was dried over $MgSO_4$. Solvent was removed under reduced pressure and the crude product was purified by silica gel flash column chromatography eluting with hexane/CH_2Cl_2/EtOAc (v/v/v = 2/1/1) to give **Compound 92b** (39 mg, 84%).

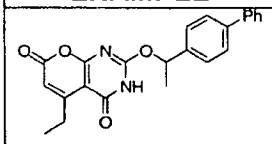
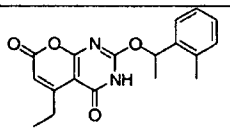
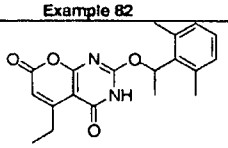
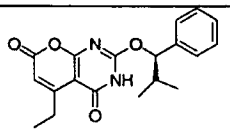
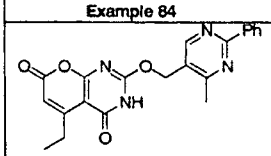
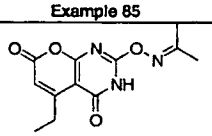
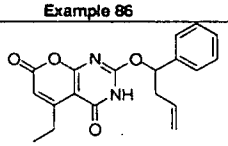
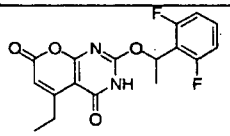
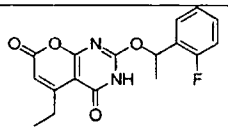
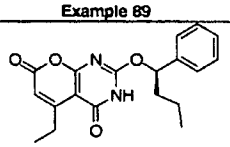
Step C:



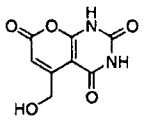
Compound 92b Example 92

Ceric ammonium nitrate (70.9 mg, 0.129 mmol) was added to a solution of **Compound 92b** (20.8 mg, 0.059 mmol) in MeCN (3.0 mL) and water (0.3 mL) at room temperature. The reaction mixture was stirred for 2 hours before it was diluted with EtOAc. The organic phase was washed with HCl (0.5 M), water, brine and dried over $MgSO_4$. Solvent was removed under reduced pressure and crude product was purified using preparative TLC with hexane/CH_2Cl_2/MeOH (v/v/v = 2/8/1) as eluent to give **Example 92** (8 mg, 58%).Electrospray MS $[M+1]^+$ 235.1.

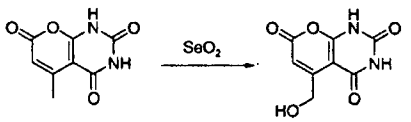
Examples 82-91 were prepared by procedures similar to those used for the preparation of **Example 49**, using **Example 10** and the appropriate corresponding alcohols.

PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$	PREPARATIVE EXAMPLE	Electrospray LCMS $[M+1]^+$
 Example 82	389.1	 Example 83	327.1
 Example 84	341.1	 Example 85	341.1
 Example 86	391.1	 Example 87	264.1
 Example 88	339.1	 Example 89	349.1
 Example 90	331.1	 Example 91	341.1

PREPARATIVE EXAMPLE 92



Example 92



Example 2 Example 92

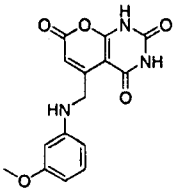
Example 2 (0.71 g, 3.66 mmol, 1 eq) and SeO_2 (0.46 g, 1.1 eq) were mixed together in 1,4-dioxane (10.5 mL) and THF (1.5 mL) and the mixture was heated to 90°C in air for 24 hr. 5% of the resulting crude product was purified by directly loading

it onto a reverse-phase HPLC column to afford the desired product **Example 92** (7.4 mg) as a white solid.

^{1}H NMR (CD_3OD): δ 4.80 (s, 2 H) 6.20 (s, 1 H)

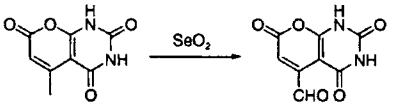
Mass of $C_8H_7N_2O_5$ $(MH)^+$: 211. Found: 211.

PREPARATIVE EXAMPLE 93



Example 93

Step A:

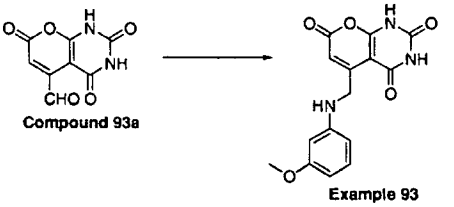


Example 2 Compound 93a

Compound 93a was prepared by a procedure similar to that used to prepare alcohol **Example 92**, except that the alcohol was allowed to oxidize further to the corresponding aldehyde. After purification several times using reverse-phase HPLC, **Compound 93a** (90 mg) was obtained.

Mass of $C_8H_5N_2O_5$ $(MH)^+$: 209. Found: 209.

Step B:



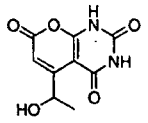
Compound 93a Example 93

Compound 93b (90 mg, 0.43 mmol, 1 eq)) was mixed with 3-methoxyaniline (109 mg, 2 equiv.) and sodium triacetoxyborohydride (185 mg, 2 equiv.) in 2 mL of THF. After stirring overnight, the reaction mixture was quenched with methanol. Preparative TLC afforded 15.3 mg of the desired product **Example 93.**

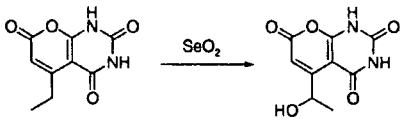
^{1}H NMR (CD_3OD): δ 3.60 (s, 3 H) 4.60 (s, 2 H) 5.75 (s, 1 H) 6.20 (m, 3 H) 6.95 (m, 1 H)

Mass of $C_{15}H_{14}N_3O_5$ $(MH)^+$: 316. Found: 316.

PREPARATIVE EXAMPLE 94



Example 94



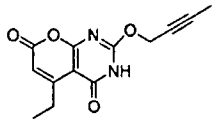
Example 1 Example 94

Example 94 was prepared by a procedure similar to that used to prepare **Example 92**, except that **Example 1** was oxidized instead of **Example 2**.

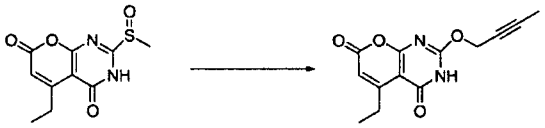
^{1}H NMR (CD_3OD): δ 1.38 (d, 2 H, J = 6.8 Hz) 5.50 (q, 1 H, J = 6.8 Hz) 6.20 (s, 1 H)

Mass of $C_9H_9N_2O_5$ $(MH)^+$: 225. Found: 225.

PREPARATIVE EXAMPLE 95



Example 95



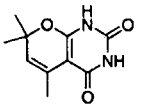
Example 10 Example 95

2-butyn-1-ol (140 mg, 2 mmol, 2 equiv.) in 4 mL of THF was treated with 1.6 M n-BuLi (1.2 mL, 2 equiv.) at 0°C for 5 min to provide an alkoxide solution. **Example 10** (0.25 g, 1 mmol, 1 equiv.) was then added to the alkoxide solution. After stirring 1.5 hr, 0.12 g of acetic acid (2 equiv.) was added to the solution. The solvent was removed and extraction with diethyl ether and water provided a white solid. The solid was washed with cold diethyl ether and dried under vacuum. 80 mg of the desired product **Example 95** was obtained.

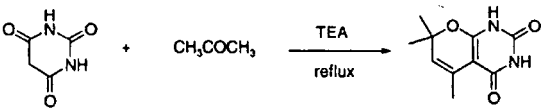
^{1}H NMR ($CDCl_3$): δ 1.20 (t, 2 H, J = 6.8 Hz) 1.83 (s, 3 H) 3.00 (q, 2 H, J = 6.98 Hz) 5.00 (s, 2 H) 6.00 (s, 1 H)

Mass of $C_{13}H_{13}N_2O_4$ $(MH)^+$: 261. Found: 261.

PREPARATIVE EXAMPLE 96



Example 96

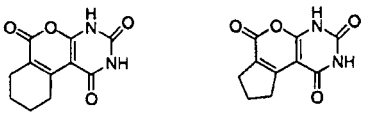


Example 96

Barbituric acid (1.0 g, 7.81 mmol) was taken up in excess acetone. Triethylamine (2 mL) was added, and the reaction mixture was refluxed overnight after which it was cooled and filtered. The crude solid was purified by preparative TLC (8:1:1/EtOAc:DCM:MeOH) to yield the desired product, **Example 96**.

Electrospray MS $[M+1]^+$ for **Example 96** is 209.0

PREPARATIVE EXAMPLES 97 and 98

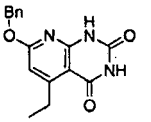


Example 97 Example 98

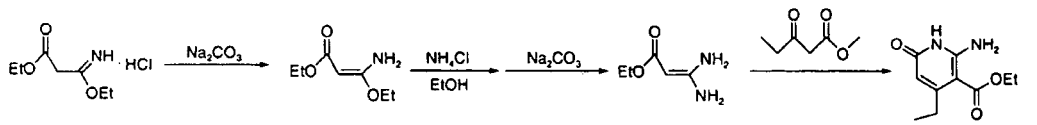
Examples 97 and **98** were prepared by methods analogous to the method used to prepare **Example 1**, except that 2-oxo-cyclohexanecarboxylic acid methyl ester and 2-oxo-cyclopentanecarboxylic acid methyl ester, respectively, were used instead of methylpropionylacetate.

Electrospray MS $[M+1]^+$ for **96** and **97** are 235.1.

PREPARATIVE EXAMPLE 99



Example 99



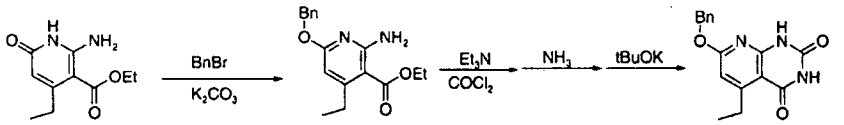
Compound 99a Compound 99b Compound 99c Compound 99d

Commercially available (Aldrich) **Compound 99a** (75 g, 383 mmol) was stirred with cold aqueous Na_2CO_3 (15%, 450 mL) for 2 h. Extraction with EtOAc and drying over Na_2CO_3 provided **Compound 99b** as a colorless oil, which was immediately

treated with NH_4Cl (19.5 g, 364 mmol) in 200 mL of dry EtOH at 50°C for 60 h. The crude product mixture was cooled and the solvent was removed. The resulting light yellow solid was treated with cold K_2CO_3 (30 %, 300 mL H_2O) for 0.5 h. Extraction with EtOAc gave **Compound 99c** as a light yellow solid (37.92 g). This solid was reacted with methyl propionylacetate (38.0 g, 292 mmol), 2 mL pyridine, in 400 mL of dry EtOH at 100°C for 24 h. After cooling and filtration, the solid was washed with EtOH and 18 g of **Compound 99d** as a white solid was obtained (22% yield from **Compound 99a**).

^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3 H, J = 7.3 Hz) 1.40 (t, 3 H, J = 7.1 Hz) 2.90 (q, 2 H, J = 7.3 Hz) 4.30 (q, 2 H, J = 7.1 Hz) 5.75 (s, 1 H)

Mass of $C_{10}H_{15}N_2O_3$ $(MH)^+$: 211. Found: 211.



Compound 99d Compound 99e Example 99

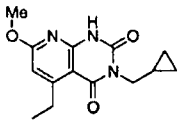
Compound 99d (3.0 g, 14.28 mmol) was treated with BnBr (2.44 g, 1 eq) and K_2CO_3 (3.94 g, 2 eq) in 100 mL acetone at 70°C for 17 h. The solvent was removed and chromatographic purification (5% EtOAc in hexane) provided 2.53 g pure **Compound 99e** in 58% yield.

Compound 99e (0.3 g, 1 mmol) was treated with Et_3N (0.22 g, 2.2 eq), $COCl_2$ (1.9 M in toluene, 0.53 mL, 1 equiv) in 5 mL DCM at -78°C for 45 min. The reaction mixture was warmed to room temperature in 1 h. NH_3 (0.5 M in 1,4-dioxane, 2 mL, 1 eq) was added and the reaction mixture was stirred overnight. The solvent was then removed, 3 mL anhydrous THF was added along with t-BuOK (1 M in THF, 1 mL, 1 equiv), and the mixture was stirred overnight. The solvent was removed, hexane and a small amount of MeOH were added and the resulting white solid was collected. The solid was further washed with anhydrous diethyl ether to give 3.8 mg of **Example 99** as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.20 (t, 3 H, J = 7.3 Hz) 3.10 (q, 2 H, J = 7.3 Hz) 5.40 (s, 2 H) 6.40 (s, 1 H) 7.20-7.40 (m, 4 H) 8.30 (m, 2 H)

Mass of $C_{16}H_{16}N_3O_3$ $(MH)^+$: 298. Found: 298.

PREPARATIVE EXAMPLE 100



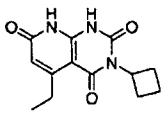
Example 100

Example 100 was prepared following procedures similar to those used to prepare **Example 99**, except that methyl iodide was used instead of BnBr, and cyclopropylmethylamine was used instead of ammonia.

^{1}H NMR ($CDCl_3$): δ 0.40 (m, 4 H) 1.18-1.25 (m, 4 H) 3.10 (q, 2 H, J = 7.2 Hz) (3.82 (d, 2 H, J = 7.4 Hz) 3.90 (s, 3 H) 6.38 (s, 1 H) 8.10 (br s, 1 H)

Mass of $C_{14}H_{18}N_3O_3$ $(MH)^+$: 276. Found: 276.

PREPARATIVE EXAMPLE 101



Example 101



Compound 101a Example 101

Intermediate **Compound 101a** was prepared using procedures similar to those used to prepare Example 99, except that cyclobutylamine was used instead of ammonia.

^{1}H NMR ($CDCl_3$): δ 1.20 (t, 2 H, J = 7.3 Hz) 1.60-1.80 (m, 2 H) 2.10 (m, 2 H) 3.00 (m, 2 H) 3.10 (q, 2 H, J = 7.3 Hz) 5.30 (m, 1 H) 5.40 (s, 2 H) 6.40 (s, 1 H) 7.20-7.40 (m, 5 H) 8.20 (br s, 1 H)

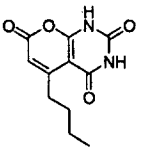
Mass of $C_{20}H_{22}N_3O_3$ $(MH)^+$: 352. Found: 352.

Compound 101a (70 mg) was treated with 3% Pd/C (50 mg), 10 mL MeOH under a hydrogen atmosphere (hydrogen balloon) overnight. After filtration, prep HPLC purification provided 1.2 mg of **Example 101**.

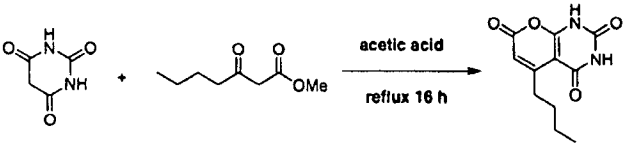
^{1}H NMR ($CDCl_3$): δ 1.20 (t, 2 H, J = 7.3 Hz) 1.60-1.80 (m, 2 H) 2.10 (m, 2 H) 2.95 (m, 2 H) 3.20 (q, 2 H, J = 7.3 Hz) 5.30 (m, 1 H) 6.40 (s, 1 H) 8.00 (br s, 1 H).

Mass of $C_{14}H_{17}N_3O_3$ $(MH)^+$: 276. Found: 276.

PREPARATIVE EXAMPLE 102



Example 102



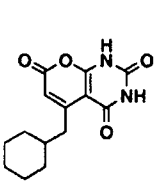
Example 102

In a 25 mL round bottomed flask equipped with a magnetic stirring bar and a nitrogen balloon was placed 1.0 g of barbituric acid (7.8 mmol) and 1.52 mL of 3-oxoheptanoic acid methyl ester (9.6 mmol, 1.23 equiv.). 8 mL of acetic acid was added to the reaction mixture and was refluxed for 16 h after which the reaction was cooled to room temperature. The excess acetic acid was concentrated and dried in vacuo to give crude product **Example 102** along with unreacted starting materials. The crude product was stirred with 20 mL of boiling water for a few minutes and filtered. The precipitate was washed with boiling water (2 x 10 mL) and dried to yield 0.65 g (35% yield) of **Example 102**.

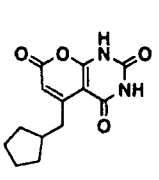
^{1}H NMR (DMSO): δ 0.9 (t, 3 H, J = 7.5 Hz) 1.32-1.40 (m, 2 H) 1.45-1.51 (m, 2 H) 2.84-2.87 (t, 2 H, J = 7.5 Hz) 5.82 (s, 1 H) 11.34 (s, 1 H) 12.72 (br s, 1 H)

Mass of $C_{11}H_{12}N_2O_4$ $(MH)^+$: 236.22. Found: 237.1.

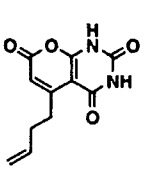
EXAMPLES 103-135



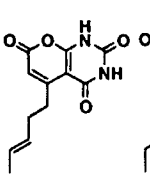
Example 103



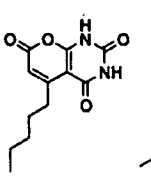
Example 104



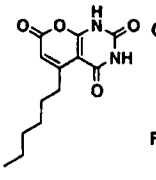
Example 105



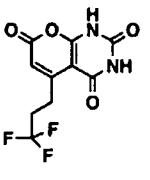
Example 106



Example 107



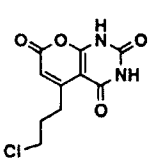
Example 108



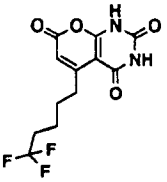
Example 109



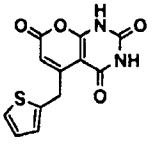
Example 110



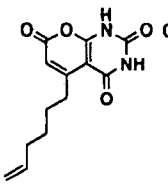
Example 111



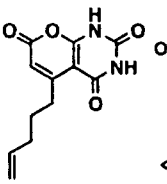
Example 112



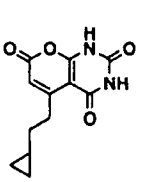
Example 113



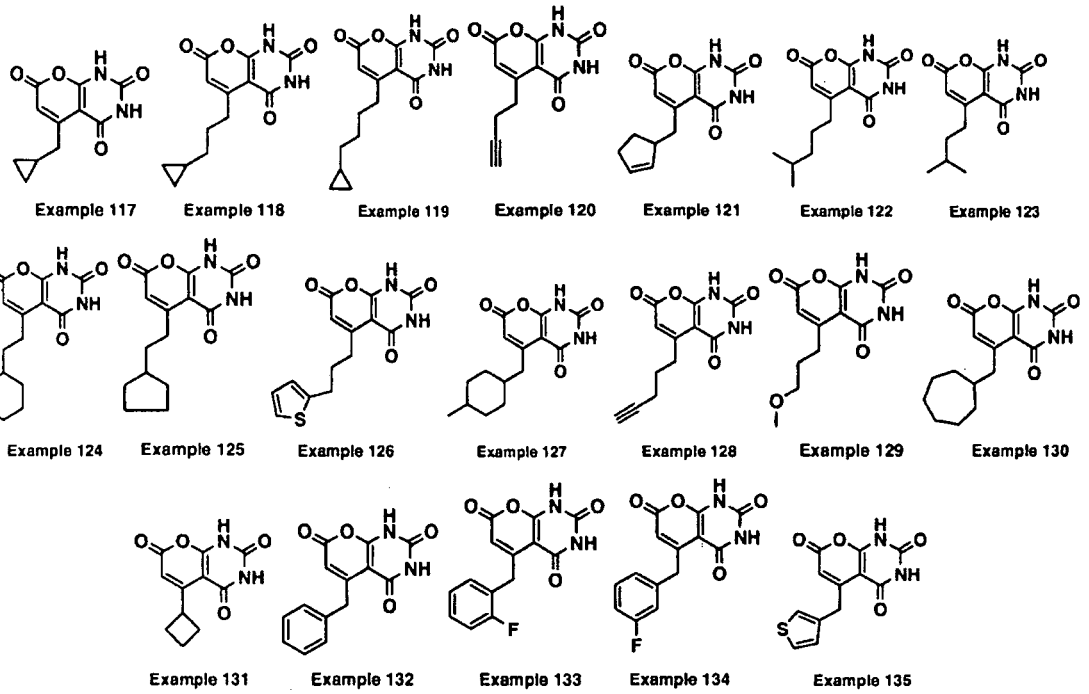
Example 114



Example 115



Example 116



Examples 103-135 where prepared using procedures similar to those used to prepare **Example 102**, except that an appropriately substituted keto-ester was used instead of 3-oxoheptanoic acid methyl ester.

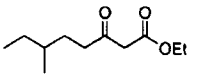
The examples **200, 210, 241, 242, 245, 246, 252-260, 274-278, 280, 281, 282, 284, 285, 291** were prepared by a procedure similar to that used for the preparation of Example **30 and 31**.

The examples **201, 202, 204-209, 211-218, 224-240, 243, 244, 247-251, 261-273, 279, 283, 286-290, 293, 294-297** were prepared by a procedure similar to that used for the preparation of example **102**, using barbituric acid and the corresponding keto ester.

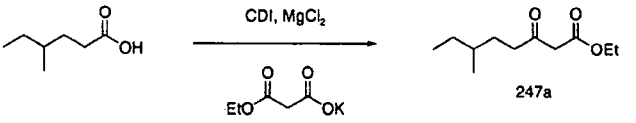
The preparation of ketoesters starting material where appropriate is shown below.

The preparation of keto ester starting material for examples **247** is as follows

Preparative example 247a

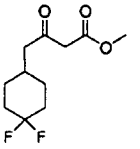


247a



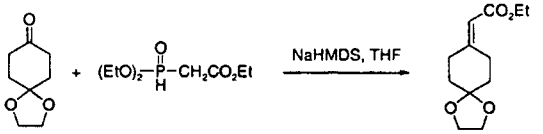
4-Methylhexanoic acid (3.0 g, 23.08 mmol) was taken in 40 mL THF. 1,1'-Carbonyldiimidazole (4.49 g, 27.69 mmol) was added and the reaction was stirred at room temperature for 1 h after which $MgCl_2$ (2.2 g, 23.08 mmol) and ethyl potassium malonate (5.89 g, 34.62 mmol) was added. The reaction was allowed to run at room temperature overnight. The crude reaction mixture was filtered through a short pad of silica gel and eluted with EtOAc/hexanes (1:3) to yield compound **247a**.

Preparative example 223a



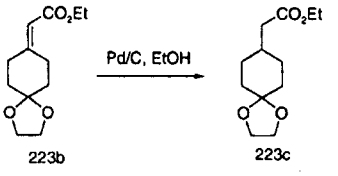
223a

The starting material for the preparation of example **223** is as follows.

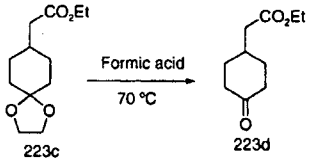


223b

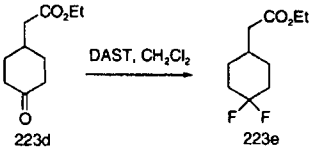
Step A: A solution of triethyl phosphonate (44.8g, 200 mmol) in THF (30 ml) at 0 °C was treated with a 1M solution (200 ml) of sodium bis(trimethylsilylamide) in THF. The resulting mixture was stirred at room temperature for 0.5 hour, and then cooled to 0 °C. A solution of 1,4-cyclohexanedione mono ethylene ketal (15.6g, 200 mmol) in THF (50 ml) was added dropwise, and the resulting solution was stirred at room temperature for 18 hours. The reaction mixture was then cooled to 0 °C, treated with cold aqueous citric acid, and the mixture was extracted with EtOAc. The extract was washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/EtOAc to afford **223b** (21g, 91%).



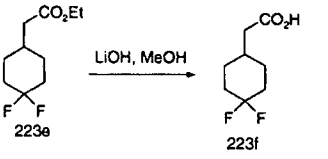
Step B: The compound **223b** (20g) was dissolved in EtOH (150 ml) and treated with 10% Pd/C under 1 atm of hydrogen for 3 days. The mixture was filtered and the filtrate was evaporated to **223c** (20.3g, 100%).



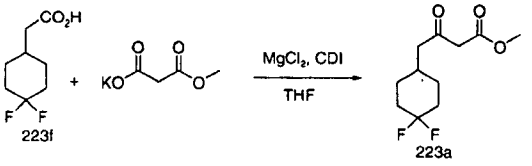
Step C: The compound **223c** (7g) was dissolved in formic acid (50 ml) and heated at 70 °C for 1 h. The solution was concentrated and the residue was taken up in EtOAc and washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel to afford **223d** (5g).



Step D: The compound **223d** (4.6 g) was dissolved in CH_2Cl_2 (10 ml) and treated with diethylaminosulfur trifluoride (DAST, 5 ml) at room temperature for 3 hours. The reaction mixture was poured into ice/water (30 ml) and extracted with CH_2Cl_2. The extract was washed with satd. aqueous $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated to afford **223e** as brown oil (3.2 g, 62%).



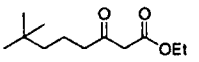
Step E: The compound **223e** (3.2 g, 15.5 mmol) was dissolved in MeOH (5 ml) and treated with LiOH (559 mg, 23.3 mmol) overnight. The reaction mixture was acidified by 3 N HCl to pH 4 and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4 and concentrated to afford **223f** as brown oil (3 g, 100%).



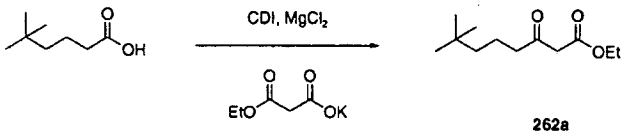
Step F: The compound **223f** (900 mg, 5.0 mmol) was dissolved in THF (15 ml), added with CDI (972 mg, 6.0 mmol) and stirred for 45 min. Then methyl malonate potassium salt (1.02 g, 6.0 mmol) and $MgCl_2$ (570 mg, 6.0 mmol) were added into the above solution. The resulting mixture was stirred overnight and filtered through a short pad of silica gel and washed with EtOAc. The filtrate was concentrated and chromatographed on silica gel to afford **223a** as colorless oil (400 mg, 34%).

The starting materials for structures **262, 263** were prepared in a manner similar to **218a**.

Preparative example 262a



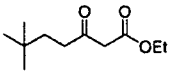
262a



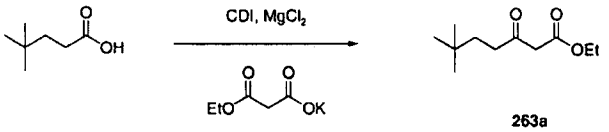
262a

Prepared in the same manner as in example **218a**.

Preparative example 263a



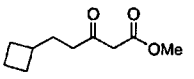
263a



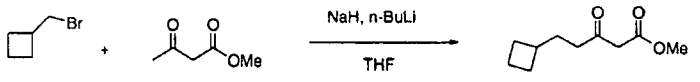
263a

Prepared in the same manner as in example **218a**.

Preparative example 266a



266a

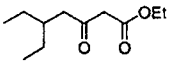


266a

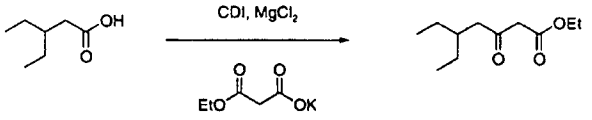
Sodium hydride (1.42 g, 35.56 mmol) was taken in THF (20 mL) in a round bottomed flask equipped with a stirring bar and nitrogen balloon. It was cooled to 0 °C

and methyl acetoacetate (3.84 mL, 35.56 mmol) dissolved in 10 mL THF was added dropwise. The reaction mixture was stirred at 0 °C for 30 min after which *n*-BuLi (2.5 M solution in hexanes, 14.2 mL, 35.56 mmol) was added dropwise. The reaction was allowed to run for 30 min at 0 °C and then cooled to – 25 °C. Bromomethylcyclobutane (4.82 g, 32.32 mmol) dissolved in 20 mL THF was added dropwise and the reaction was stirred at – 25 °C for 4 h followed by room temperature overnight. It was quenched with the addition of sat. NH_4Cl, extracted with EtOAc (2 x 30 mL), dried over $MgSO_4$, concentrated in vacuo. The crude product was purified by biotage (5% EtOAc/hexanes) to yield compound **266a**.

Preparative example 267a



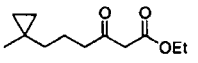
267a



267a

Prepared in the same manner as in example **218a**.

Preparative example 268a

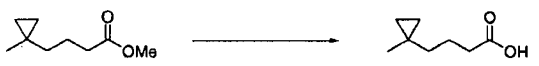


268a



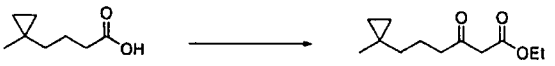
268b

Trifluoroacetic acid (7.84 mL, 105.48 mmol) and diiodomethane (8.5 mL, 105.48 mmol) in 50 mL DCM was cooled to 0 °C. Diethylzinc (1.0 M solution in hexanes, 105.5 mL, 105.48 mmol) was added dropwise. The reaction was allowed to stir at 0 °C for 20 min after which 5-Methyl-5-hexenoic acid methyl ester (5.0 g, 35.16 mmol) in 20 mL DCM was added dropwise. The reaction was allowed to stir at room temperature overnight. The reaction was quenched by the addition of sat. NH_4Cl, extracted with DCM (2 x 30 mL), dried over $MgSO_4$, concentrated in vacuo to yield compound **268b** which was carried over to the next step without further purification.



268b **268c**

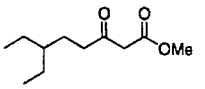
Ester **268b** (5.0 g, 32 mmol) was taken in MeOH (50 mL) and NaOH (3.2 g, 80 mmol) was added to it. The reaction was allowed to stir at room temperature overnight. The reaction was diluted with water (50 mL) and acidified with conc HCl. It was extracted with Et_2O (2 x 30 mL), washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product **268c** was used as such without any further purification.



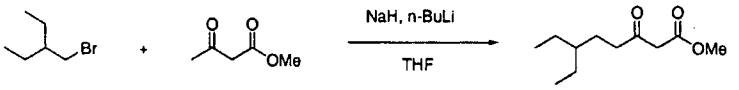
268c **268a**

Prepared in the same manner as in example **262a**.

Preparative example 269a



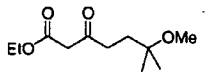
269a



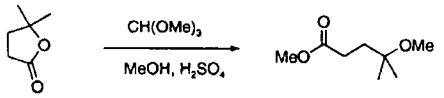
269a

Prepared in the same manner as in example **266a**.

Preparative example 279a



279a



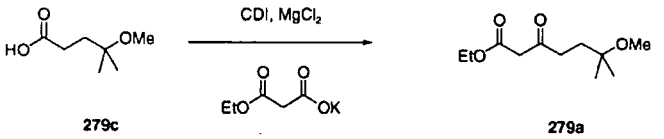
279b

5,5-Dimethyl-dihydro-furan-2-one (5.0 g, 43.8 mmol), trimethyl orthoformate (11.5 mL, 105.12 mmol), and sulfuric acid (0.43 g, 4.38 mmol) were taken in MeOH (50 mL). The reaction mixture was heated to 50 °C overnight. After cooling, the solvent was removed in *vacuo*, quenched with sat. $NaHCO_3$ and extracted with EtOAc (2 x 30 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in *vacuo* to yield compound **279b** which was used without any further purification.



279b 279c

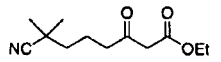
Prepared in the same manner as in example **268c**.



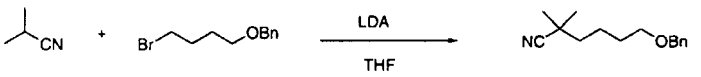
279c 279a

Prepared in the same manner as in example **262a**.

Preparative example 288a

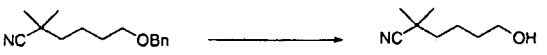


288a



288b

Lithium diisopropylamide (2.0 M solution in THF/heptane/ethyl benzene, 43.4 mL, 86.82 mmol) was taken in THF (30 mL) and cooled to – 78 °C. Isobutyronitrile (6 g, 86.82 mmol) in THF (10 mL) was added dropwise and the reaction was stirred at – 78 °C for 1 h and 0 °C for 2 h. Benzyl 4-bromobutyl ether (21.1 g, 86.82 mmol) in THF (10 mL) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl and extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in *vacuo*. The crude compound obtained was purified by biotage (5% EtOAc/hexanes) to yield compound **288b**.



288b 288c

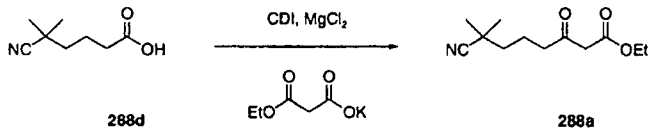
Compound **288b** was taken up in CH_2Cl_2 (25 mL) in a 100 mL round bottomed flask equipped with a stirring bar and nitrogen balloon and cooled to – 78 °C. Boron trichloride (1.0 M solution in hexanes, 43.2 mL, 43.2 mmol) was added dropwise and the reaction was allowed to gradually warm to 0 °C. After 1 h the reaction was quenched by the addition of sat. $NaHCO_3$, extracted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo* to yield the

crude compound which was purified by filtering through a short pad of silica gel eluting with 50% EtOAc/hexanes to yield compound **288c**.



288c 288d

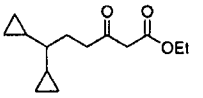
Compound **288c** (3.0 g, 21.2 mmol) was taken in acetone (20 mL) and cooled to 0 °C. Jones reagent was added dropwise until there was no change in color to green upon addition of the reagent. The excess reagent was quenched by the addition of *i*-PrOH, and water (20 mL) extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo* to yield compound **288d** which was used without further purification.



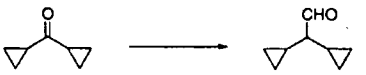
288d 288a

Prepared in the same manner as in example **262a**.

Preparative example 293a



293a



293b

Lithium bis(trimethylsilyl)amide (1.0 M solution in THF, 108.9 mL, 108.9 mmol) was taken up in 100 mL THF in a 500 mL round bottomed flask equipped with a stirring bar and nitrogen balloon. The solution was cooled to 0 °C and (methoxymethyl)triphenylphosphonium chloride (37.3 g, 108.9 mmol) was added portionwise and the dark red solution was stirred at 0 °C for 45 min. Dicyclopropyl ketone (10 g, 90.78 mmol) in THF (10 mL) was added dropwise and the reaction was stirred at 0 °C for 3 h after which the reaction mixture was poured into hexane. The mixture was filtered through silica gel eluting with hexane. Solvent removal gave the crude enol ether.

The crude enol ether was taken up in THF (100 mL) and 10 % HCl (100 mL) was added. The reaction was refluxed overnight. Upon cooling, diluted with water and

extracted with Et_2O (2 x 50 mL), washed with brine, dried over $MgSO_4$, concentrated in *vacuo*. The crude mixture **293b** was used as such without further purification.



293b 293c

Sodium hydride (6.44 g, 161 mmol) was taken in THF (30 mL) in a 250 mL round bottomed flask equipped with a magnetic stirring bar and nitrogen balloon. The mixture was cooled to 0 °C. Triethylphosphonoacetate (36.1 g, 161 mmol) in 20 mL THF was added dropwise and the mixture was stirred at room temperature for 1 h after which it was cooled back to 0 °C and compound **293b** (10 g, 80.5 mmol) in 20 mL THF was added dropwise and the reaction was allowed to stir at room temperature for 2 h. The reaction was quenched by the addition of water and was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in *vacuo*. The crude was purified by biotage (2% EtOAc/haxanes) to yield compound **293c**.



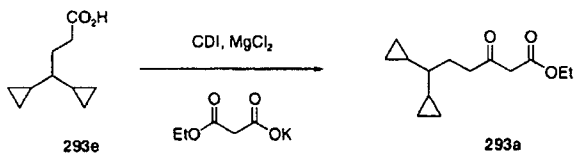
293c 293d

Compound **293c** was taken up in 100 mL EtOH in a 200 mL round bottomed flask. To the solution was added Pd/C (10 wt%, 7.0 g, 5.7 mmol) and the mixture was hydrogenated using a hydrogen balloon under ambient temperature for 12 h. The mixture was filtered through celite and eluted with EtOH which upon solvent removal gave crude compound **293d**.



293d 293e

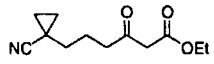
Prepared in the same manner as in example **268c**.



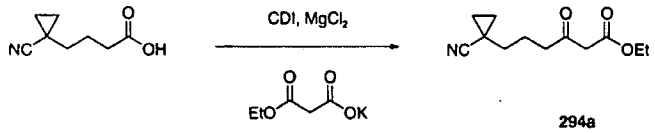
293e 293a

Prepared in the same manner as in example **262a**.

Preparative example 294a



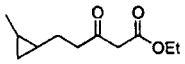
294a



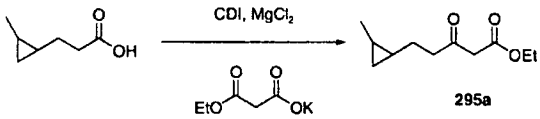
294a

Prepared in the same manner as in example **288a**.

Preparative example 295a



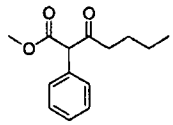
295a



295a

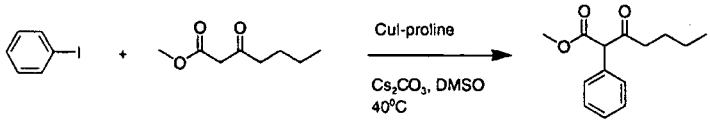
Prepared in the same manner as in example **262a**.

Preparative example 292a



292a

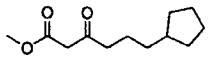
The starting material for the preparation of example **292** is as follows.



292a

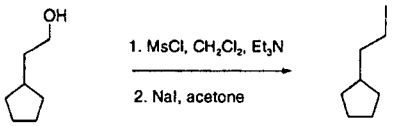
Into the solution of iodobenzene (10.2 g, 50 mmol) in anhydrous DMSO (150 mL) and 3-oxoenanthic acid methyl ester (15.8 g, 100 mmol) was added copper(I) iodide (1.9 g, 10 mmol), L-proline (2.3g, 20 mmol), and cesium carbonate (65.2g, 200 mmol). After stirred under N_2 at 40 ^{0}C for 18 hours, the reaction mixture was dissolved into ethyl acetate (250 mL), washed with water (4 x 150 ml). The organic solution was dried with sodium sulfate, and concentrated under reduced pressure. The resulting crude product was purified using silica gel flash column chromatography eluting with ethyl acetate/hexanes (v/v = 5/95) to give compound **292a** (4.5 g, 38%).

Preparative example 297a



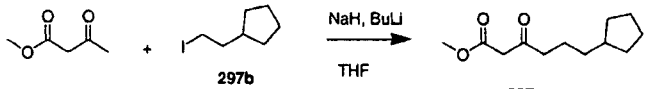
297a

The starting material for the preparation of example **297** is as follows.



297b

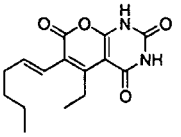
To a solution of 2-cyclopentyl ethanol (11.4 g, 100 mmol), anhydrous CH_2Cl_2 (80 mL), and triethyl amine(12 g, 120 mmol), which cooled to 0 ^{0}C, was added via syringe MsCl (13.7 g, 120 mmol). After stirring under N_2 at 0 ^{0}C for 1 hour then at room temperature for 18 hours, the reaction mixture was washed with water (2 x 100 mL), dried with sodium sulfate, and concentrated under reduced pressure to give a clear oil (19g, 100%). The oil was dissolved into anhydrous CH_2Cl_2 (250 mL) and mixed with NaI (20g, 200 mmol). After stirring at room temperature for 18 hours, the reaction mixture was filtered from solid. The resulting filtrate was concentrated under reduced pressure to give a brown paste. The paste was dissolved into diethyl ether (300 mL), washed with water (2 x 150 mL), dried with sodium sulfate, concentrated under reduced pressure to give compound **297b** (20g, 89%).



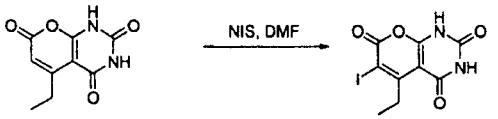
297b 297a

To a solution of methyl acetoacetate (5.8 g, 50 mmol) and anhydrous THF (100 mL), which cooled to 0 ^{0}C, was added NaH (60%, 2.4g, 60 mmol). After stirring under N_2 at 0 ^{0}C for 0.5 hour, n-BuLi (2.5 M in hexanes, 20 mL) was added *via* syringe. After stirring at 0 ^{0}C for 0.5 hour, the reaction mixtures was cooled to -25 ^{0}C, the compound **297b** was added *via* syringe. The reaction mixture was stirred at 0 ^{0}C for 0.5 hour, then room temperature for 18 hours. The reaction mixture was quenched with saturated ammonium chloride (200 mL) and extracted with ethyl acetate (2 x 200 mL)washed with water (2 x 100 mL). The organic solution was dried with sodium sulfate, and concentrated under reduced pressure to give a brown oil, which purified using silica gel flash column chromatography eluting with ethyl acetate/hexanes (v/v = 7/93) to give compound **297a** (3.2 g, 32%).

Preparative example 214

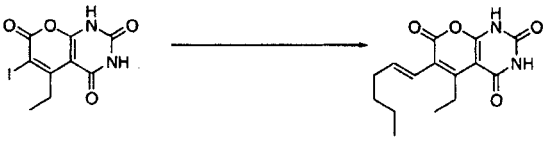


214



214a 214b

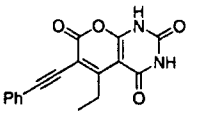
Compound **214a** (10 g, 48.04 mmol) was taken in DMF (50 mL) in a round bottomed flask equipped with a magnetic stirring bar. *N*-Iodosuccinimide (22 g, 97.79 mmol) was added portionwise and the reaction mixture was heated to 50°C overnight. After cooling to ambient temperature, H_2O (100 mL) was added. The product was filtered, washed with water followed by ether to give a white powdery mixture (> 95% yield). The product **214b** was used as such for the next step without any further purification.



214b 214

Compound **214b** (0.1 g, 0.3 mmol) was taken in C_6H_6 (1 mL) in a 10 mL round bottomed flask. $Pd(OAc)_2$ (0.004 g, 0.018 mmol), PPh_3 (0.014 g, 0.054 mmol), and Na_2CO_3 (0.5 mL, 2M solution) was added and the reaction mixture was allowed to stir at room temperature for 30 min. *trans*-1-Hexen-1-ylboronic acid (0.042 g, 0.33 mmol) in EtOH (0.5 mL) was added and the reaction mixture was allowed to reflux (80 °C) overnight. After cooling, the mixture was diluted with H_2O (2 mL), extracted with EtOAc (2 x 10 mL), dried over $MgSO_4$, concentrated and dried to yield the crude compound **214**. Purification by preparative TLC (10% MeOH/DCM) to yield compound **214**.

Preparative example 219



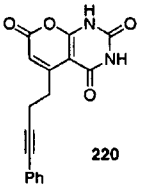
219



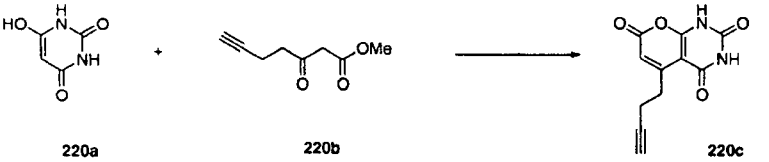
214b 219

Compound **214b** (0.1 g, 0.3 mmol) was taken in DMF (3.0 mL) in a 10 mL round bottomed flask. $PdCl_2(PPh_3)_2$ (0.011 g, 0.015 mmol), phenylacetylene (0.061 g, 0.6 mmol), CuI (0.006 g, 0.03 mmol), and triethylamine (0.091 g, 0.9 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (5 mL), neutralized with 1N HCl, and extracted with EtOAc (2 x 10 mL), dried over $MgSO_4$, concentrated and dried to yield crude **219**. The crude product was taken in ether and filtered to yield pure compound **219**.

Preparative example 220

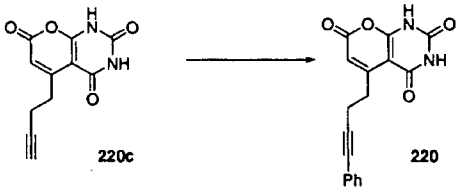


220



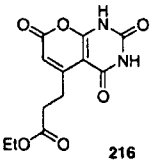
220a 220b 220c

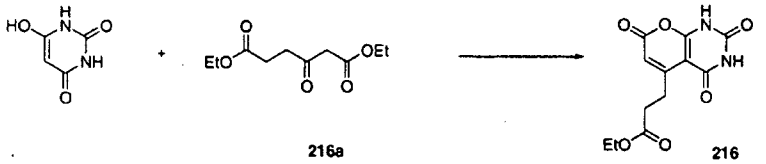
Barbituric acid **220a** (1.0 g, 7.81 mmol) and keto ester **220b** (1.45 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the acetic acid was removed in *vacuo* and hot water was added to remove excess barbituric acid. The procedure was repeated a few times until no starting material was left. It was followed by washing with ether. The product **220c** was dried and needed no further purification.



Compound **220c** (0.1 g, 0.431 mmol) was taken in DMF (1 mL) in a 10 mL round bottomed flask. Iodobenzene (0.053 g, 0.258 mmol), $PdCl_2(PPh_3)_2$ (0.003 g, 0.0043 mmol), CuI (0.002 g, 0.0086 mmol), and Et_2NH (0.157 g, 2.15 mmol) was added and the reaction mixture was stirred at room temperature overnight. The reaction was diluted with EtOAc (2 mL), neutralized with 1N HCl and extracted with EtOAc (2 x 10 mL). It was dried over $MgSO_4$, concentrated in *vacuo*. The crude product was purified by preparative TLC (20 % MeOH/DCM) to yield compound **220**.

Preparative example 216

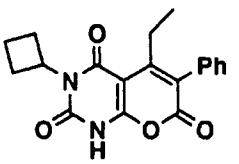




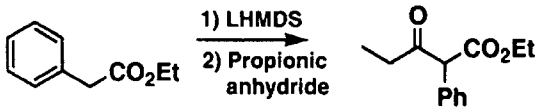
Barbituric acid (1.0 g, 7.81 mmol) and Diethyl β-ketoadipate **216a** (2.03 g, 9.4 mmol) was taken in glacial acetic acid (8 mL) and the reaction mixture was heated to reflux overnight. After cooling to room temperature, the acetic acid was removed in *vacuo* and hot water was added to remove excess barbituric acid. The procedure was repeated a few times until no starting material was left. It was followed by washing with ether. The product **216** was dried and needed no further purification.

The starting material for the preparation of example **203** is as follows.

Preparative example 203



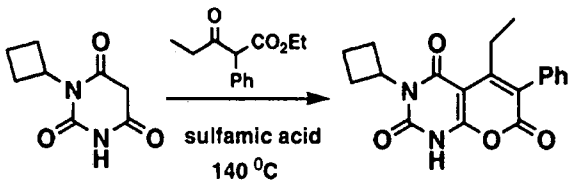
Step A:



203a

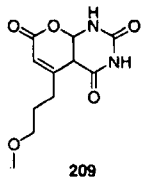
To a solution of ethylphenylacetate (8.2g, 0.05 mol) in THF at -78 ^{0}C was added LHMDS (1M in THF, 100 ml, 0.10 mol) and stirred for 20 min. Propionic anhydride (6.5 ml, 0.05 mol) was added rapidly. The mixture was allowed to warm up to 0 ^{0}C and stirred for 30 min. It was quenched with NH_4Cl (aq.) and extracted with EtOAc. Usual work up afforded the crude material which was chromatographed on silica gel to obtain product.

Step B:



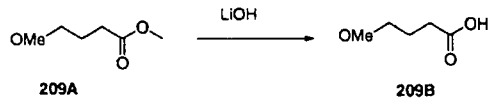
Compound **203** was obtained by normal condensation procedure with cyclobutylbarbituric acid.

Preparative example 209



209

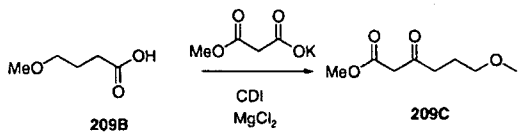
Step A:



209A 209B

Starting material **209a** (9.9 g, 75 mmol) was dissolved in THF (100 mL) and water (25 mL). LiOH (3.4 g, 80.9 mmol), the resulting mixture was stirred at room temperature overnight. 1 N HCl (100 mL) was added and extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$) to give compound **209b** (8.8 g, 93%).

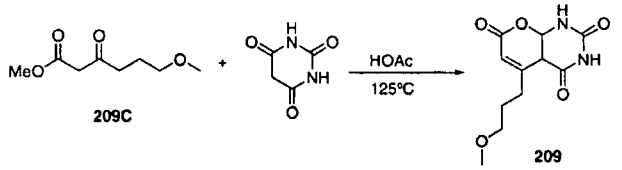
Step B:



209B 209C

Compound 209c (1.9 g, 16.1 mmol) was dissolved in THF (50 mL), CDI (12.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. $MgCl_2$ (1.5 g, 16.1 mmol) and $KOCOCH_2CO_2Me$ (3.8 g, 24.2 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was separated by silica gel chromatography, with Biotage 40S+ column, eluted with EtOAc: hexanes, 1:10, to give 2.1 g (74%) yellow liquid as **Compound 209d**.

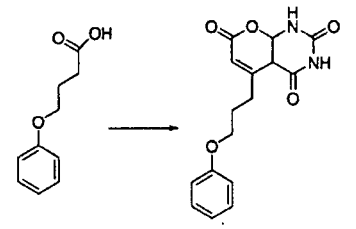
Step B:



209C 209

Compound 209c (1.13 g, 6.49 mmol) and barbituric acid (0.5 g, 3.90 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125°C overnight. The mixture was cooled to room temperature, HOAc was removed and the residue was taken up in MeOH, and filtered. The volume of the mother liquid was reduced until solid started to come out, the beige solid was collected to give **Compound 209** (153 mg, 10%). Electrospray MS [M+1]: 253.1.

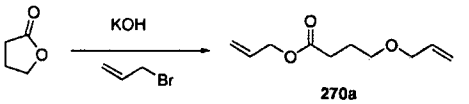
Compound 208 was prepared in a similar fashion as in **Compound 209**, from the commercially available **Compound 208a**.



compound 208A compound 208

Preparative example 270

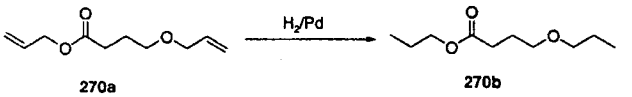
Step A:



270a

Starting lactone (10 g, 116 mmol) was mixed with allylbromide (30 mL, 346 mmol), toluene (75 mL), and KOH (19.5 g, 348 mmol). The mixture was heated 110°C overnight. The mixture was cooled to room temperature; water (100 mL) was added. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to give a yellow liquid as the desired **Compound 270a** (11.8 g, 55.2%).

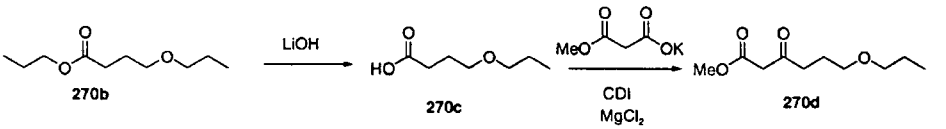
Step B:



270a 270b

Compound 270a (3.0 g, 16.3 mmol) was dissolve in EtOH (20 mL), 10 % Pd/C (300 mg) was added. The slurry was stirred under H_2 overnight. The mixture was filtered through Celite, and the filtrate was concentrated to give a yellow liquid as the desired **Compound 270b** (2.5 g, 81%).

Step C:

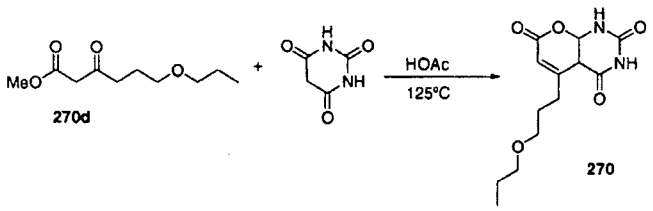


270b 270c 270d

Compound 270b (3.0 g, 16.3 mmol) was dissolve in THF (20 mL)-H_2O (7 mL), LiOH (1.66 g, 39.5 mmol) was added. The resulting mixture was stirred at room temperature overnight. 1 N HCl (75 mL) was added, and extracted with Et_2O. The organic extracts were combined, dried ($MgSO_4$) filtered and concentrated. The

residue was dissolved in THF (50 mL), CDI (12.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. MgCl2 (1.3 g, 13.6 mmol) and $KOCOCH_2CO_2Me$ (2.9 g, 18.5 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was separated by silica gel chromatography, with Biotage 40S+ column, eluted with EtOAc: hexanes, 1:10, to give 1.5 g (46%) yellow liquid as **Compound 270d**.

Step D:



Compound 270d (448 mg, 2.22 mmol) and barbituric acid (340 mg, 2.65 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125 ^{0}C overnight. The mixture was cooled to room temperature, HOAc was removed and the residue was taken up in MeOH, and filtered. The mother liquid was concentrated and separated by preparative TLC, eluted with 1:10:10, HOAc:DCM:EtOAc, to give desired **Compound 270** (72 mg, 11.4%) as a white solid. Electrospray MS [M+1]: 281.2.

Preparative example 271

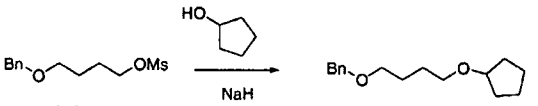
Step A:



271a

Starting alcohol (5.2 g, 28.0 mmol) was dissolved in DCM (100 mL), triethylamine (6 mL, 42.7 mmol) and MsCl (2.6 mL, 33.6 mmol) was added. The resulting solution was stirred at room temperature for 1 h. The mixture was diluted with EtOAc and washed with 1 N HCl (50 mL x 2). The aqueous layers were combined, extracted with EtOAc. The organic layers were combined, washed with brine, dried (MgSO4), filtered, and concentrated to give **Compound 271a** (7.26 g, 100%).

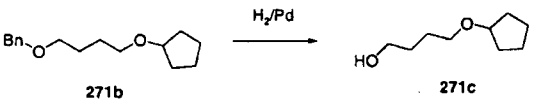
Step B:



271a 271b

Cyclopentanol (3.8 mL, 42 mmol) was dissolved in THF (50 mL) under nitrogen. NaH (0.85 g, 95% oil dispersion, 33.7 mmol) was added. The resulting slurry was stirred at room temperature for 1 h. A solution of mesylate **271a** (7.26 g, 28 mmol) in DMF (30 mL) was added via syringe. The resulting mixture was heated at 85 ^{0}C overnight. The mixture was cooled to room temperature, and diluted with EtOAc, and washed with water (50 mL x 3). The aqueous layers were combined and extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified over silica gel column, eluted with EtOAc-hexanes (1:10) to give 4.95 g (71%) of **Compound 271b** as an amber liquid.

Step B:

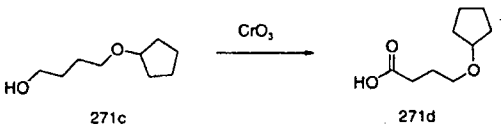


271b 271c

Compound 271b (4.95 g, 20 mmol) was dissolved in EtOH (100 mL), 10% Pd/C (0.55 g) was added and stirred under 1 atm of hydrogen balloon overnight. Filtered through Celite, the filtrate was concentrated *in vacuo*. The residue was

purified over silica gel column, eluted with EtOAc-hexanes (1:3) to give 3.1 g (98%) of **Compound 271c** as a colorless liquid.

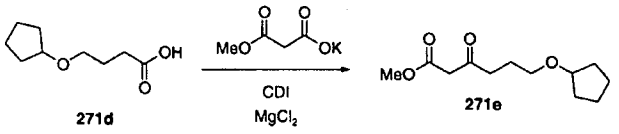
Step C:



271c 271d

CrO_3 was mixed with 4.7 mL of conc. H_2SO_4. The mixture was diluted with water to 36 mL. **Compound 271c** was dissolved in acetone (30 mL), and Jones reagent was added. The mixture was stirred at room temperature for 1 h, diluted with water and extracted with DCM. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to give 1.99 g (71%).

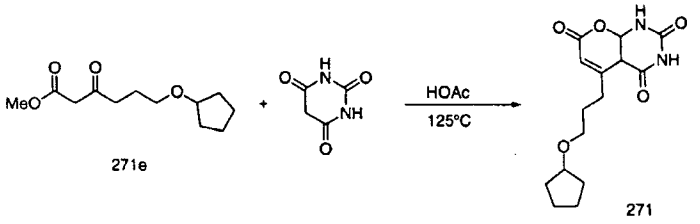
Step D:



271d 271e

Compound 271d (2.40 g, 14.0 mmol) dissolved in THF (50 mL), CDI (2.48 g, 15.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 h. $MgCl_2$ (1.5 g, 15.3 mmol) and $KOCOCH_2CO_2Me$ (3.3 g, 20.9 mmol) were added, the resulting mixture was stirred at room temperature overnight. EtOAc (100 mL), water (50 mL) were added. The aqueous layer was separated and extracted with EtOAc. The aqueous layer was extracted with EtOAc. The organic extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was filtered through a pad of silica gel, eluted with EtOAc: hexanes, 1:3, to give 2.2 g (69%) yellow liquid as **Compound 270e.**

Step D:



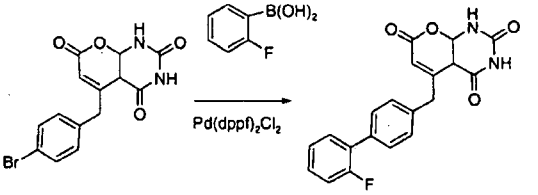
271e 271

Compound 271e (448 mg, 2.22 mmol) and barbituric acid (340 mg, 2.65 mmol) was mixed with HOAc (2 mL) in a sealed tube, and heated in an oil bath at 125°C overnight. The mixture was cooled to room temperature, HOAc was removed

and the residue was taken up in MeOH, and filtered. The mother liquid was concentrated and separated by preparative TLC, eluted with 1:10:10, HOAc:DCM:EtOAc, to give desired **Compound 271** (55 mg, 4%) as a white solid. Electrospray MS [M+1]: 307.2.

Compound 273, Compound 287 and **Compound 290** are prepared in a similar fashion as **Compound 271** from the corresponding alcohols.

Preparative example 205

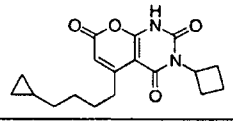


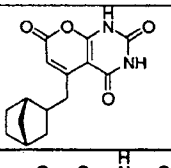
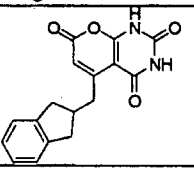
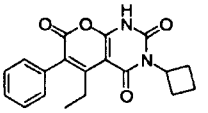
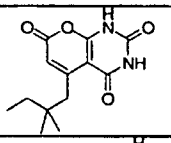
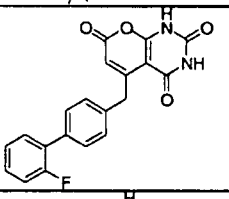
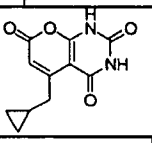
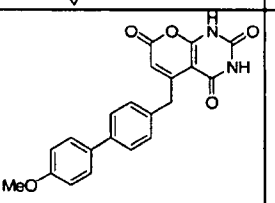
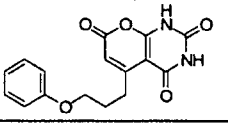
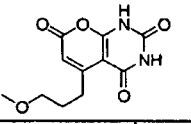
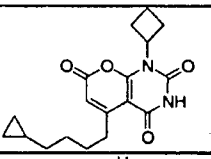
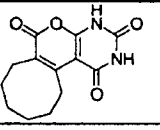
205a 205

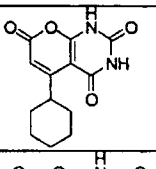
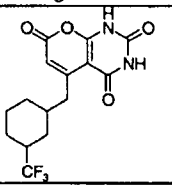
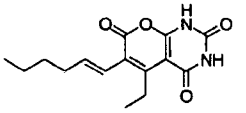
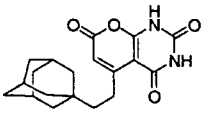
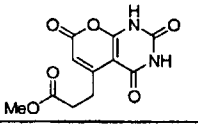
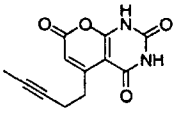
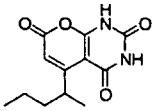
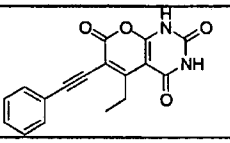
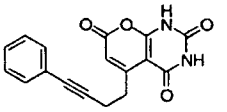
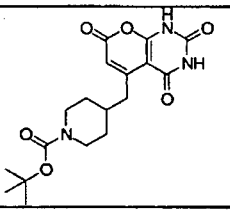
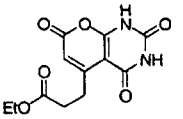
Compound 205a (50 mg, 0.14 mmol) was dissolved in DMF (2 mL) and H_2O (2 mL), $Pd(dppf)_2Cl_2$ and K_2CO_3 were added. The resulting mixture was heated at 85 ^{0}C under nitrogen for 5 h. The mixture was cooled to room temperature and filtered through Celite. The filtrated was concentrated. The residue was dissolved in MeOH, and DCM was added until precipitation persisted. The solid was collected as the desired **Compound 205** (21 mg, 40%). Electrospray MS [M+1]: 481.5.

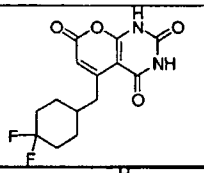
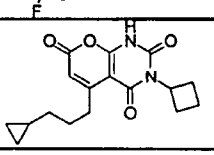
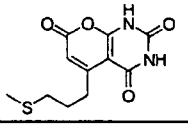
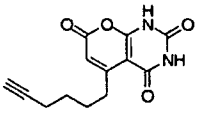
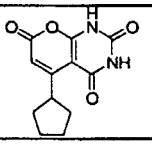
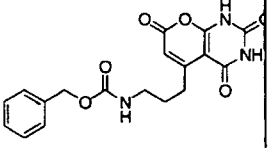
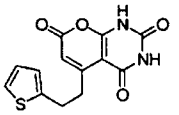
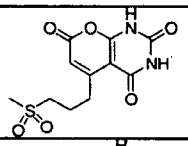
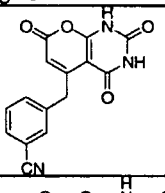
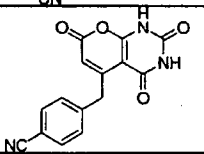
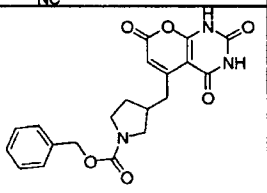
Compound 207 was prepared in a similar fashion as **Compound 205**, using the corresponding boronic acid.

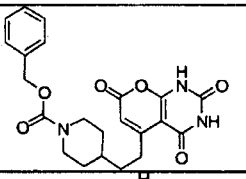
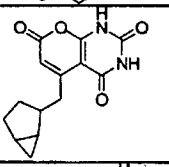
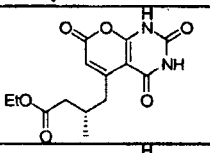
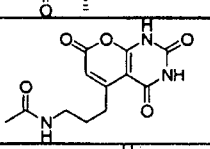
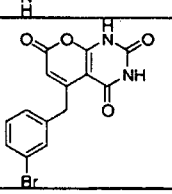
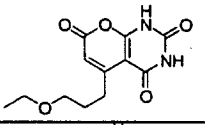
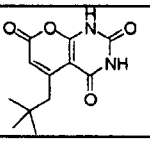
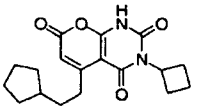
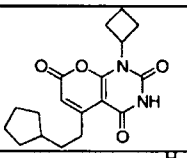
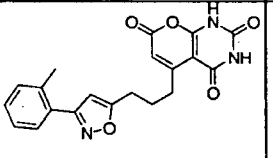
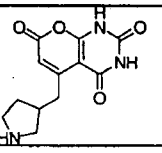
Several compounds of the invention are shown in the Table below as well as in the Tables presented later in this specification. The compounds shown in the table below were made using methods described in the preparative examples presented above herein. The LCMS data is also shown wherever available. The activity (EC_{50}) data is also shown, wherever measured and available, and is designated A, B or C, where A = 0.001 nM to 100 nM; B is >100 <1000 nM and C is >1000 nM.

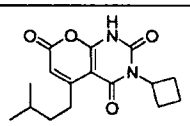
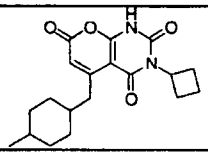
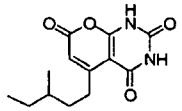
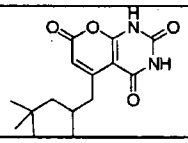
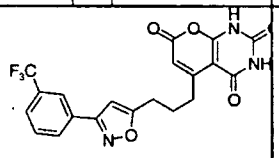
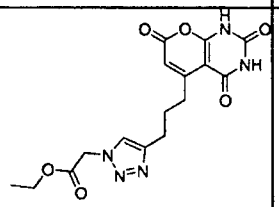
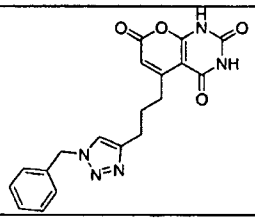
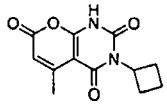
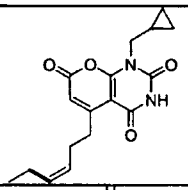
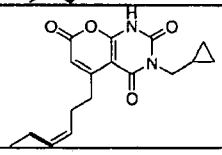
Compound No.	STRUCTURE	NA EC50 camp (nM)	Electrospray LCMS [M+1]+
200		B	331.2

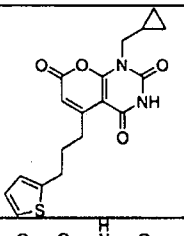
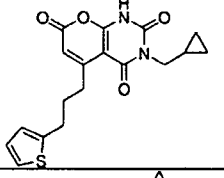
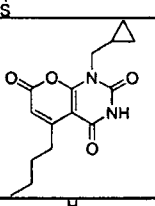
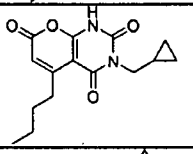
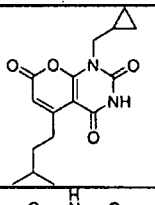
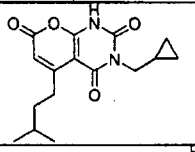
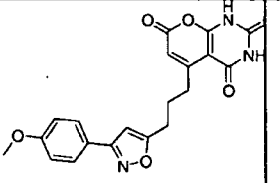
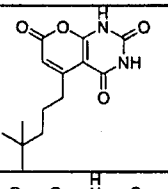
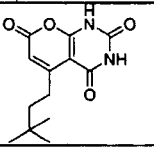
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202		B	311.2
203		C	339.1
204		C	265.1
205		B	365.2
206		B	235.1
207		C	377.2
208		C	316.2
209		B	253.1
210		B	331.2
211		C	263.1

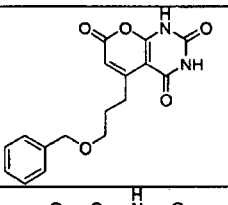
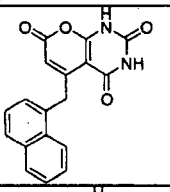
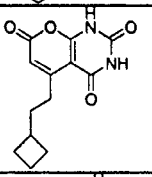
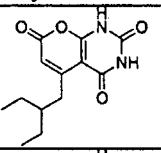
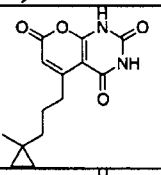
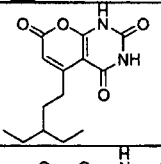
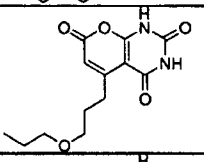
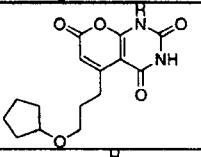
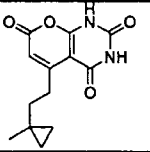
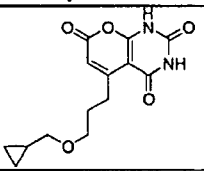
212		B	263.1
213		B	345.2
214		C	291.2
215		C	343.2
216		B	267.1
217		C	247.1
218		B	251.1
219		C	309.2
220		C	309.2
221		C	378.2
222		C	281.2

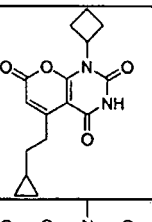
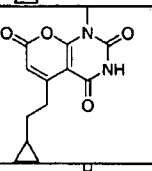
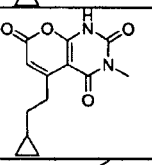
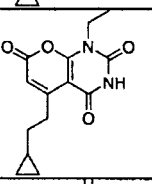
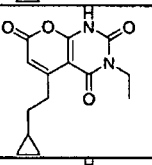
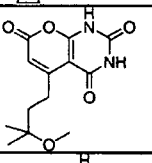
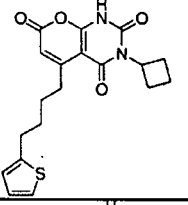
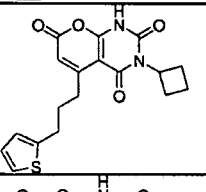
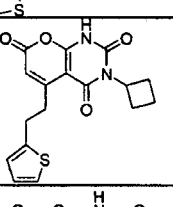
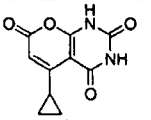
223		A	313
224		A	317.2
225		A	269.1
226		A	261.1
227		C	249.1
228		C	372.2
229		A	391.2
230		B	301.2
231		C	318.2 (M+Na)
232		C	368.2 (M+Na)
233		C	398

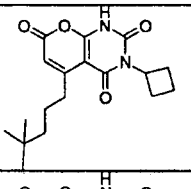
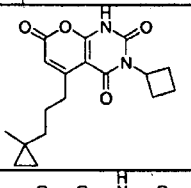
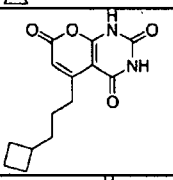
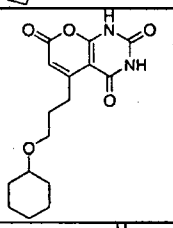
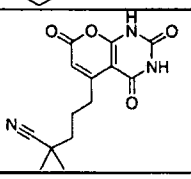
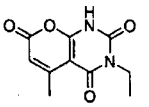
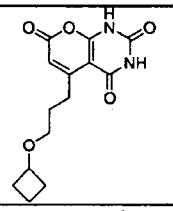
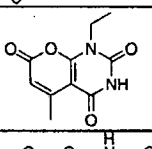
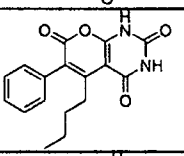
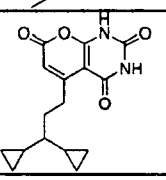
234		C	426
235		A	275.2
236		C	309.2
237		C	280.2
238		B	349.2
239		A	267.1
240		C	251
241		A	331.2
242		C	331.2
243		B	380
244		C	264

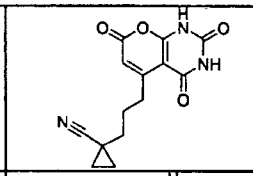
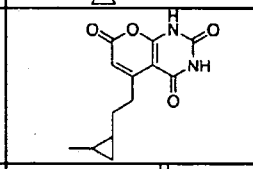
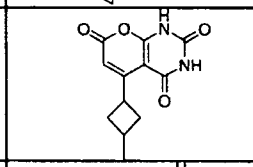
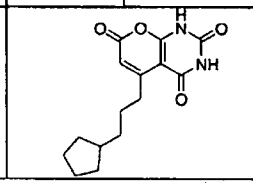
245		A	305.2
246		C	345.2
247		A	265.1
248		C	293.2
249		B	434
250		C	376
251		B	380
252		A	249.1
253		C	317.2
254		C	317.2

255		C	359.2
256		C	359.2
257		C	291.2
258		B	291.2
259		C	305.2
260		C	305.2
261		B	396
262		A	279.2
263		C	265.1

264		C	329.2
265		C	321.2
266		A	263.1
267		C	265.1
268		A	277.2
269		B	279.2
270		A	281.2
271		B	307.2
272		B	263.1
273		B	293.2

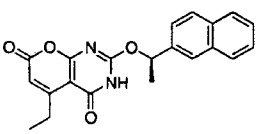
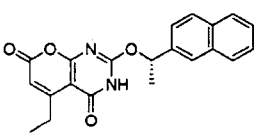
274		B	303.2
275		B	263.1
276		B	263.1
277		C	277.2
278		B	277.2
279		C	281.2
280		C	373.2
281		B	359.2
282		B	345.2
283		B	221.1

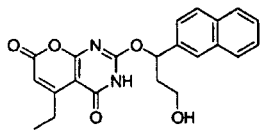
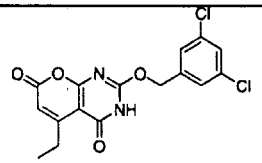
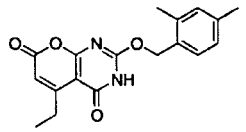
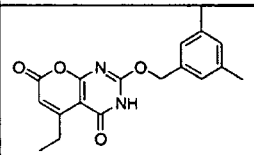
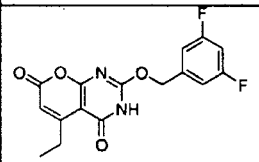
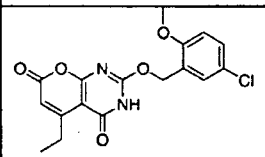
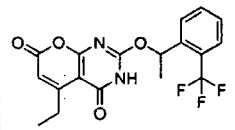
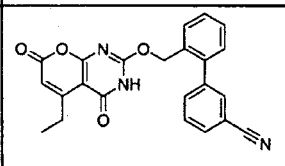
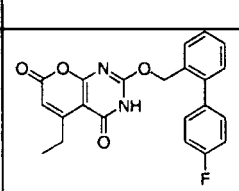
284		B	333.1
285		B	331.2
286		A	277.2
287		C	321.2
288		C	290.2
289		C	223.1
290		B	315.2 (M+Na)
291		C	223.1
292		B	313.2
293		B	303.2

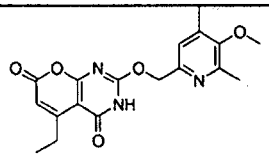
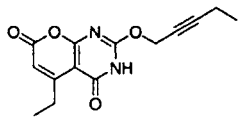
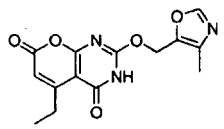
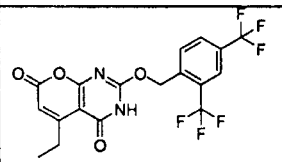
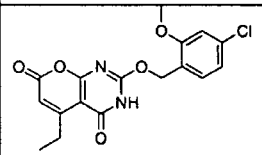
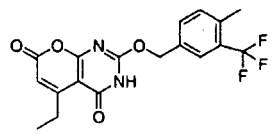
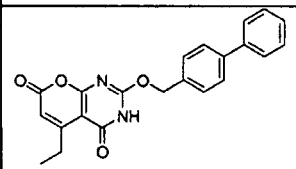
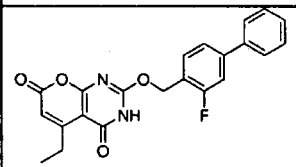
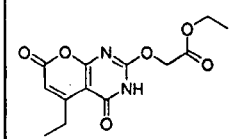
294		B	288.2
295		B	263.1
296		B	249.1
297		A	291.2

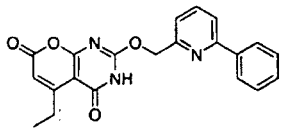
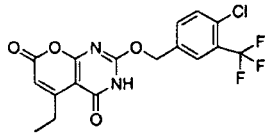
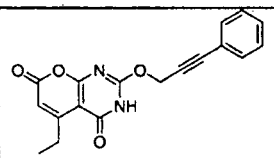
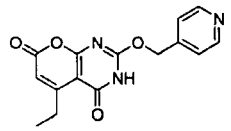
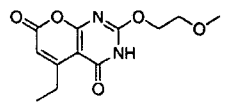
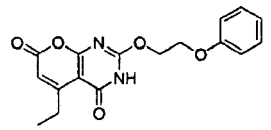
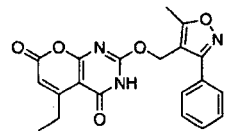
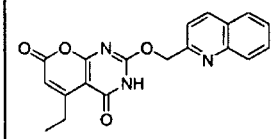
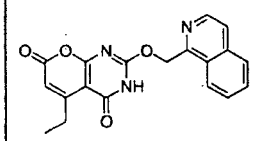
The compounds **500** to **690** were prepared by a procedure similar to that used for the preparation of **Example 49,** using **Example 10,** and the appropriate corresponding alcohol.

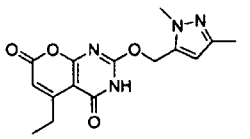
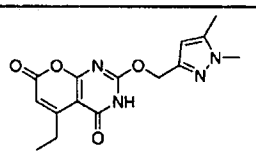
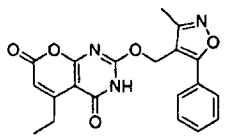
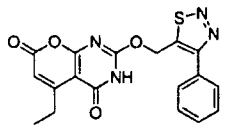
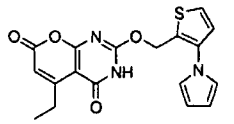
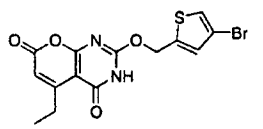
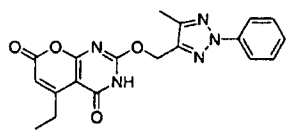
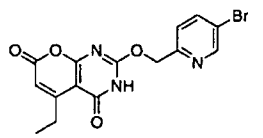
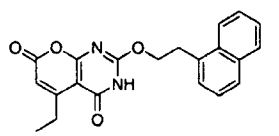
Compounds **691** and **698** were prepared by a procedure similar to Example 49, using appropriate oxyaminocarbamate and sulfoxide which was prepared using Example 10.

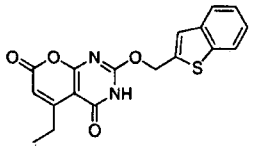
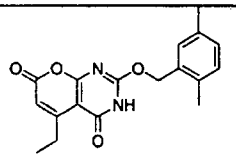
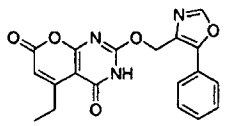
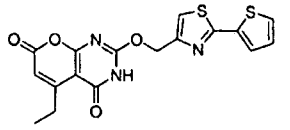
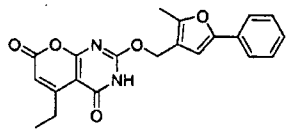
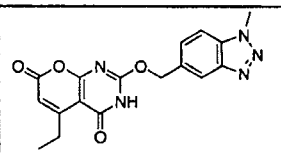
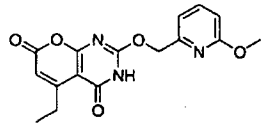
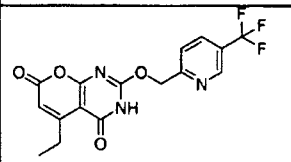
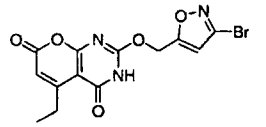
Compound No.	Structure	NA EC50 camp (nM)	Electrospray LCMS [M+1]+
500		B	363.1
501		A	363.1

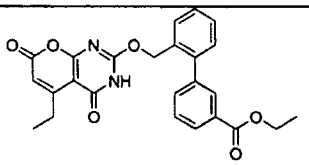
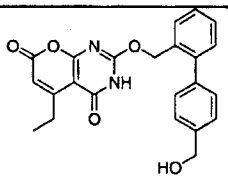
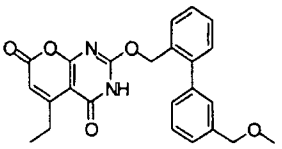
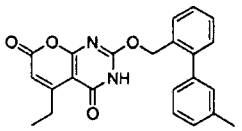
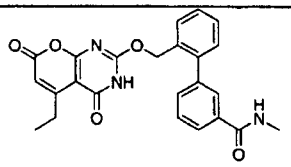
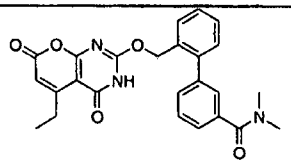
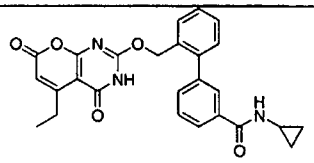
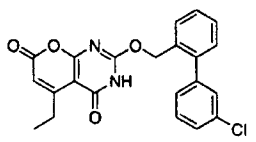
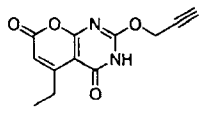
502		B	343
503		B	368
504		B	327
505		B	327
506		C	335
507		A	363
508		C	381.1
509		B	400
510		C	393

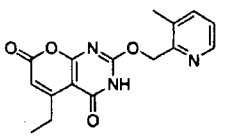
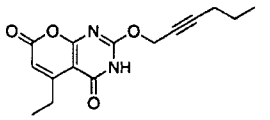
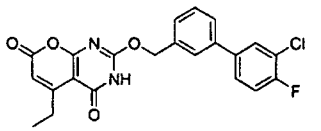
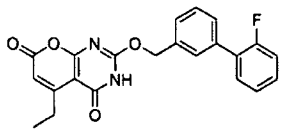
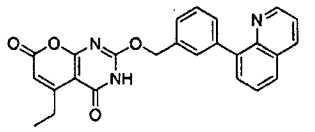
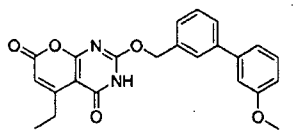
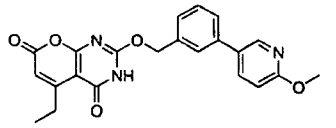
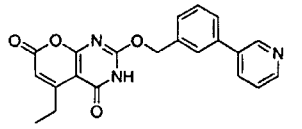
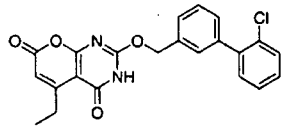
511		C	358.2
512		A	275
513		B	304
514		C	435
515		B	363
516		C	381
517		C	375.2
518		B	393.2
519		C	295.1

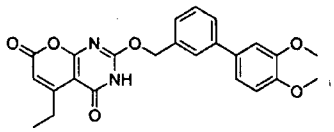
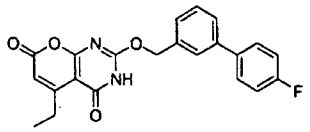
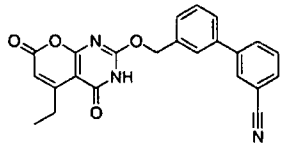
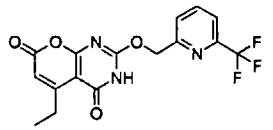
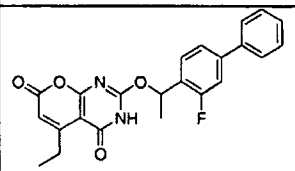
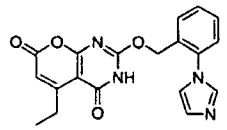
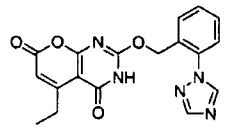
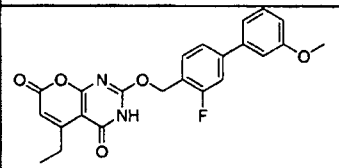
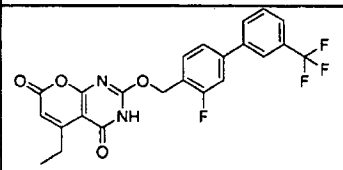
520		C	376.2
521		B	401.2
522		B	323
523		A	300.2
524		B	267.1
525		B	329.2
526		B	380
527		B	350
528		B	350

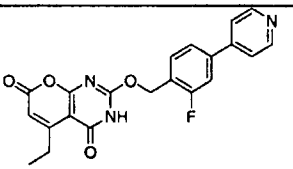
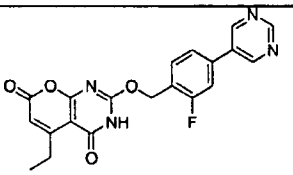
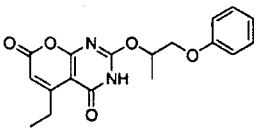
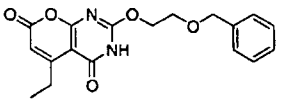
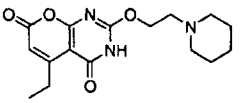
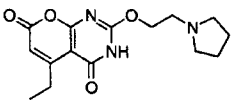
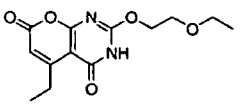
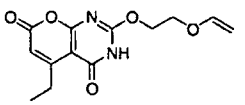
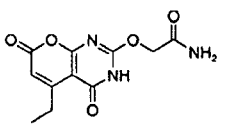
529		B	317
530		B	317
531		B	380
532		B	383
533		C	370
534		B	384
535		B	380
536		B	379
537		C	363

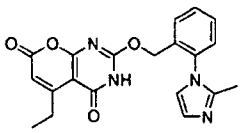
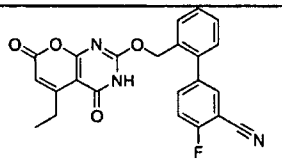
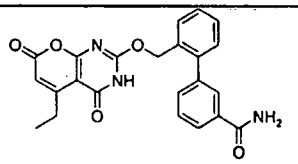
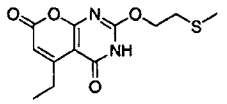
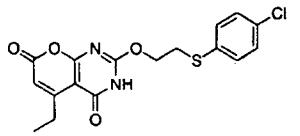
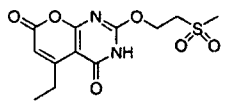
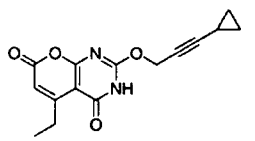
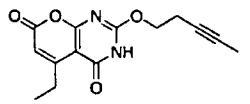
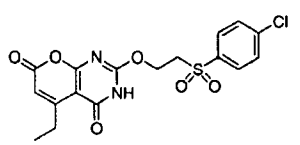
538		B	355
539		B	327
540		B	366
541		B	388
542		C	379
543		B	354
544		B	330.2
545		B	368.2
546		B	369.99

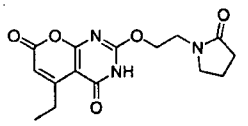
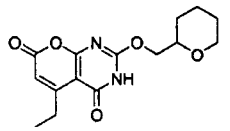
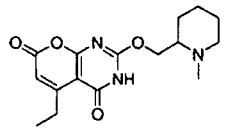
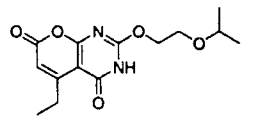
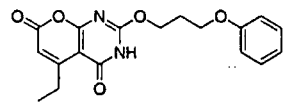
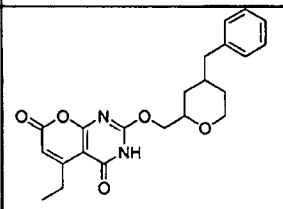
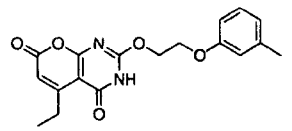
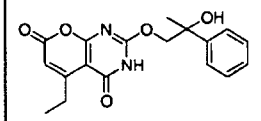
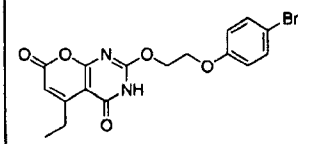
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555		B	247

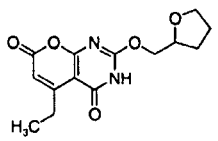
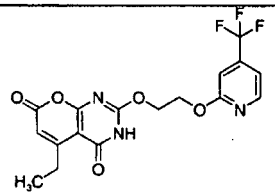
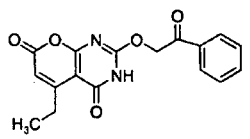
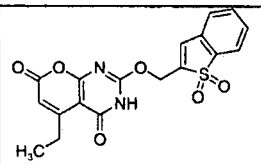
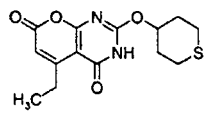
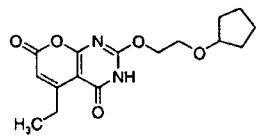
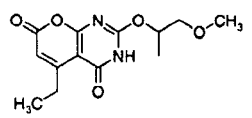
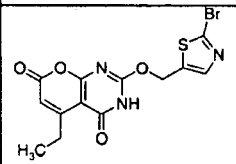
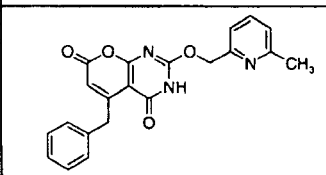
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559		B	393
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562		B	406
563		B	376
564		B	409

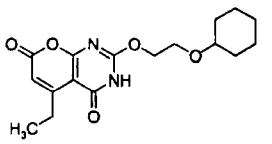
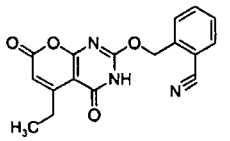
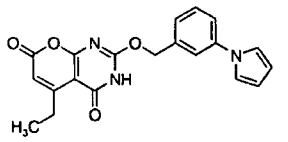
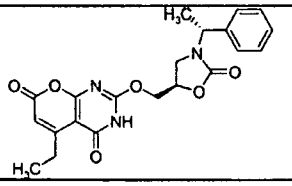
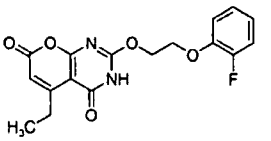
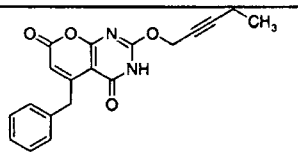
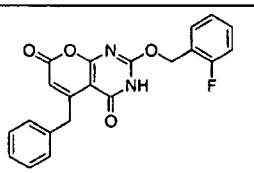
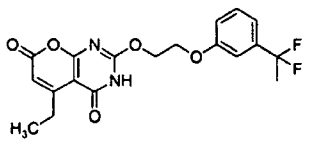
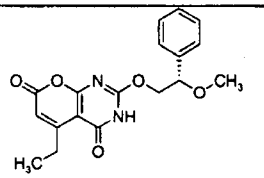
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567		B	400
568		B	368.2
569		A	407.2
570		B	365.1
571		B	366.1
572		B	423.1
573		B	461.1

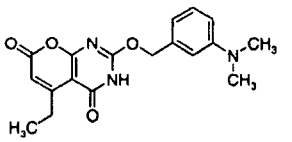
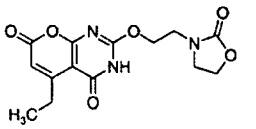
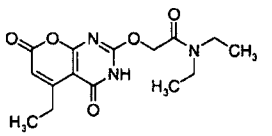
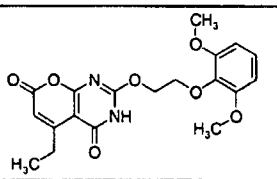
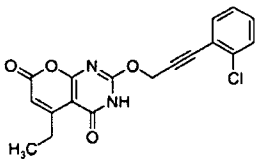
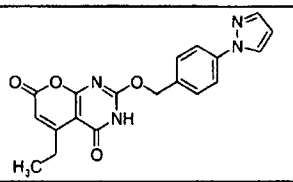
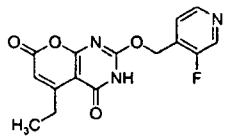
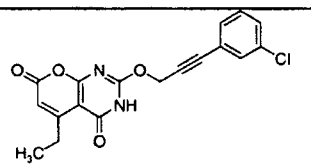
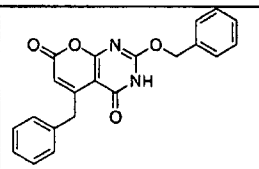
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575		B	395.1
576		C	343.2
577		B	343.2
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579		C	306.2
580		C	281.2
581		C	279.2
582		B	266.1

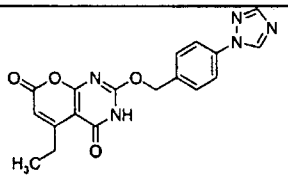
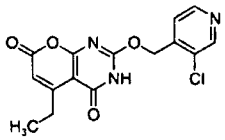
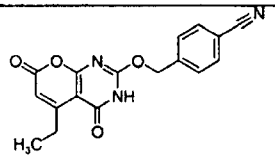
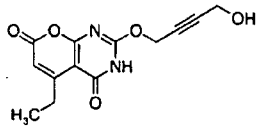
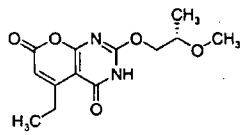
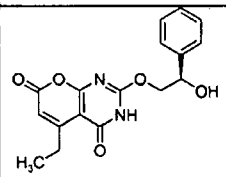
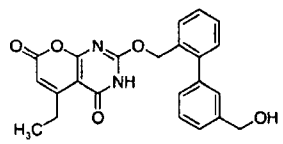
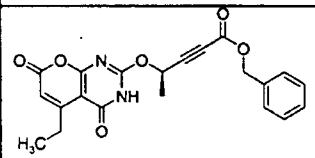
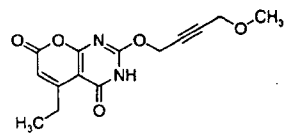
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584		B	418
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587		C	379.1
588		C	315.1
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591		A	411.1

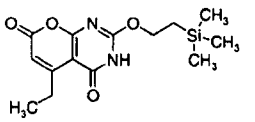
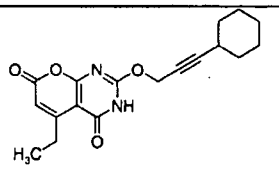
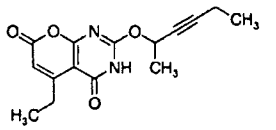
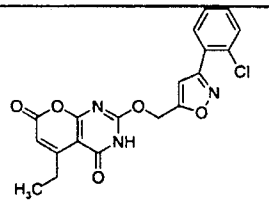
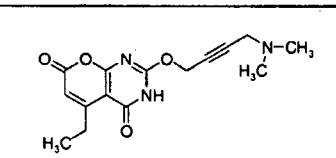
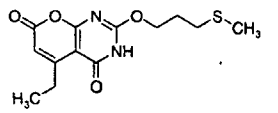
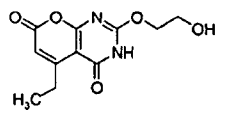
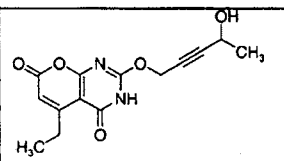
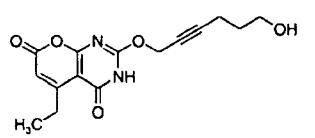
592		B	320.2
593		C	307.2
594		C	320.2
595		B	295.2
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597		C	398.1
598		B	343.1
599		B	343.1
600		C	409.1

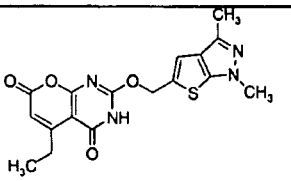
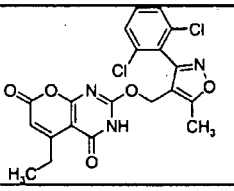
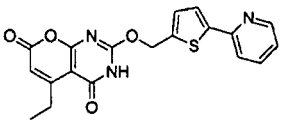
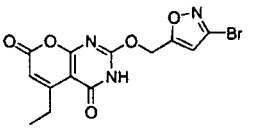
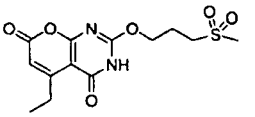
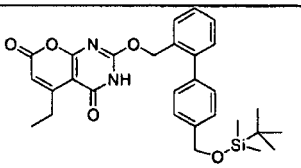
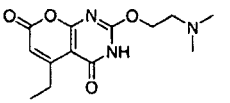
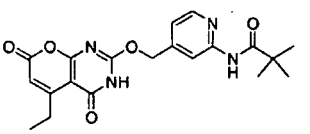
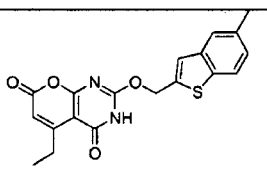
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602		B	398.1
603		B	327.2
604		B	387.2
605		C	309.2
606		C	321
607		B	281.2
608		B	384.2
609		C	376.1

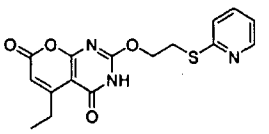
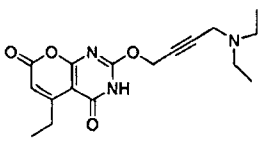
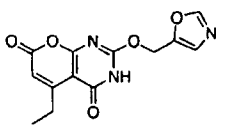
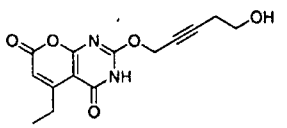
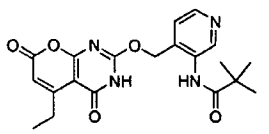
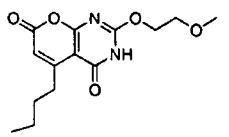
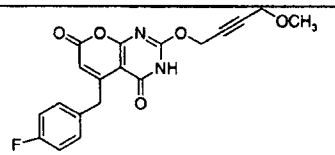
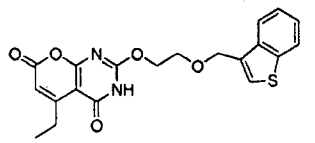
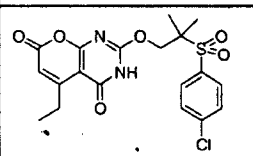
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612		C	364.2
613		B	412.1
614		B	347.1
615		B	337.1
616		B	379.2
617		B	397.2
618		B	343.2

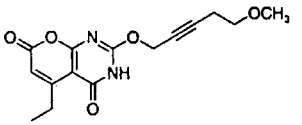
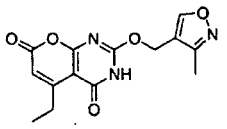
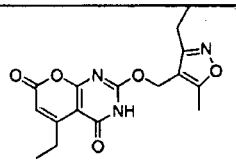
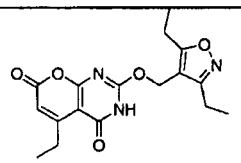
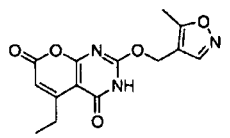
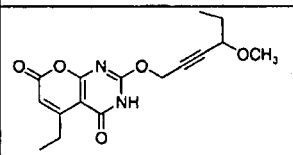
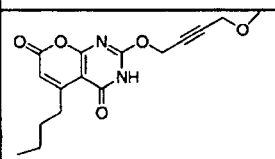
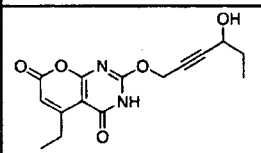
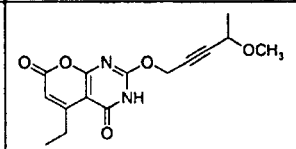
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620		C	322.2
621		B	322.2
622		B	389.2
623		A	357.2
624		B	365.2
625		B	318.2
626		A	358
627		C	361.2

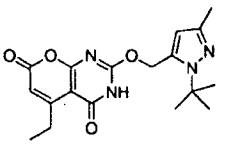
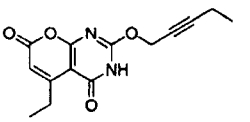
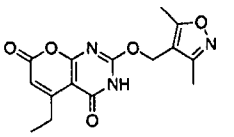
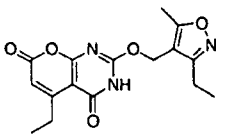
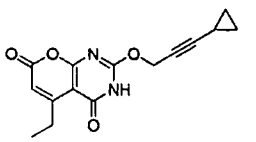
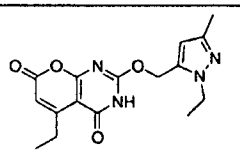
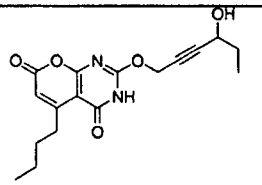
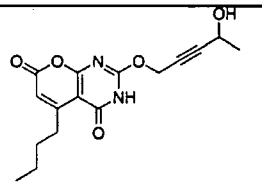
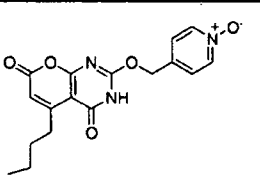
628		C	366.2
629		B	334.2
630		C	324.2
631		B	277
632		B	281.2
633		B	329.2
634		B	405
635		C	395
636		B	291

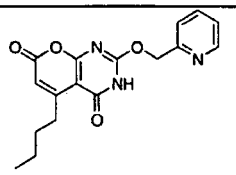
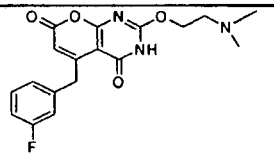
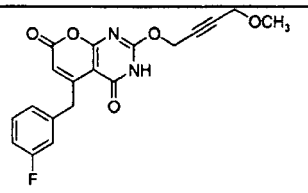
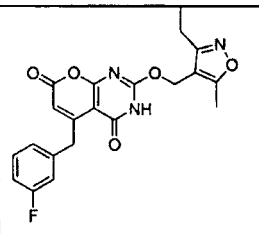
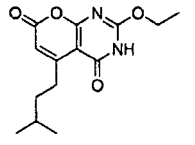
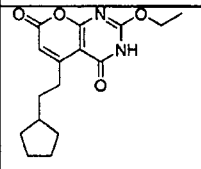
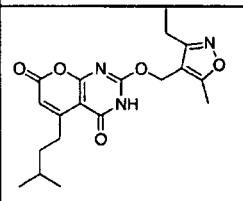
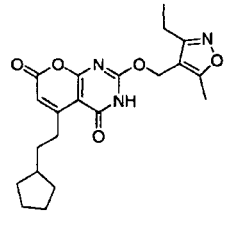
637		B	309.2
638		B	329
639		B	283
640		B	400.1
641		A	304
642		B	297.2
643		B	253.1
644		A	291
645		A	305

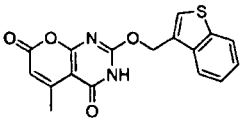
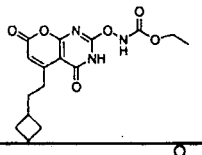
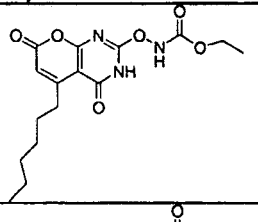
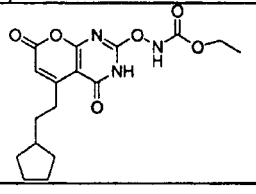
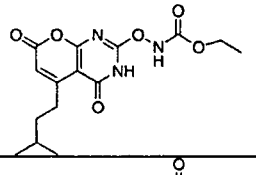
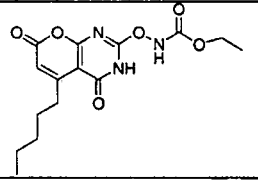
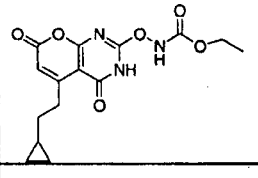
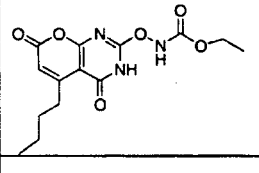
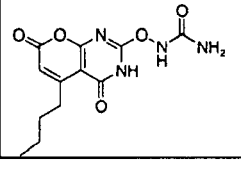
646		C	373.2
647		B	448.2
648		B	382.2
649		B	368
650		B	329.2
651		B	520
652		A	280.1
653		C	399.2
654		A	M+Na 391.2

655		B	346.2
656		C	332
657		C	290
658		B	291
659		C	399.2
660		C	317.2 (M+Na)
661		B	371.2
662		A	399.2
663		C	439.2

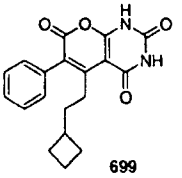
664		B	305
665		C	304
666		A	332
667		B	346
668		C	304
669		B	319
670		A	319.2
671		A	305
672		B	305

673		B	359
674		A	303
675		B	346
676		B	360
677		A	315
678		B	331
679		A	333
680		A	319
681		C	344.2

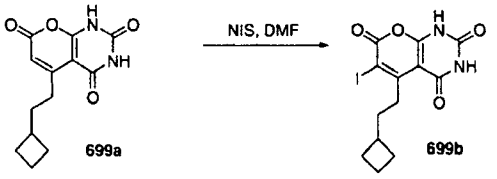
682		C	328.2
683		C	360.2
684		A	371.2
685		B	412.2
686		B	279.2
687		B	305.2
688		B	374.2
689		B	400.2

690		C	241.1
691		A	350.2
692		A	352.2
693		B	364.2
694		C	338.2
695		A	338.2
696		B	336.2
697		--	324.2
698		--	295.2

Preparative example 699



699



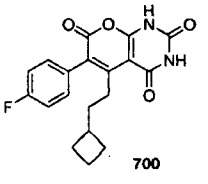
699a 699b

Compound **699a** (0.925 g, 3.53 mmol) was taken in DMF (10 mL) in a round bottomed flask equipped with a magnetic stirring bar. *N*-Iodosuccinimide (1.59 g, 7.05 mmol) was added portionwise and the reaction mixture was heated to 50°C overnight. After cooling to ambient temperature, H_2O (25 mL) was added. The product was filtered, washed with water followed by ether to give a white powdery mixture (> 95% yield). The product **699b** was used as such for the next step without any further purification.



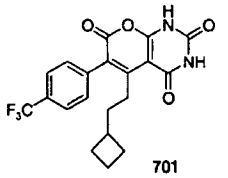
699b 699

Compound **699b** (0.1 g, 0.258 mmol) was taken in 5 mL DME/H_2O (4:1) in a 10 mL round bottomed flask. $PdCl_2(PPh_3)_2$ (0.018 g, 0.0258 mmol), Na_2CO_3 (0.082 g, 0.774 mmol), and phenylboronic acid (0.057 g, 0.464 mmol) was added, and the reaction mixture was allowed to reflux (80 °C) for 6 h. After cooling, the mixture was concentrated and purified by flash chromatography (CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to yield compound **699**.



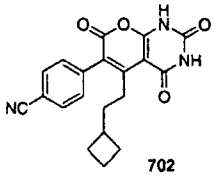
700

Compound **700** was prepared in the same manner as in example **699**.



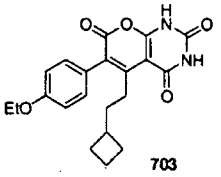
701

Compound **701** was prepared in the same manner as in example **699**.



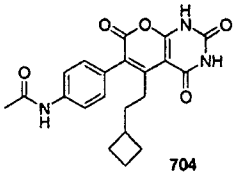
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Compound **702** was prepared in the same manner as in example **699**.



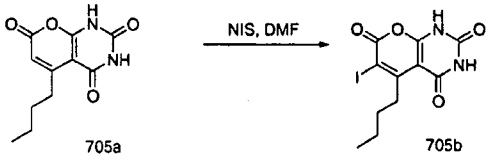
703

Compound **703** was prepared in the same manner as in example **699**.



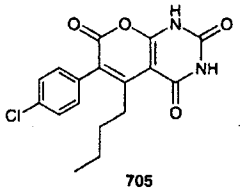
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Compound **704** was prepared in the same manner as in example **699**.



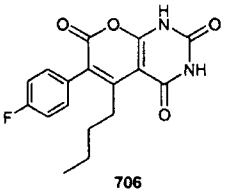
705a 705b

Compound **705b** was prepared in the same manner as in example **699b**.



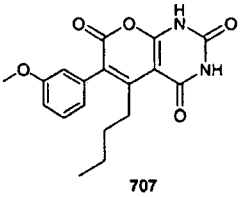
705

Compound **705** was prepared in the same manner of compound **699.**



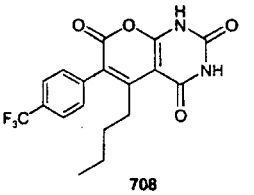
706

The compound **706** was prepared in the same manner of compound **699.**



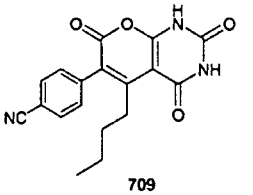
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The compound **707** was prepared in the same manner of compound **699.**



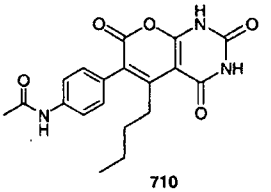
708

The compound **708** was prepared in the same manner of compound **699.**



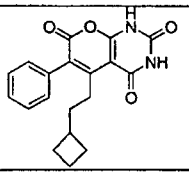
709

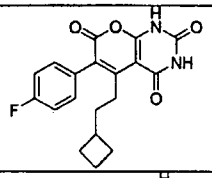
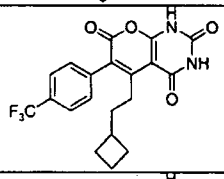
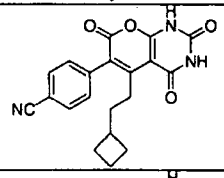
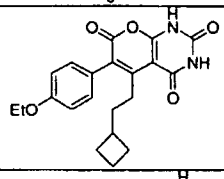
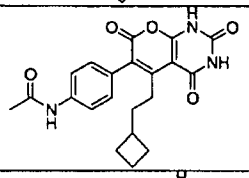
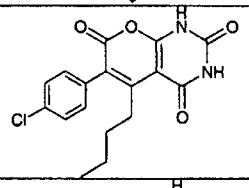
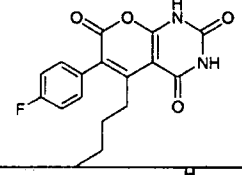
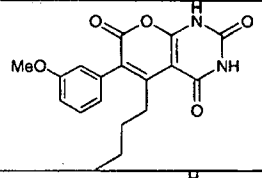
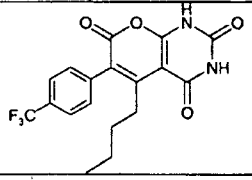
The compound **709** was prepared in the same manner of compound **699.**

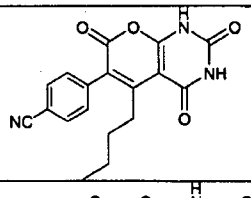
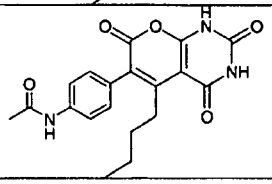


710

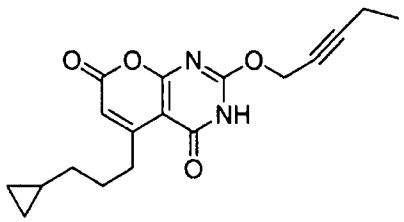
The compound **710** was prepared in the same manner of compound **699.**

Compound No.	STRUCTURE	NA EC_{50} camp (nM)	Electrospray LCMS [M+1]+
699		C	339.2

700		C	357.2
701		C	407.2
702		C	364.2
703		C	383.2
704		C	396.2
705		C	347.2
706		C	331.2
707		C	343.2
708		B	381.2

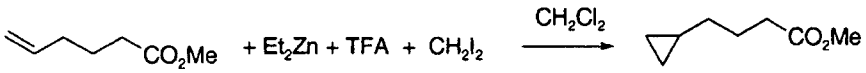
709		C	338.2
710		C	370.2

Preparative example 711



711

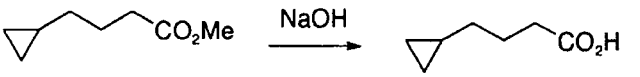
Step A:



711 A

To a solution of diethyl zinc (3.0 eq, 1.0 M in THF) in CH_2Cl_2 (0.2 M) at 0 °C, was added TFA (3.0 equiv, dropwise via an addition funnel). The resulting mixture was allowed to stir at 0 °C for 15 minutes after the addition was complete. CH_2I_2 (3.0 equiv) was then added to the reaction mixture dropwise via syringe and the resulting reaction was allowed to stir at 0 °C for 10 minutes. To the resulting reaction was added hex-5-enoic acid methyl ester (1.0 equiv) and the reaction mixture was stirred for about 15 hours, allowing the mixture to increase to room temperature. The reaction was then quenched by careful addition of aqueous 1 N HCl and the the aqueous layer was extracted with CH_2Cl_2 (3x). The combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711A** in quantitative yield.

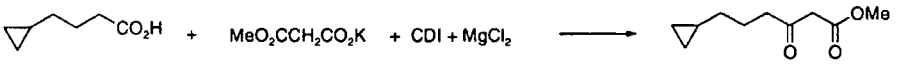
Step B:



711A **711B**

Aqueous NaOH solution (2.0 equiv, 2.0 N) was added to a solution of **711A** (1.0 equiv) in THF and MeOH (v/v = 2/1, 0.2 M) at room temperature. The mixture was allowed to stir for 4 hours and the solvent was then removed *in vacuo*. The resulting aqueous solution was extracted with ether and the resulting solution was then acidified using 5 M HCl. The aqueous layer was extracted with ether (3x) and the combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711B** in quantitative yield.

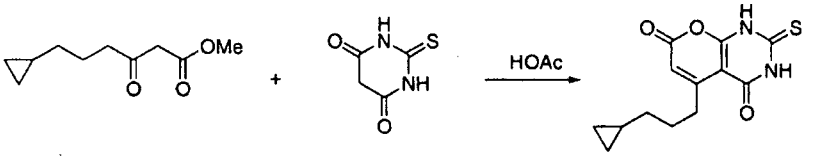
Step C:



711B **711C**

CDI (1.2 equiv) was added to a solution of **711B** in THF (0.5 M) at room temperature. The reaction mixture was allowed to stir for 1 hour, then monomethyl melonate ester potassium salt (1.5 equiv) and $MgCl_2$ (1.0 equiv) were added. The resulting reaction was allowed to stir for about 15 hours and was then quenched with aqueous HCl (1.0 N). The aqueous layer was extracted with EtOAc (3x). The combined organic phases were washed with water, then brine, then dried over $MgSO_4$ and concentrated *in vacuo* to provide compound **711C** in quantitative yield.

Step D:



711C **711D**

A mixture of 4,6-dihydroxy-2-mercapto-pyrimidine (1.0 eq) and **711C** (1.25 equiv) in HOAc (1.0 M) was heated to reflux and allowed to stir at this temperature for about 15 hours. The reaction mixture was then cooled and concentrated *in vacuo* and

the resulting residue was purified using flash column chromatography on silica gel to provide compound **711D** (37% yield).

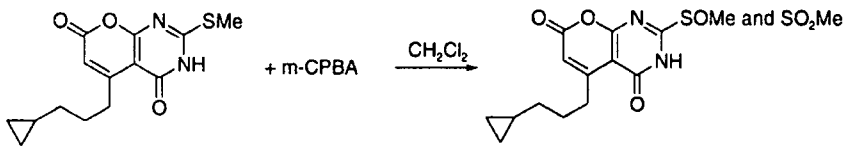
Step E:



711D **711E**

MeI (1.8 equiv) was added to a suspension of **711D** (4.0 g, 17.86 mmol) in DMF (0.3 M) at room temperature. The reaction mixture was allowed to stir at room temperature for about 15 hours, then poured into water and the resulting solution was filtered through a sintered funnel. The collected solid material was washed with water and dried under vacuum to provide compound **711E** (96% yield).

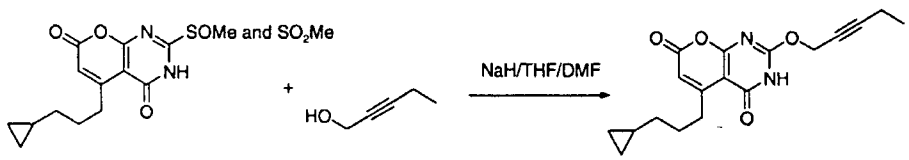
Step F:



711E **711F**

m-CPBA (2.0 equiv) was added to a suspension of **711E** (1.0 equiv) in CH_2Cl_2 (0.15 M) at room temperature. After stirring for 3 hours, the reaction was quenched with Me_2S (3.0 eq) and concentrated *in vacuo* to provide a crude product which was washed with Hexane/EtOAc (v/v = 3/1) to provide compound **711F** as a mixture of sulfone and sulfoxide (90% yield, w/w = 1/2).

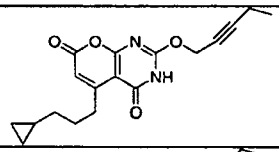
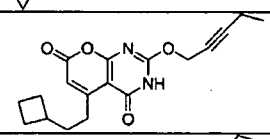
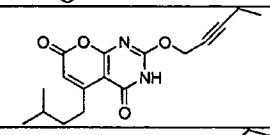
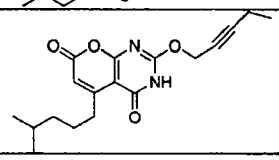
Step G:

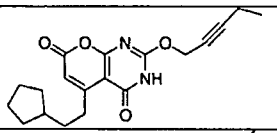
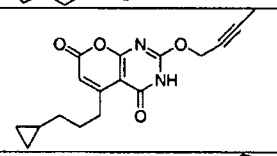
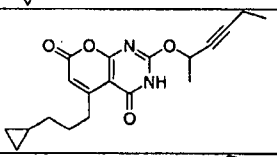
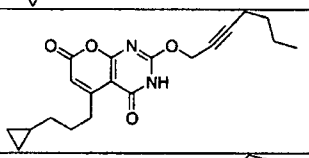
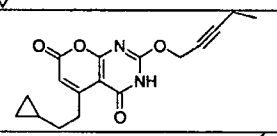
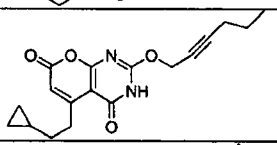
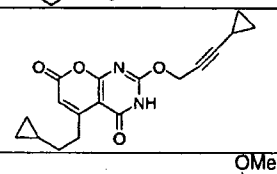
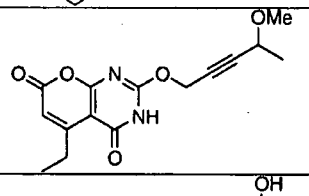
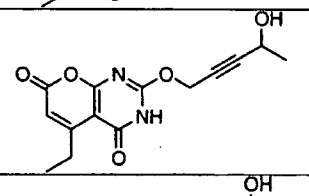
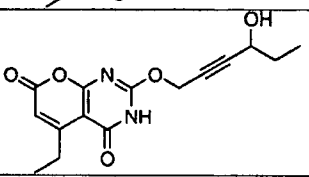
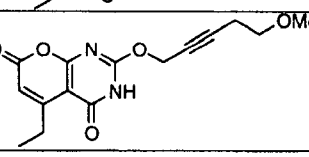


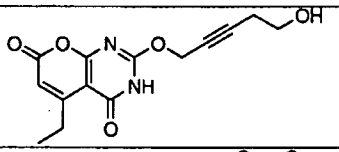
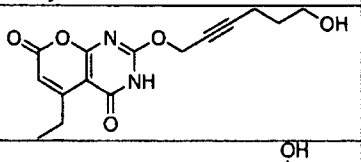
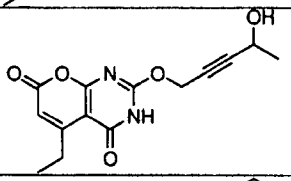
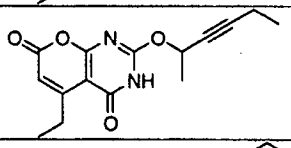
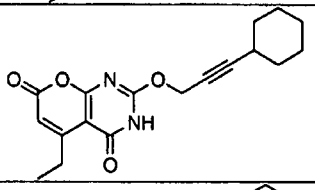
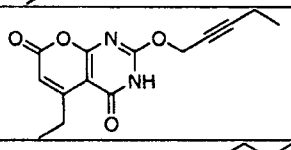
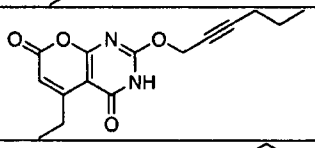
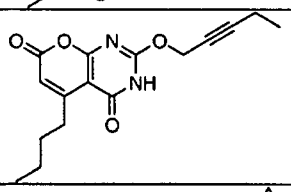
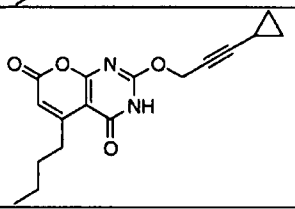
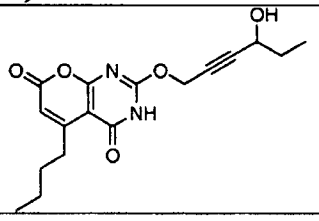
711F **711G**

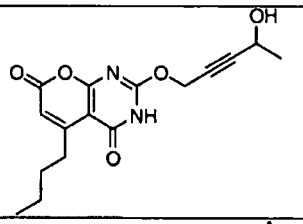
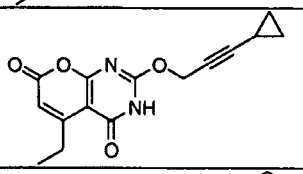
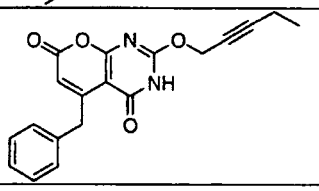
Pent-2-yne-1-ol (2.0 equiv) was added dropwise to a suspension of NaH (2.0 equiv) in THF at room temperature. The reaction mixture was stirred for 1 hour to provide a clear solution to which was then added dropwise a solution of **711F** (1.0 equiv) in DMF. The reaction mixture was stirred for about 2 hours at room temperature and was then quenched with HOAc (2.0 equiv). The resulting solution was diluted with EtOAc and washed sequentially with 0.1 M HCl, water and brine, then dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: hexane/CH_2Cl_2/EA (v/v/v = 7/3/2)) to provide compound **711** (50% yield). Electrospray MS $[M+1]^+$ 329.2.

Using the method described above, and appropriate materials, Compounds **712-739** were prepared:

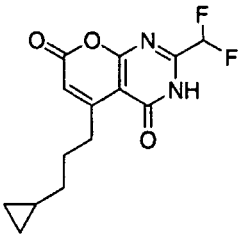
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
712		329.2
713		329.2
714		317.2
715		331.2

716		343.2
717		315.2
718		343.2
719		357.2
720		315.2
721		329.2
722		327.2
723		305
724		305
725		319
726		305

727		291
728		305
729		291
730		289
731		329
732		275
733		289
734		303
735		315
736		333

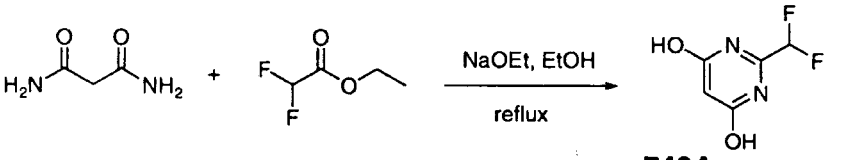
737		319
738		287
739		337.1

Preparative example 740



740

Step:1

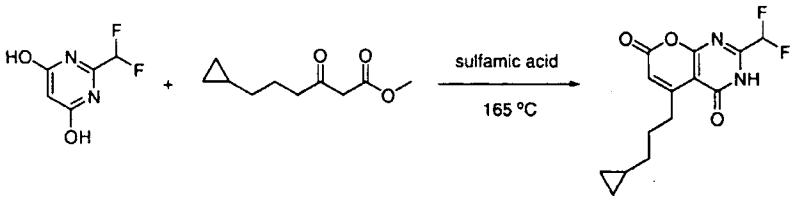


740A

A mixture of malonamide (40.00 g, 392.22 mmol) and NaOEt (21%, 292.00 ml, 784.53 mmol) in MeOH (1 L) was stirred at room temperature for 1 hour. Difluoroacetic acid ethyl ester (58.00 g, 467.74 mmol) was then added to the reaction mixture and the reaction was heated to reflux and allowed to stir at this temperature for about 15 hours. The reaction mixture was cooled to room temperature and the solid product was collected by filtration and washed sequentially with EtOH, EtOAc

and hexane, then sucked dry under vacuum to provide 45.0 g product as white powder (71% yield).

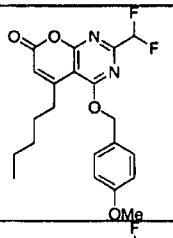
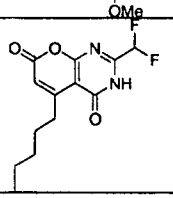
Step:2

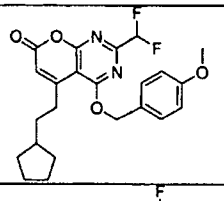
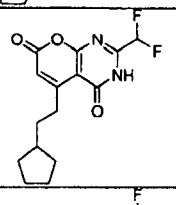
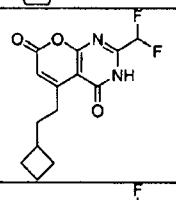
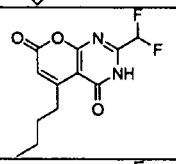
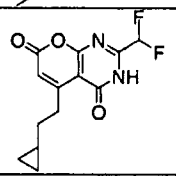
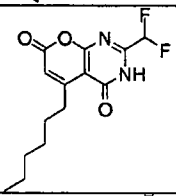
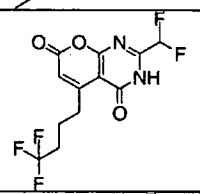
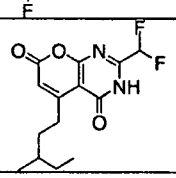


740A **740B** **740**

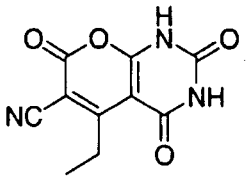
A mixture of compound **740A** (10.50g, 64.81 mmol), compound **740B** (14.90g, 80.98 mmol), and sulfamic acid (6.29g, 64.84 mmol) was heated to 165 °C and allowed to stir at this temperature for 30 minutes. The reaction mixture was then cooled to about 70 °C, then poured into into a mixture of CH_2Cl_2/MeOH (1:1, 50 mL) and the resulting solution was filtered. The solid collected by filtration was then washed repeatedly with CH_2Cl_2/MeOH (1:1) and the eluates were combined and concentrated *in vacuo* to provide compound **740** as white crystals (3.30 g, 17%).

Using the method described above, and appropriate materials, Compounds **742**, **743**, **745**, **746**, **748**, **750**, **752**, **754**, **757** and **812** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
742		405.2
743		285.1

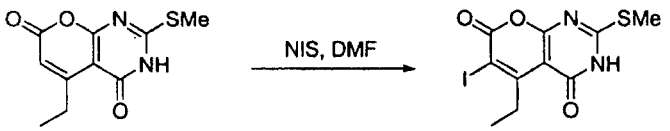
745		431.2
746		311.2
748		297.2
750		271.1
752		283.2
754		299.2
757		325.2
812		299.2

Preparative example 758



758

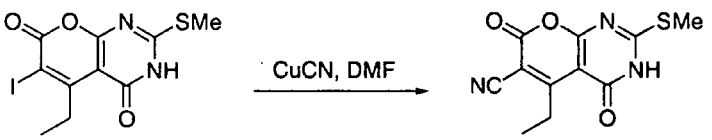
Step A:



758A **758B**

NIS (6.72 g, 29.9 mmol) was added to a solution of **758A** (5 g, 21 mmol) in DMF (70 mL). The reaction mixture was heated to 50 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was then cooled to room temperature and water (100 mL) was added. The resulting solution was filtered, and the collected solid was washed with water then ether to provide compound **758B** as a yellow powder (65% yield) which was used without further purification.

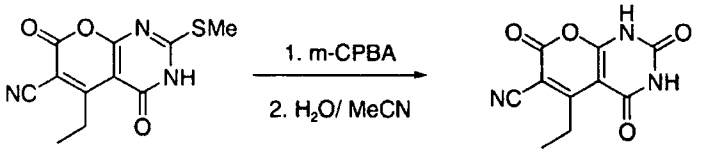
Step B:



758B **758C**

CuCN (0.246 g, 2.75 mmol) was added to a solution of **758B** (1.0 g, 2.75 mmol) in DMF (10 mL). The reaction was refluxed for 2 h, under N_2. After cooling to room temperature, H_2O (50 mL) was added. The precipitated product was filtered, washed with water then ether to afford **16** (95% yield).

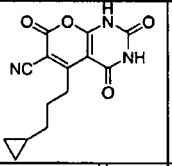
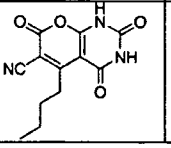
Step C:



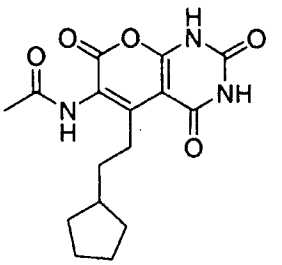
758C **758**

m-CPBA (0.936 g, 4.18 mmol) was added to a solution of **758C** (0.55 g, 2.09 mmol) in CH_2Cl_2 (15 mL). The resulting reaction was allowed to stir at room temperature for 4 hours, then Me_2S was added and the resulting solution was allowed to stir for an additional 10 minutes and concentrated *in vacuo*. The resulting residue was diluted with 10 mL CH_3CN/ H_2O (1:1) and the resulting solution was stirred at room temperature for 12 hours then concentrated *in vacuo* and purified by preparative TLC (15% MeOH/DCM) to provide compound **758**. Electrospray MS: $[MH^+]$ = 262.1

Using the method described above, and appropriate materials, compounds **759** and **760** were prepared:

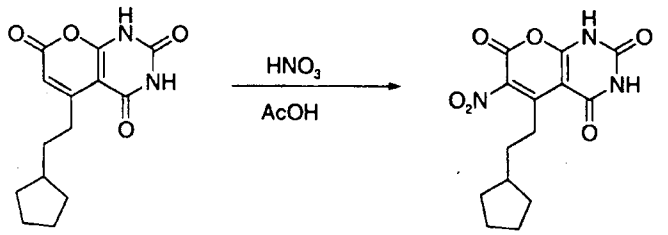
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
759		288.2
760		262.1

Preparative example 761



761

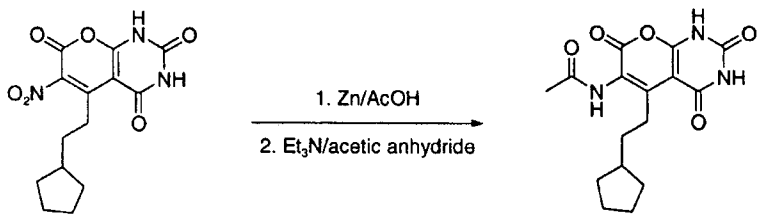
Step A:



761A **761B**

Fuming HNO_3 (0.9 mL) was added drop wise to a solution of **761A** (0.5 g, 1.81 mmol) in HOAc (1.8 mL) under N_2. The reaction was heated to 100 °C and allowed to stir at this temperature for 30 minutes, then the reaction mixture was poured into cold water (5 mL). The precipitate formed was isolated and washed with acetonitrile (1 mL) to afford compound **761B** (0.3 g, 51%). Electrospray MS: $[MH^+]$ = 322.2

Step B:

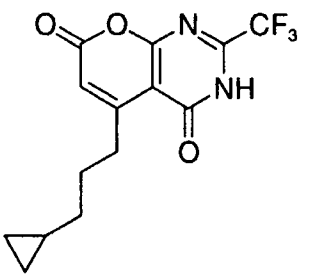


761B **761**

Zn dust (0.47 g, 7.2 mmol) was added to a solution of **761B** (0.23 g, 0.72 mmol) in HOAc (3 mL) and MeOH (2 mL), and the resulting reaction was stirred at room temperature for about 18 hours. The reaction was filtered and the filtrate was concentrated *in vacuo* to provide a residue which was dissolved in CH_2Cl_2 (2 mL). To the resulting solution was added Et_3N (2 mL) followed by acetic anhydride (2 mL). The resulting reaction was allowed to stir at room temperature for 24 hours, then was concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (eluent: $MeOH/CH_2Cl_2$ (v/v = 10/97)) to provide compound **761** (0.15 g, 62%). Electrospray MS: $[MH^+]$ = 334.2

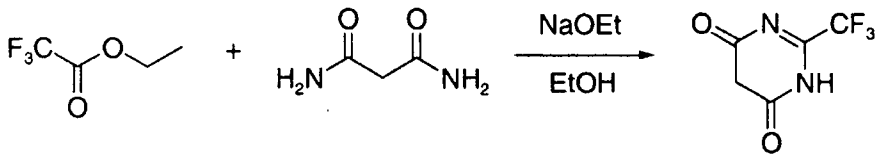
Preparative example 762

220



762

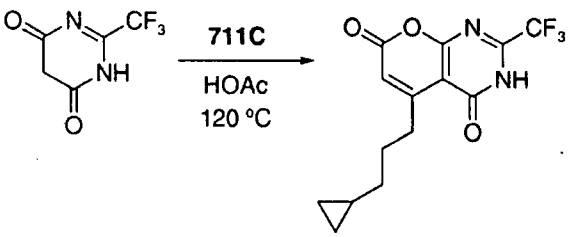
Step A:



762A

Trifluoroacetic acid ethyl ester (8.8 ml, 73.5 mmol) was slowly added to a suspension of malonamide (5 g, 49 mmol) and NaOEt (21% in EtOH, 36.5 ml, 98 mmol) in EtOH (50 mL). The resulting reaction was put under nitrogen atmosphere, heated to reflux, and allowed to stir at this temperature for about 20 hours. The reaction mixture was then filtered and the collected yellow solid was washed with EtOAc, then EtOH to provide compound **762A**.

Step B:

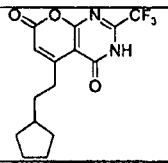
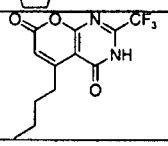


762A **762**

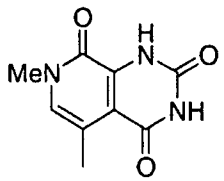
Compound **711C** (0.8g, 4.2 mmol, prepared as described above in preparative example 711, step C) was added to a solution of **762A** (0.5g, 2.8 mmol) in HOAc (1.5 mL). The resulting reaction was heated to 120 °C and allowed to stir at this temperature for 20 hours, then the reaction was cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified using flash column

chromatography on silica gel (eluent: 3% MeOH/CH_2Cl_2) followed by preparative TLC (5% MeOH/CH_2Cl_2) to to provide compound **762**.

Using the method described above, and appropriate materials, compounds **763** and **764** were prepared:

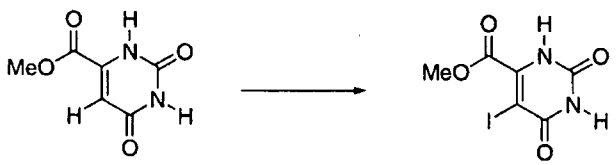
Compound No.	Structure	Electrospray LCMS [M+1]$^+$
763		329.2
764		289.2

Preparative example 765



765

Step A:

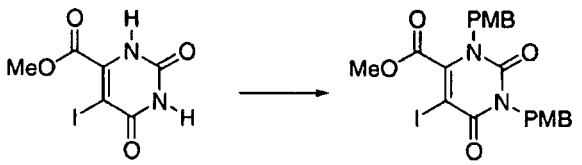


765A **765B**

N-iodosuccinimide (40 g, 177 mmol) was added to a solution of **765A** (15 g, 88 mmol) in a mixture of TFA-TFAA (300 mL, 30 mL) and the resulting reaction was heated heated to 85 °C and allowed to stir at this temperature for about 15 hours. The reaction was then cooled to room temperature and concentrated in vacuo. The resulting residue was partitioned between 200 mL of H_2O and 100 mL of EtOAc. The

precipitate was collected and washed with H_2O and EtOAc, then dried *in vacuo* to afford compound **765B** (20.2 g, 78%).

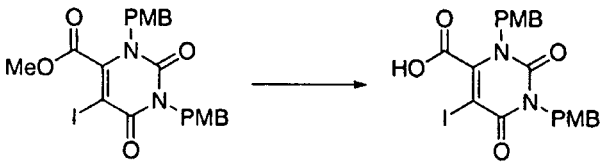
Step B:



765B **765C**

Na_2CO_3 (27g, 300 mmol) and PMBCl (34 mL, 300 mmol) were added to a solution of **765B** (20 g, 100 mmol) in DMF (300 mL). The resulting slurry was heated to 50 °C and allowed to stir at this temperature for about 15 hours. The reaction was then cooled to room temperature and partitioned between H_2O (250 mL) and EtOAc (500 mL). The organic layer was separated and washed with H_2O, then brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting residue was filtered through a pad of silica gel, eluted with EtOAc-heaxanes (1:10) followed by EtOAc-hexanes (1:1). The filtrate was concentrated *in vacuo* and the residue was recrystalized from DCM and hexanes to afford **765C** (16.6 g, 31%).

Step C:

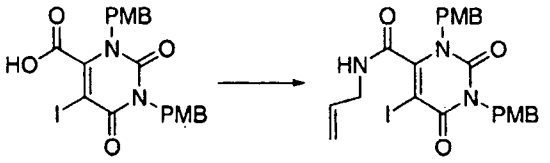


765C **765D**

Lithium iodide (15.3 g, 114 mmol) was added to a solution of **765C** (15.3 g, 28.5 mmol) in EtOAc (300 mL). The resulting slurry was stirred heated to 85 °C and allowed to stir at this temperature for about 15 hours. The reaction mixture was cooled to room temperature; then water (100 mL) was added and the resulting solution was transferred to a separatory funnel. The aqueous layer was separated and brought to a basic pH by the addition of 1 N NaOH, then the basified solution was washed with ether. The aqueous layer was then adjusted to pH = 1 by addition of 1 N HCl and the resulting acidic solution was extracted with EtOAc. The combined

organic extracts were washed with 1 N sodium thiosulfate solution, dried over $MgSO_4$, then filtered and concentrated *in vacuo* to provide compound **765D** (13.5 g, 90%).

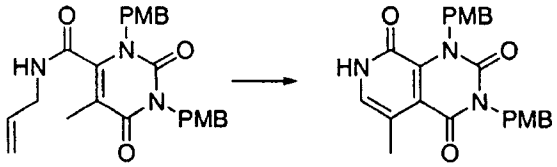
Step D:



765D **765E**

Oxalyl chloride (0.2 mL, 2.32 mmol) was added to a solution of **765D** (1.0 g, 1.91 mmol) in CH_2Cl_2 (10 mL), followed by addition of a drop of DMF. The resulting mixture was allowed to stir at room temperature for 30 minutes, then concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (10 mL), and to the resulting solution was added allylamine (0.2 mL, 19.8 mmol) . The resulting reaction was allowed to stir at room temperature for about 15 hours, then the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 N HCl. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1), to provide compound **765E** (0.61 g, 60%).

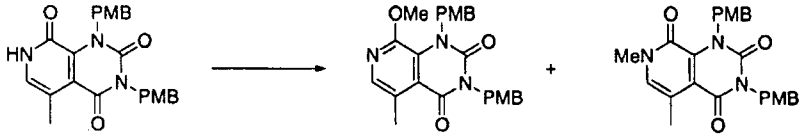
Step E:



765E **765F**

In a sealed tube, Et_3N (0.42 ml, 2.99 mmol) and $Pd(OAc)_2$ (38 mg, 0.17 mmol) were added to a solution of **765E** (1.0 g, 1.91 mmol) in DMF (6 mL). The resulting reaction was heated at 85 °C and allowed to stir at this temperature for about 15 hours, then cooled to room temperature and filtered through Celite. The filtrate was concentrated *in vacuo* and the resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1) to provide compound **765F** (0.27 g, 36%).

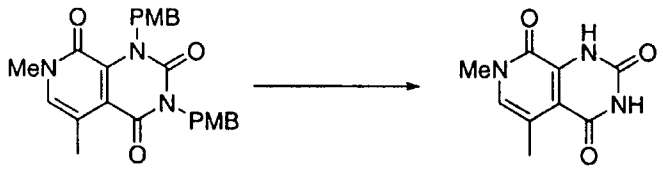
Step F:



765F 765G 765H

A solution of **765F** (262 mg, 0.60 mmol) in DMF/THF (1:1, 12 mL) was cooled to 0 °C and NaH (30 mg, 1.18 mmol, 95% oil dispersion) was added. The resulting reaction was allowed to stir at 0 °C was stirred for about 30 minutes, then iodomethane (0.1 mL, 1.60 mmol) was added and the reaction was allowed to stir at room temperature for about 15 hours. The reaction was quenched with water, and the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified using flash column chromatography on silica gel (eluent: EtOAc-hexanes, 1:1) to provide compounds **765G** (5 mg, 4% yield) and **765H** (121 mg, 90%).

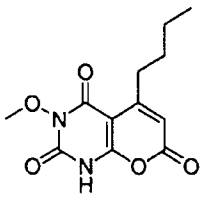
Step G:



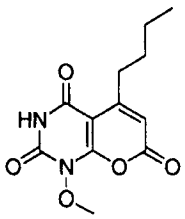
765H 765

TFA (0.5 mL) and TfOH (0.1 mL) were added to a solution of **765H** (100 mg, 0.22 mmol) in CH_2Cl_2 (6 mL). The resulting reaction was allowed to stir at room temperature for about 15 hours, then concentrated in vacuo to provide a crude residue which was purified using preparatory TLC (eluent: acetic acid/CH_2Cl_2/EtOAc, 1:10:10) to provide compound **765** (12 mg, 26%). Electrospray MS $[M+1]^+$ 208.1

Preparative examples 766 and 767

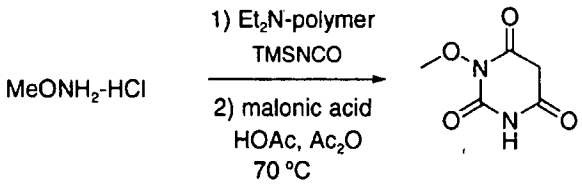


766



767

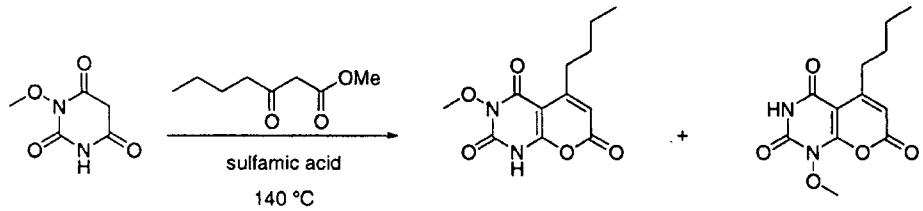
Step A:



766A

Diethylaminomethyl-polystyrene (40 g, 3.2 mmol/g,128 mmol) was added to a solution of methoxylamine hydrochloride (5.0 g, 60 mmol) in MeOH (300 mL). The reaction mixture was stirred for 1 h. Then, TMSNCO (8.1 mL, 60 mmol) was added and the solution was stirred for 4 h. The polymer was filtered and washed twice with MeOH (50 mL, each). The volatiles were removed and the residue was dissolved in acetic acid (40 mL) then malonic acid (5.1 g, 60 mmol) and Ac_2O (40 mL) were added. The mixture was heated at 70 °C for 10h. The reaction was concentrated in vacuo and the residue was dissolved in MeOH (100 mL), stirred for 10 min. and concentrated. The resulting residue was triturated in 1:1 EtOAc/Et2O and filtered to obtain **34** (4.2 g).

Step B:

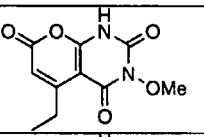
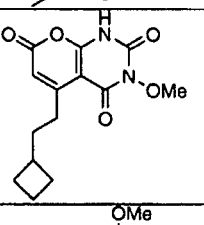
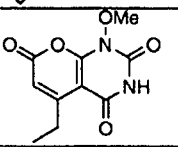
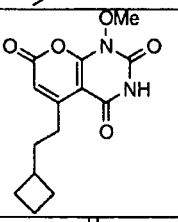
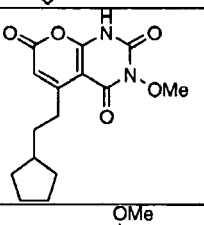
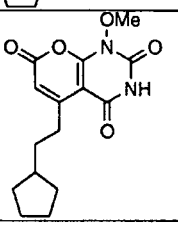


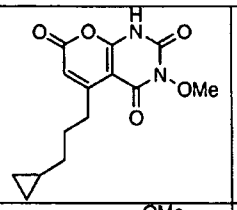
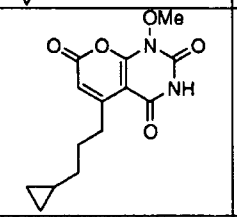
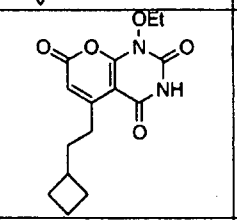
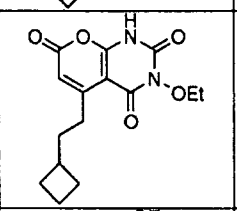
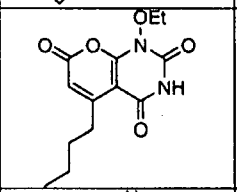
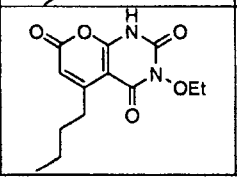
766A **766** **767**

Sulfamic acid (613 mg, 6.32 mmol) was added to a mixture of 3-oxo-heptanoic acid methyl ester (2.0 g, 12.6 mmol) and **766A** (1.0 g, 6.32 mmol). The mixture was

heated at 140 °C for 4 hours. The resulting residue was dissolved in 10 mL of MeOH, filtered and separated using a Gilson HPLC to obtain pure **766** and **767**. Electrospray MS $[M+1]^+$ 267.1

Using the method described above, and appropriate materials, compounds **768-779** were prepared:

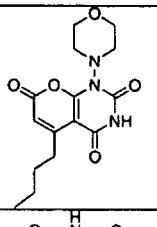
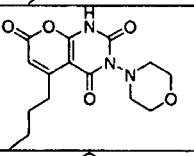
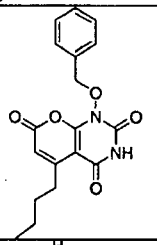
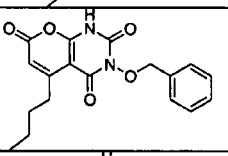
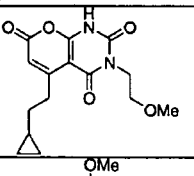
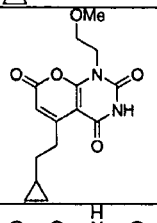
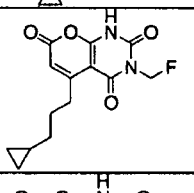
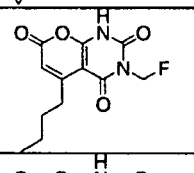
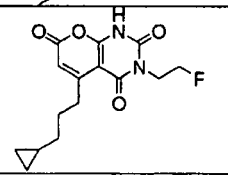
Compound No.	Structure	Electrospray LCMS $[M+1]^+$
768		239.1
769		293.1
770		293.1
771		292.2
772		306.3
773		306.31

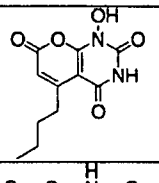
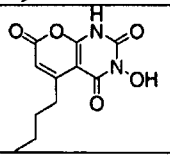
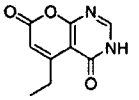
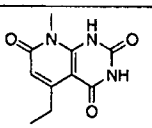
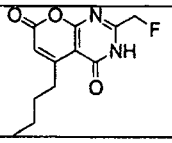
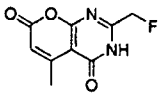
774		NA
775		NA
776		307.1
777		307.1
778		281.1
779		281.1

NA = not available

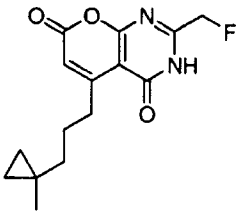
Other illustrative compounds of formula (I), include but are not limted to compounds **796-810**, which are depicted below:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$

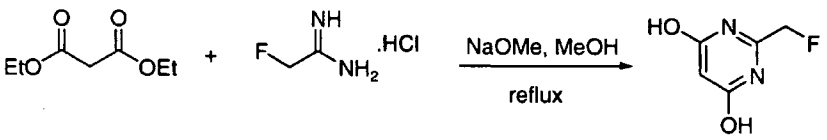
796		322.2
797		322.2
798		343.2
799		343.2
800		307.2
801		307.2
802		295.2
803		269.1
804		309.2

805		253.1
806		253.1
807		193.1
808		222.2
809		253.1
810		211.1

Preparative example 811



811



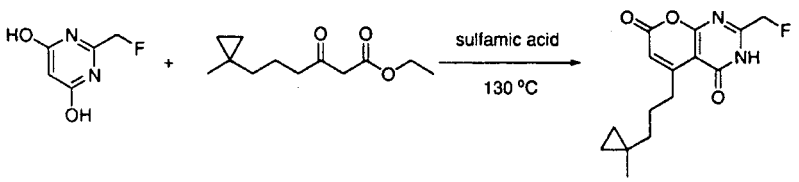
811A

Step A:

A solution of diethylmalonate (2.96 g, 18.48 mmol) and NaOMe (25 wt % in MeOH, 10.75 g, 49.76 mmol) was added to a solution of 2-fluoroacetamidine hydrochloride (2.0 g, 17.77 mmol) in MeOH (20 mL). The resulting reacton was heated to reflux and allowed to stir at this temperature for about 15 hours. The

reaction mixture was cooled to room temperature, concentrated in *vacuo*, and the resulting residue was diluted with water (20 mL). The resulting solution was neutralized using concentrated HCl and the solid formed was collected by filtration, washed sequentially with H_2O and Et_2O, then sucked dry to provide compound **811A** as a pale brown powder (1.8 g, 69%).

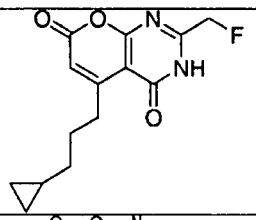
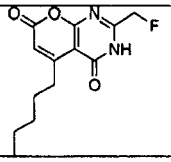
Step B

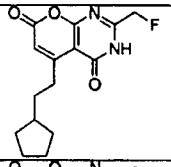
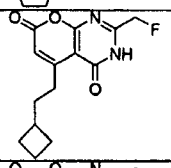
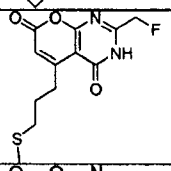
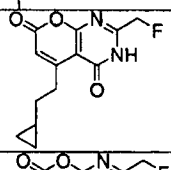
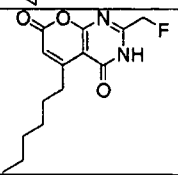
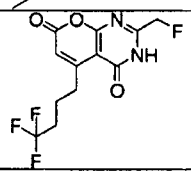


811A **811B** **811**

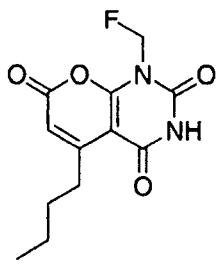
A mixture of compound **811A** (0.1 g, 0.694 mmol), compound **811B** (0.295 g, 1.39 mmol) and sulfamic acid (0.034 g, 0.347 mmol) was heated to 130 °C and allowed to stir at this temperature for about 2 hours. The reaction mixtures was then cooled to room temperature and poured into into a mixture of CH_2Cl_2/MeOH (1:1, 1 mL). The resulting solution was purified using flash column chromatography (eluent: gradient of from 20% to 50% EtOAc/hexanes) to provide compound **811** product as a white solid.

Using the method described above, and appropriate materials, Compounds **741**, **744**, **747**, **749**, **751**, **753**, **755** and **756** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
741		279
744		267.1

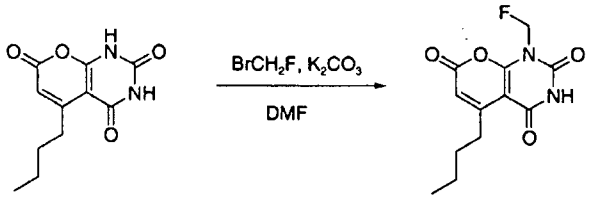
747		293.2
749		279.2
751		285.2
753		265.1
755		281.2
756		307.2

Preparative example 813



813

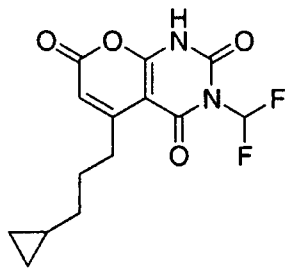
Step A:



102 **813**

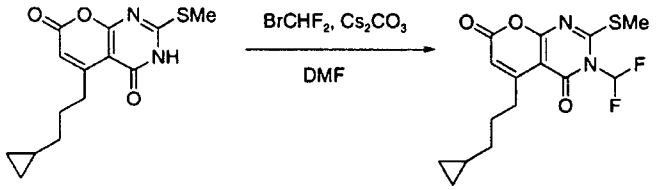
K_2CO_3 (0.35 g, 2.54 mmol) was added to a solution of compound **102** (0.4 g, 1.69 mmol) and $BrCH_2F$ (0.21 g, 1.86 mmol) in DMF (5.0 mL) at room temperature. The resulting mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with PTLC (CH2Cl2/MeOH = 20/1) to give product **813** (5 mg), Electrospray MS $[M+1]^+$ 269.1.

Preparative example 814



814

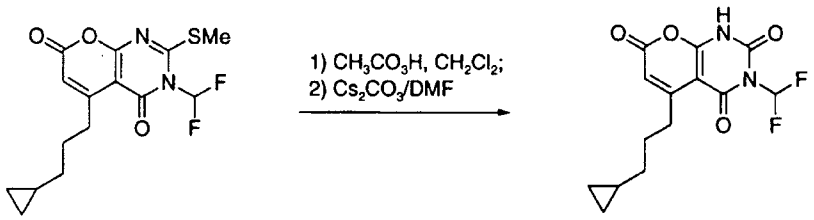
Step A:



711E **814A**

Cs_2CO_3 (1.30 g, 3.99 mmol) was added to a solution of compound **711E** (0.39 g, 1.33 mmol) and $BrCHF_2$ (0.79 g, 6.05 mmol) in DMF (5.0 mL) at room temperature. The resulting mixture was stirred overnight. The reaction mixture was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with silica gel column chromatography (EtOAc/hexane gradient) to provide compound **814A** (0.15 g).

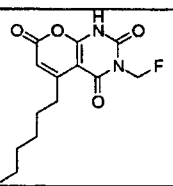
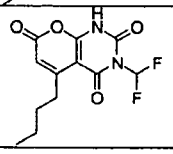
Step B:

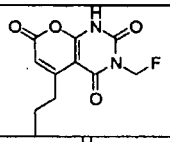
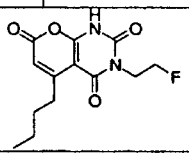
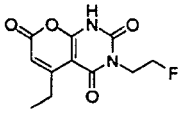
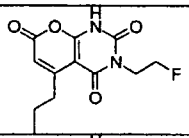
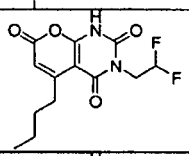
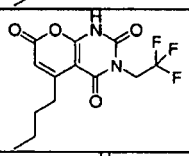
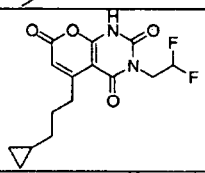
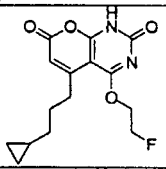
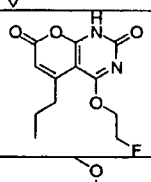
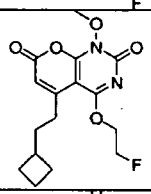
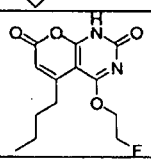


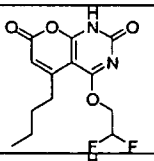
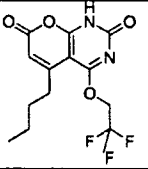
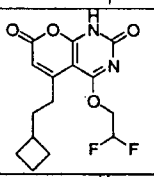
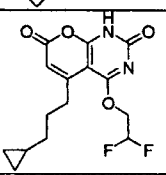
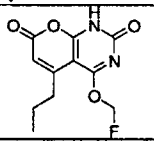
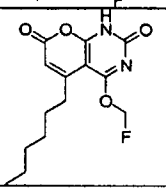
814A **814**

CH_3CO_3H (0.30 mL, 1.4 mmol) was added at room temperature to a solution of **814A** (80 mg, 0.234 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred for 3 hours before it was quenched with Me_2S (10.0 eq.). The reaction mixture was diluted with ethyl acetate and washed with water (3x). The organic phase was washed with brine, dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was taken up in DMF (2.0 mL) and treated with Cs_2CO_3 (91.6 mg, 0.281 mmol). The mixture was stirred for 1 hour before it was diluted with ethyl acetate and neutralized with aqueous HCl solution (0.5 N). The organic phase was washed with water (3x), dried (Mg_2SO_4), and concentrated *under vacuo* to provide crude product which was purified with reverse phase Gilson separation to provide compound **814** (60 mg), Electrospray MS $[M+1]^+$ 313.2.

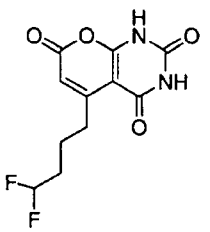
Using the method described above in Preparative Examples 813 and 814, and substituting the appropriate bromo compound in Step A, Compounds **815-833** were prepared:

Compound No.	Structure	Electrospray LCMS $[M+1]^+$
815		297.2
816		287.2

817		255.1
818		283.2
819		255.1
820		269.1
821		301.2
822		319.2
823		327.2
824		309.2
825		269.1
826		339.2
827		283.2

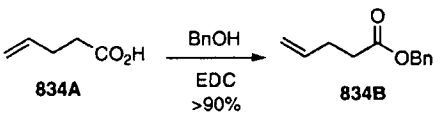
828		301.2
829		319.2
830		327.2
831		327.2
832		255.1
833		297.2

Preparative Example 834



834

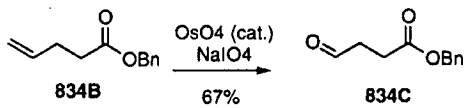
Step1:



834A **834B**

To a solution of 4-pentenoic acid (**834A**, 60 g, 0.594 mol) and benzyl alcohol (56 mL, 0.54 mol) in dichloromethane (1 L) was added EDC (207 g, 1.08 mol) at 0°C and the reaction was stirred until homogeneous (~5 min). DMAP (6.7 g, 0.054 mol) was then added and reaction mixture was allowed to warm to room temperature, then stirred under nitrogen for an additional 2 hours. The reaction mixture was washed with 1N HCl (aq.), then saturated $NaHCO_3$ (aq.), then dried over sodium sulfate and concentrated *in vacuo* to provide compound **834B** in nearly quantitative yield (>95%).

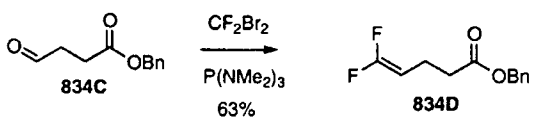
Step2:



834B 834C

To a solution of compound **834B** (2.3 g, 0.012 mol) and 4% osmium tetraoxide in water (3 mL, 0.04 eq) in 3:1 (v/v) THF/H_2O (45 mL:15 mL) was added sodium periodate (7.7 g, 0.036 mol) and the resulting reaction was stirred under nitrogen at room temperature overnight. Sodium periodate was then added and a precipiate formed from the resulting exotherm. The reaction mixture was filtered, dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified using flash column chromatograpy on silica gel (0-20% EtOAc/Hexane) to provide compound **834C** (1.6 g, 0.083 mol, 67%).

Step 3:

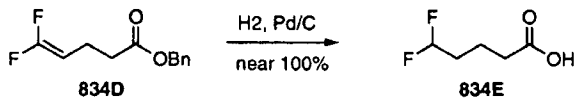


834C 834D

To a solution of hexamethyl phosphorous triamide (25.4 g, 0.156 mol) in THF (300 mL) at -78°C was added dibromodifluoromethane (16.4 g, 0.078 mol) and the resulting suspension was allowed to warm to room temperature. Compound **834C** (7.5 g, 0.039 mol) was added and RM refluxed at 66°C under nitrogen overnight. The

reaction mixture was filtered, dried over sodium sulfate and concentrated *in vacuo*. The resulting residue was purified using flash column chromatograpy on silica gel (0-10% EtOAc/Hexane) to provide compound **834D** (5.5 g, 0.024 mol, 62 %).

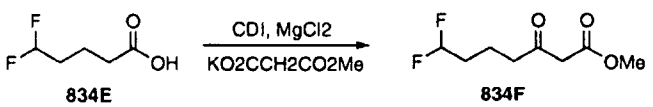
Step 4:



834D **834E**

To a solution of compound **834D** (5.5 g, 0.024 mol) in EtOAc (120 mL) was added 10% Pd/C (1.3 g, 0.05 eq) and the resulting solution was placed on Parr shaker under 50 psi hydrogen gas overnight. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to provide compound **834E** (3.3 g, 0.024 mol, >99%).

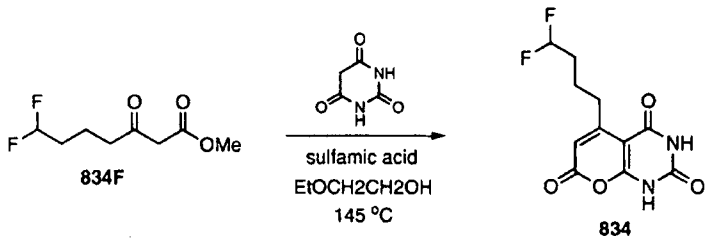
Step 5



834E **834F**

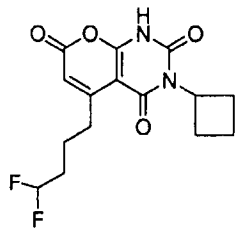
To solution of compound **834E** (6 g, 0.0434 mol) in THF (150 mL) was added CDI (8.5 g, 1.2 eq) and the resulting reaction was stirred at room temperature under nitrogen for 1 hour. MgCl2 (4.1 g, 1 eq) and monomethyl malonate potassium salt (10.2 g, 1.5 eq) were than added and the resulting reaction was stirred at room temperature under nitrogen overnight. The reaction mixture was then partitioned between 1N HCl (aq.) (200 mL) and EtOAc (200 mL). The aqueous layer was collected and extracted with EtOAc (3 x 100 mL) and the combined organic layers were washed with brine (50 mL), dried over sodium sulfate, filtered and concentrated *in vacuo*. The crude residue obtained was purified using flash chromatography on silica gel (0-20% EtOAc/Hexane) to provide compound **834F** (6.7 g, 0.0347, 80%)

Step 6:

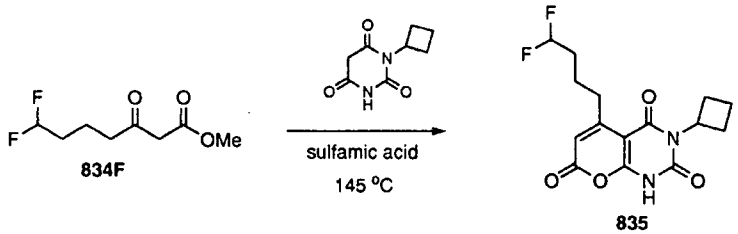


To a solution of barbituric acid (7 g, 1.1 eq) and compound **834F** (9.7 g, 0.05 mol) in EtOEtOH (15 mL) was added sulfamic acid (2.4 g, 0.5 eq) and the resulting reaction was stirred at 147°C for 4 hours. The reaction mixture was concentrated *in vacuo* and the resulting residue triturated with hot water three times to provide compound **834** (2 g, 0.007 mol, 15 %).

Preparative Example 835

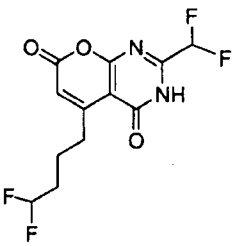


835

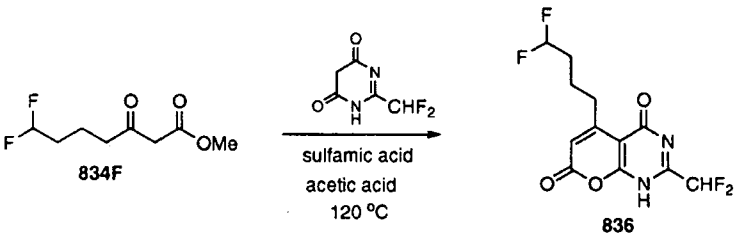


N-cyclobutyl barbituric acid (782, 4.3 mmol) and compound **834F** (1 g, 1.2 eq) were heated at 140°C for 2 hours in the presence of sulfamic acid (417 mg, 1 eq). The mixture was suspended in 10 mL DMF and the suspension was then filtered. The filtrate was injected into a Gilson HPLC in twenty injections and purified on a C18 column eluted with 0.1% TFA in water/acetonitrile (gradient 10-100% water/acetonitrile at a flow rate of 25 mL/min) to provide compound **835** (retention time: 10.1 min; 120 mg, 0.037 mmol, 9%).

Preparative Example 836

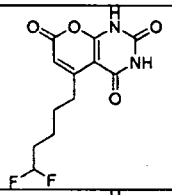
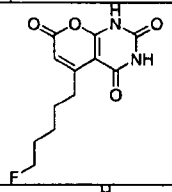
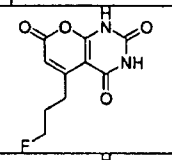
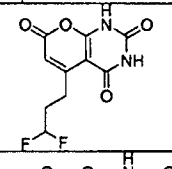
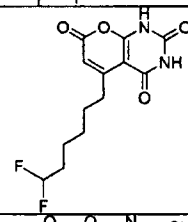
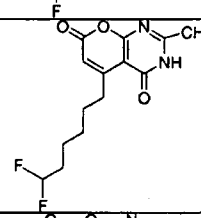
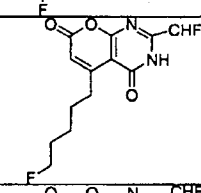
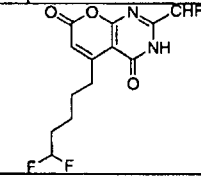


836



To a mixture of difluorobarbituric acid (1 g) and compound **834F** (1 g) in a 15 mL microwave vial was added acetic acid (3 mL). The vial was sealed and the resuting solution was microwaved at 180 °C for 20 minutes. The reaction mixture was then concentrated *in vacuo* and purified using flash chromatography on silica gel (gradient elution of 0-80% EtOAC/Hexane). The blue UV band that eluted off the column was collected and concentrated in vacuo and the resulting residue was purified using preparative TLC (2:1 EtOAc/Hexane) to provide compound **836** (40 mg, 3%).

Using the methods described above in Preparative Examples **834-836** with the approrpriate difluoro β-keto ester and barbituric acid or barbituric acid derivative, Compounds **837-844** were prepared:

Compound No.	Structure
837	
838	
839	
840	
841	
842	
843	
844	

Nicotinic Acid Receptor Assay

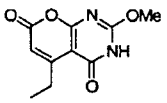
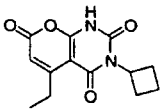
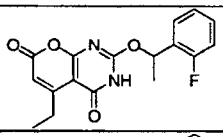
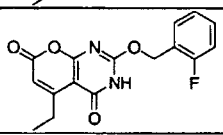
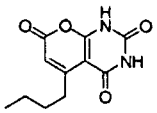
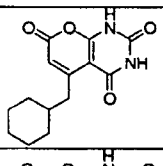
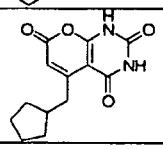
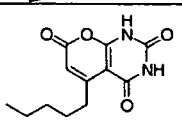
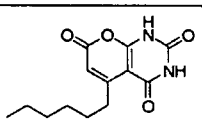
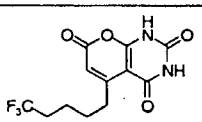
The nicotinic acid receptor agonist activity of the inventive compounds was determined by following the inhibition of forskolin-stimulated cAMP accumulation in cells using the MesoScale Discovery cAMP detection kit following the manufacturer's protocol. Briefly, Chinese Hamster Ovary (CHO) cells expressing recombinant human nicotinic acid receptor (NAR) were harvested enzymatically, washed 1X in phosphate buffered saline (PBS) and resuspended in PBS containing 0.5 mM IBMX at $3x10^6$ cells/mL. Ten µL of cell suspension was added to each well of a 384-well plate which contained 10 µL of test compounds. Test compounds were diluted with PBS containing 6 µM of forskolin. Plates were incubated for 30 minutes at room temperature after the addition of cells. Lysis buffer containing cAMP-Tag was added to each well (10 µL/well) as per the manufacturer's protocol. Plates were then incubated from 45 minutes to overnight. Prior to reading, 10 µL of read buffer was added to each well, and the plate was read in a Sector 6000 plate imager. The signal was converted to cAMP concentration using a standard curve run on each plate. Compound EC_{50} values were determined from concentration gradients of test compounds.

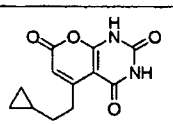
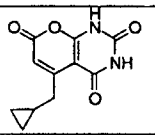
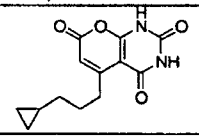
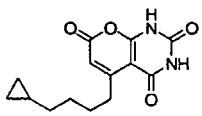
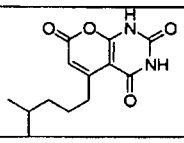
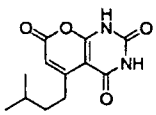
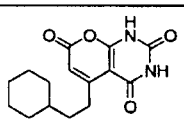
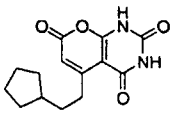
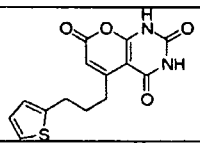
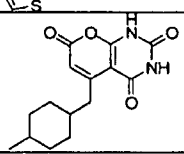
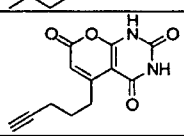
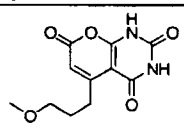
Compounds of Formula (I) of the present invention, and salts, solvates, or esters thereof, have cAMP EC_{50} values of less than about 10,000 nM, preferably about 1000 nM or less, more preferably about 500 nM or less, even more preferably about 100 nM or less.

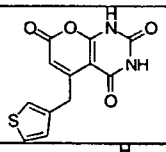
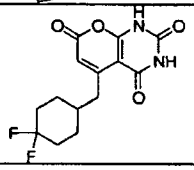
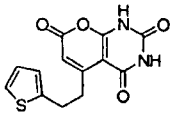
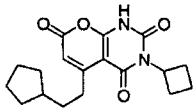
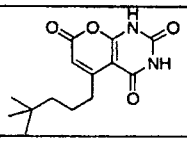
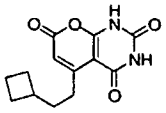
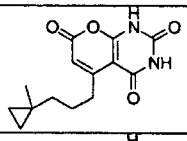
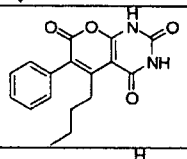
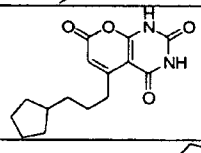
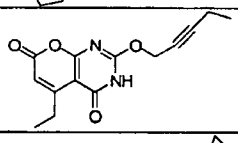
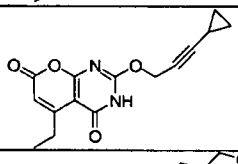
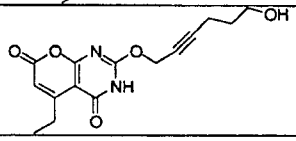
Examples 1, 5, 10, 29, 39, 71, 101-116, and 118-135 have cAMP EC_{50} values of 100 nM or less.

The activity of selected illustrative compounds of the invention as determined using the above-described assay is presented in the following Table:

Nicotinic Recepor Agonist Activity of Selected Illustrative Compounds of the Invention

Compound No.	Structure	NA EC_{50} camp (nM)
11		125.0
35		9.0
90		475.3
74		183.0
102		31.0
103		74.3
104		47.0
107		18.7
108		28.0
112		14.4

116		12.6
117		155.0
118		4.2
119		10.1
122		5.3
123		4.3
124		78.5
125		1.2
126		26.5
127		57.3
128		6.3
129		106.5

135		4.8
223		26.45
229		47.4
241		12.95
262		49.9
266		1.2
268		2.1
292		300
297		56.75
512		95.5
589		33.8
645		26.2

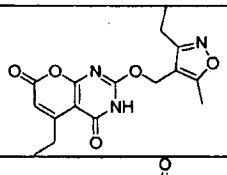
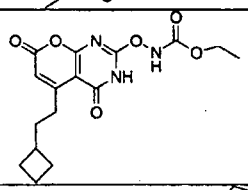
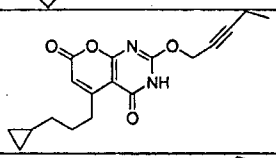
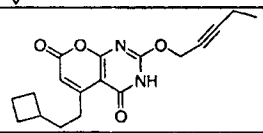
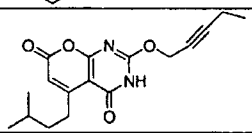
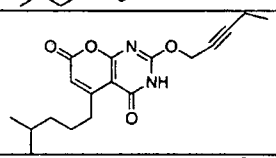
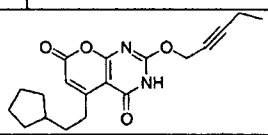
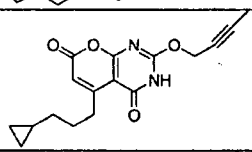
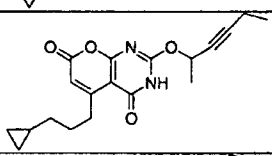
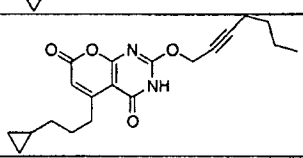
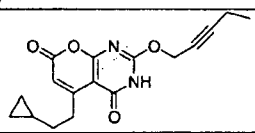
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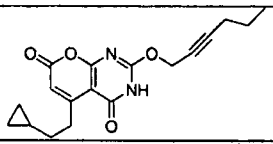
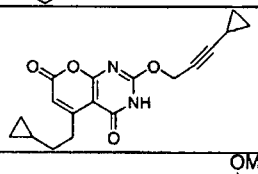
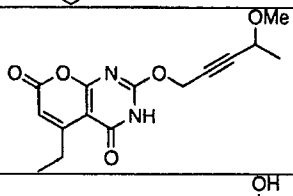
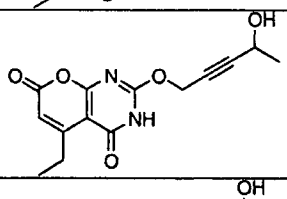
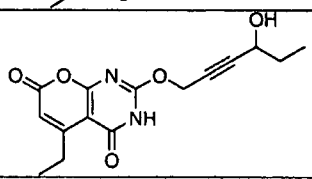
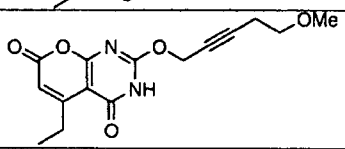
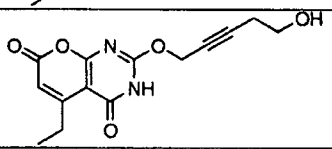
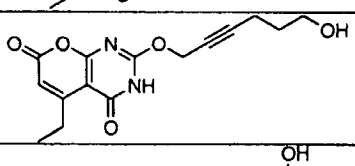
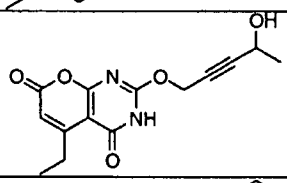
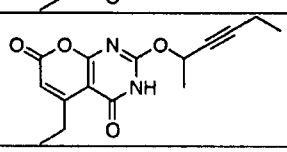
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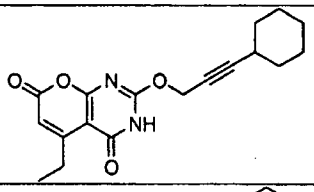
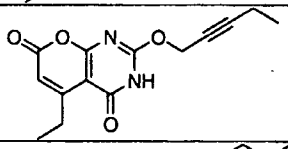
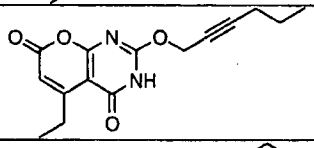
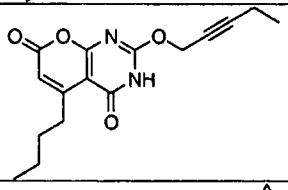
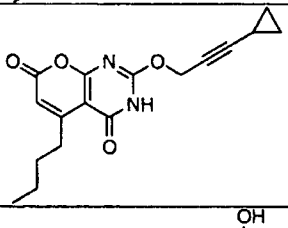
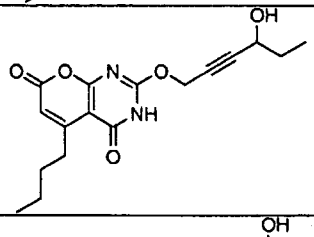
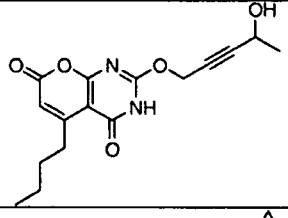
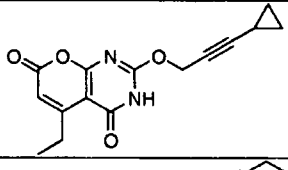
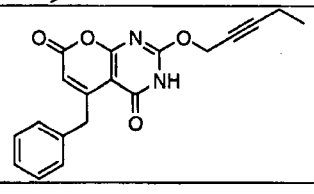
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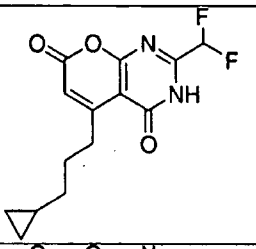
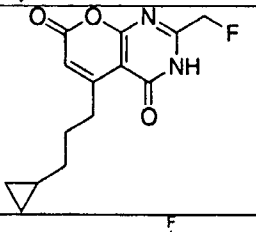
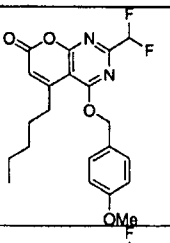
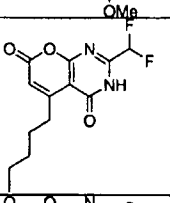
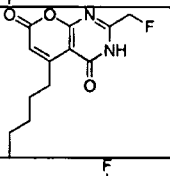
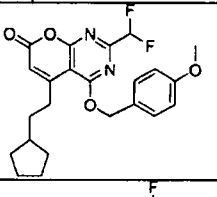
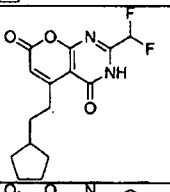
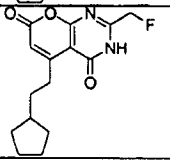
Patente De Invención

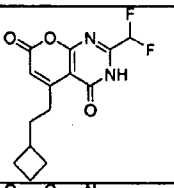
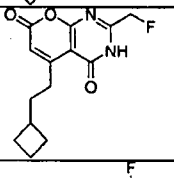
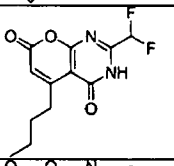
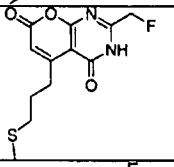
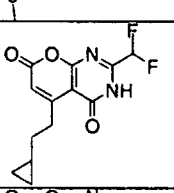
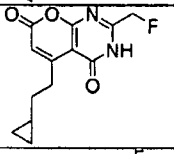
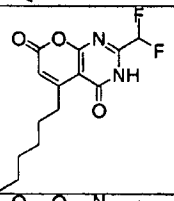
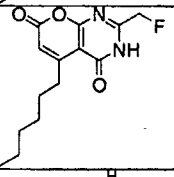
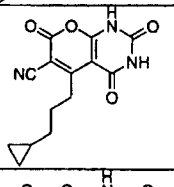
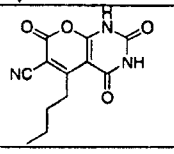
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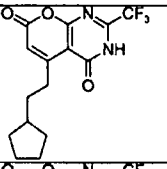
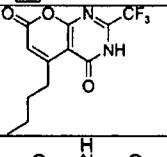
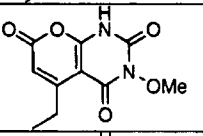
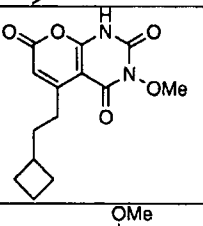
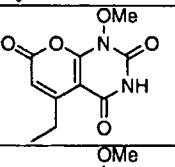
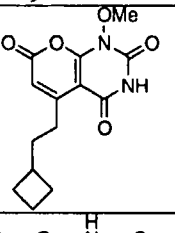
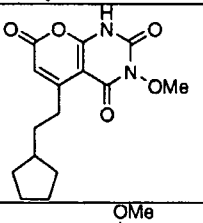
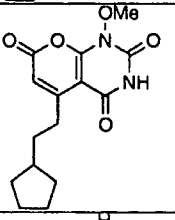
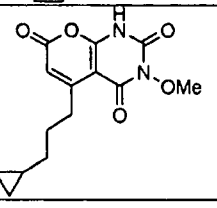
666		63.3
691		47.5
712		57.0
713		22.0
714		66.0
715		671.0
716		171.5
717		259.0
718		162.5
719		152.0
720		89.5

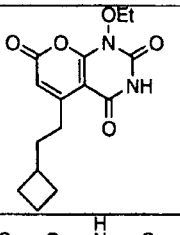
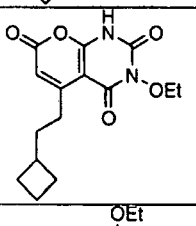
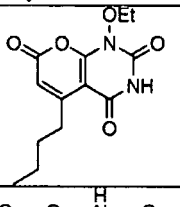
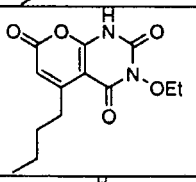
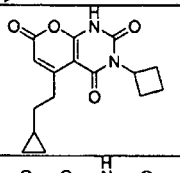
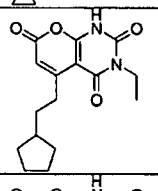
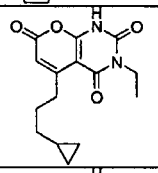
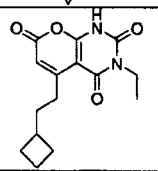
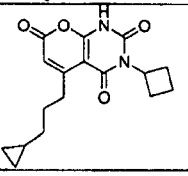
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722		111.5
723		296
724		59.5
725		675
726		219
727		179
728		26.2
729		49.9
730		155.8

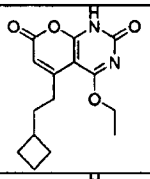
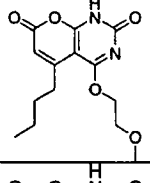
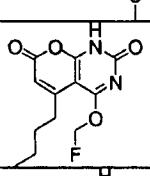
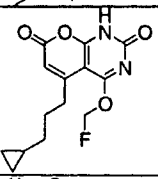
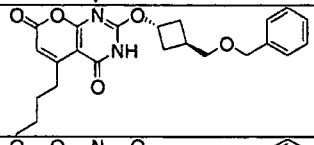
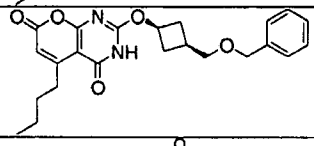
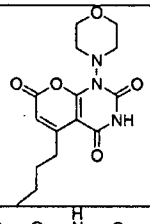
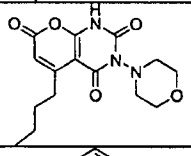
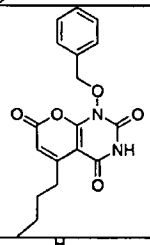
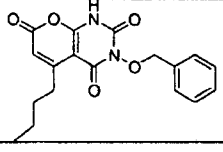
731		177.4
732		95.5
733		52.6
734		71.8
735		94
736		32.9
737		59.5
738		33.8
739		136.8

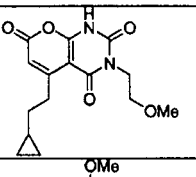
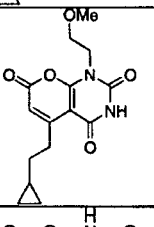
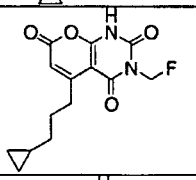
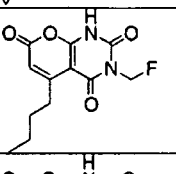
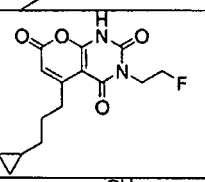
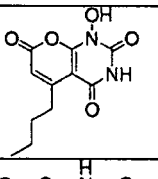
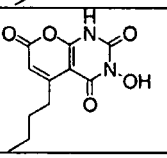
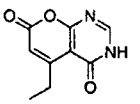
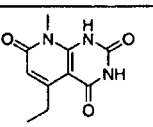
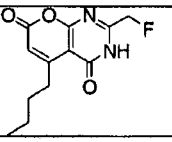
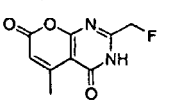
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741		123
742		1068
743		212.5
744		128
745		10000
746		1402
747		1233

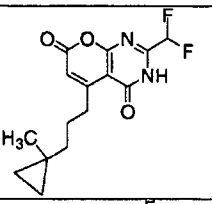
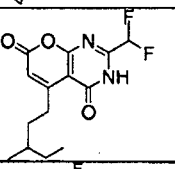
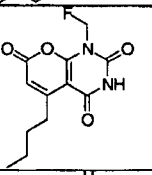
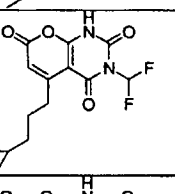
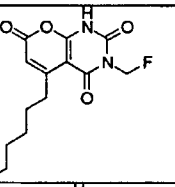
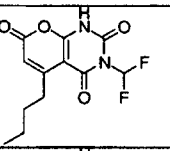
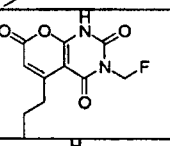
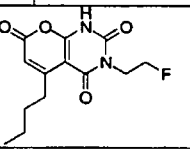
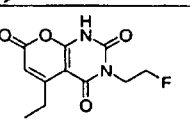
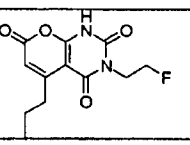
748		286
749		182.5
750		1892.5
751		487
752		248
753		228
754		308
755		286
759		2326
760		10000

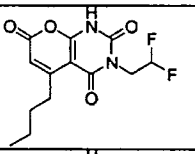
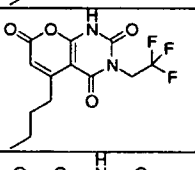
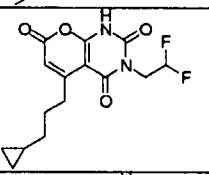
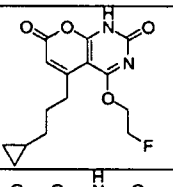
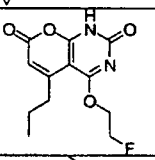
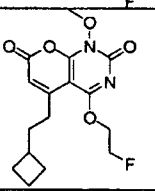
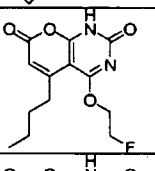
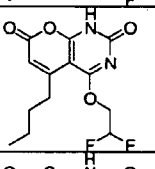
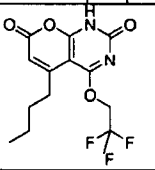
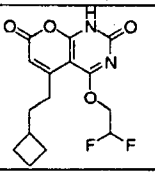
763		7734
764		8922
768		383.5
769		19
770		908
771		17
772		39
773		48.5
774		28.0

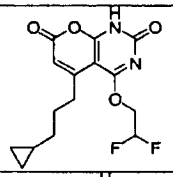
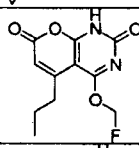
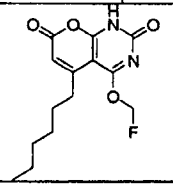
776		10000
777		5600
778		9150
779		2851
780		36
781		68
782		94
783		64
784		17.9

786		5331
787		681.5
788		38.5
789		88
791		50
792		44
796		>10000
797		>1000
798		>10000
799		>10000

800		>10000
801		>10000
802		12
803		3450
804		178
805		2063
806		256
807		>10000
808		>10000
809		187
810		>10000

811		22
812		40
813		256
814		161
815		10000
816		291
817		1450
818		308
819		1536
820		10000

821		142
822		10000
823		10000
824		91
825		616
826		3251
827		690
828		407
829		882
830		112

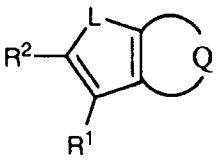
831		531
832		304
833		511

The activity of compounds **834-844** was also determined using the above-described assay and the EC_{50} values measured ranged from about 3 nM to about 1600 nM. Several selected compounds demonstrated EC_{50} values ranging from about 3 nM to about 100 nM.

The activity of several other compounds of the present invention is shown earlier in this specification as A, B or C. It will be appreciated by those skilled in the art that the herein-described inventive compounds exhibit excellent nicotinic acid receptor agonist activity. While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

What is claimed is:

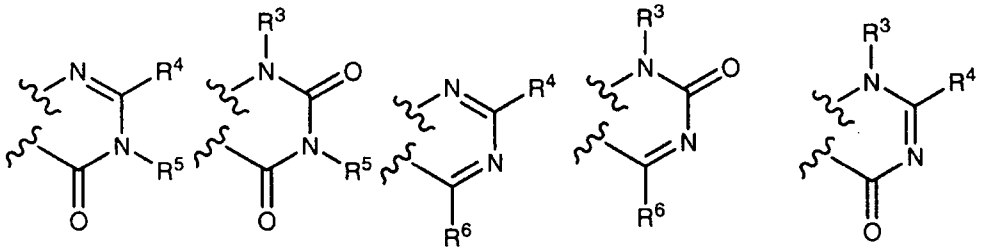
1. A compound having the formula:



(I)

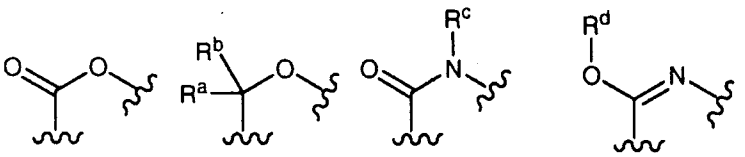
or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is selected from the group consisting of:



(a) , (b) , (c) , (d) and (e) ;

L is selected from the group consisting of:



(f) , (g) , (h) , and (i) ;

R^1 is selected from the group consisting of H, alkyl, arylalkyl, -alkylene-S-alkyl, alkenyl, alkynyl, haloalkyl, wherein an alkyl group can be optionally substituted with one or more of the following groups, which can be the same or different: -OH, cycloalkyl, -C(O)-alkyl, -alkylene-C(O)-O-alkyl, -O-R^{10}, -alkylene-O-alkyl, aryl, -alkylene-aryl, heteroaryl, -alkylene-heteroaryl, halogen, -$(CH_2)_n$-$N(R^7)_2$, -alkylene-cycloalkyl, or -alkylene-cycloalkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^1 is unsubstituted or substituted with one or more X groups, said aryl or the aryl portion of said -alkylene-aryl of R^1 is unsubstituted or substituted with one or more Y groups, and said heteroaryl or the heteroaryl portion

of said –alkylene-heteroaryl of R^1 is unsubstituted or substituted with one or more Y groups;

R^2 is selected from the group consisting of H, halogen, alkyl, haloalkyl, alkyl substituted with one or more -OH, -C(O)-alkyl, -C(O)-O-alkyl, -C(O)-OH, -O-R^{10}, -alkylene-O-alkyl, unsubstituted aryl, aryl substituted with one or more Y groups, unsubstituted heteroaryl, heteroaryl substituted with one or more Y groups, and halogen; or

R^1 and R^2 together with the ring carbon atoms to which they are shown attached, form a 5- or 6-membered cycloalkenyl ring or a 5- or 6-membered heterocyclic ring having 1 or 2 heteroatoms;

R^3 is selected from the group consisting of H, alkyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, alkenyl, aryl, and heteroaryl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^3 is unsubstituted or substituted with one or more X groups, said aryl of R^3 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^3 is unsubstituted or substituted with one or more Y groups;

R^4 is selected from the group consisting of H, halogen, alkyl, haloalkyl, -O-cycloalkyl, -O-alkynyl, -O-R^{10}, -C(O)-O-alkyl, -$S(O)_m$-R^9, -$N(R^7)_2$, -$N(R^7)$-NH-C(O)-alkyl, -$N(R^7)$-NH-C(O)-O-alkyl, -O-N=$C(R^{12})_2$, -$N(R^7)$-N=$C(R^{12})_2$, -C(O)-alkyl, unsubstituted heterocyclyl, heterocyclyl substituted with one or more X groups, -O-$N(R^7)$-C(O)-O-alkyl, -C(O)-$N(R^7)_2$, -CN, -N_3, and -O-C(O)-alkyl;

R^5 is selected from the group consisting of H, alkyl, -OH, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl -alkylene-C(O)-R^8, -alkylene-C(O)-$N(R^{11})_2$, -alkylene-C(=N-O-alkyl)-aryl, cycloalkyl, -alkylene-cycloalkyl, -alkylene-C(O)-O-alkyl, -alkylene-O-C(O)-alkyl, -alkylene-C(O)-heterocyclyl, and alkenyl,

wherein the cycloalkyl or the cycloalkyl portion of said -alkylene-cycloalkyl of R^5 is unsubstituted or substituted with one or more X groups, and the

aryl portion of said -alkylene-C(=N-O-alkyl)-aryl of R^5 is unsubstituted or substituted with one or more Y groups;

R^6 is selected from the group consisting of H, alkyl, alkenyl, alkyl substituted with one or more hydroxyl groups, -alkylene-O-alkyl, -O-R^{10}, halogen, aryl, heteroaryl, and -N(R^7)$_2$,

wherein the aryl of R^6 is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^6 is unsubstituted or substituted with one or more Z groups;

each R^7 is independently selected from the group consisting of H, alkyl, cycloalkyl, aryl, -C(O)-alkyl, and -C(O)-aryl,

wherein the cycloalkyl of R^7 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -C(O)-aryl or said aryl of R^7 is unsubstituted or substituted with one or more Y groups;

two R^7 groups, together with the N atom to which they are bonded form a heterocyclyl;

R^8 is selected from the group consisting of aryl, -OH, and heterocyclyl,

wherein the heterocyclyl of R^8 is unsubstituted or substituted with one or more X groups, and said aryl of R^8 is unsubstituted or substituted with one or more Y groups;

R^9 is selected from the group consisting of alkyl, -alkylene-cycloalkyl, alkenyl, -N(R^{11})$_2$, and -alkylene-aryl,

wherein the cycloalkyl portion of said –alkylene-cycloalkyl of R^9 is unsubstituted or substituted with one or more X groups, and the aryl portion of said -alkylene-aryl of R^9 is unsubstituted or substituted with one or more Y groups, and

with the proviso that when R^9 is -N(R^{11})$_2$, m is 1 or 2;

R^{10} is selected from the group consisting of H, alkyl, cycloalkyl, arylalkyl, haloalkyl, -alkylene-O-alkyl, -alkylene-aryl, -alkenylene-aryl, -alkylene-heteroaryl, alkenyl, -C(O)-alkyl, alkynyl, and -alkylene-cycloalkyl,

wherein an the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl

group; the cycloalkyl portion of said –alkylene-cycloalkyl of R^{10} is unsubstituted or substituted with one or more X groups; the aryl portion of said -alkylene-aryl or -alkenylene-aryl of R^{10} is unsubstituted or substituted with one or more Y groups; and the heteroaryl portion of said -alkylene-heteroaryl of R^{10} is unsubstituted or substituted with one or more Z groups;

R^{11} is selected from the group consisting of H, alkyl, and aryl,

wherein the aryl of R^{11} is unsubstituted or substituted with one or more Y groups; or

two R^{11} groups, together with the N atom to which they are attached, form a heterocyclyl;

each R^{12} is independently selected from the group consisting of alkyl, aryl, and heteroaryl,

wherein the aryl of R^{12} is unsubstituted or substituted with one or more Y groups and said heteroaryl of R^{12} is unsubstituted or substituted with one or more Z groups; or wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group;

R^a and R^b are each independently selected from the group consisting of H, alkyl, aryl, and heteroaryl,

wherein the aryl of R^a and R^b is unsubstituted or substituted with one or more Y groups, and said heteroaryl of R^a and R^b is unsubstituted or substituted with one or more Z groups;

R^c is selected from the group consisting of H, alkyl, alkylene-aryl, and -C(O)-alkyl,

wherein the aryl portion of said alkylene-aryl of R^c is unsubstituted or substituted with one or more Y groups;

R^d is selected from the group consisting of H, alkyl, and alkylene-aryl,

wherein the aryl portion of said alkylene-aryl of R^d is unsubstituted or substituted with one or more Y groups;

each X is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, and -OH;

each Y is independently selected from the group consisting of halogen, alkyl, haloalkyl, -O-alkyl, -O-haloalkyl, -CN, $-NO_2$, -OH, $-S(O_2)$-alkyl, $-S(O_2)$-aryl,

$-S(O_2)-NH_2$, $-S(O_2)-NH$-alkyl, $-S(O_2)-NH$-aryl, $-S(O_2)-N(alkyl)_2$, $-S(O_2)-N(aryl)_2$, $-S(O_2)-N(alkyl)(aryl)$, and aryl;

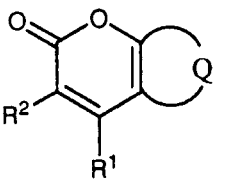
each Z is independently selected from the group consisting of alkyl, haloalkyl, halogen, -O-alkyl, -O-haloalkyl, -CN, -OH, aryl, and N-oxide;

n is 0, 1, 2, or 3;

m is 0, 1, or 2; and

with the proviso that when L is (f), and R^2, R^3 and R^5 are each H, then R^1 is not $-CH_3$.

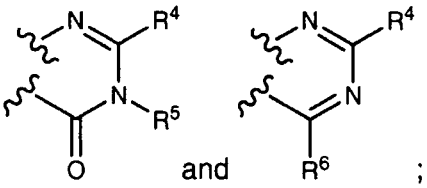
2. The compound of claim 1, having the formula:



(II)

or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

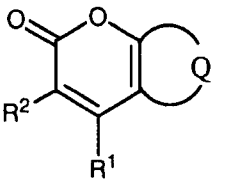
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-$N=C(R^{12})_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

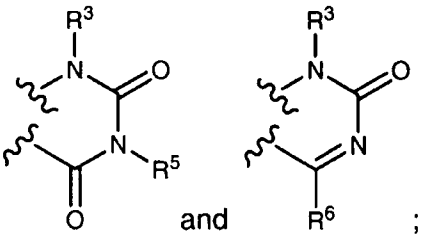
3. The compound of claim 1, having the formula:



(III)

or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof, wherein:

Q is selected from the group consisting of:



;

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

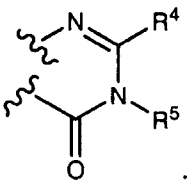
R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

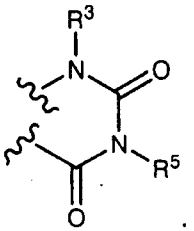
R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

4. The compound of claim 1, wherein Q is:



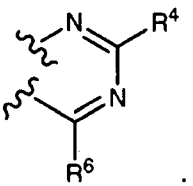
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5. The compound of claim 1, wherein Q is:

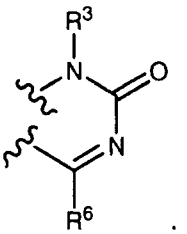


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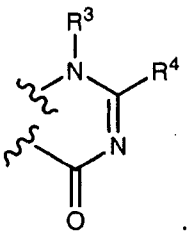
6. The compound of claim 1, wherein Q is:



7. The compound of claim 1, wherein Q is:



8. The compound of claim 1, wherein Q is:



9. The compound of claim 1, wherein

R^1 is –H, alkyl, haloalkyl, arylalkyl, -alkylene-S-alkyl or -alkylene-cycloalkyl;

R^2 is –H, -CN, or -NHC(O)-alkyl;

R^3 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl;

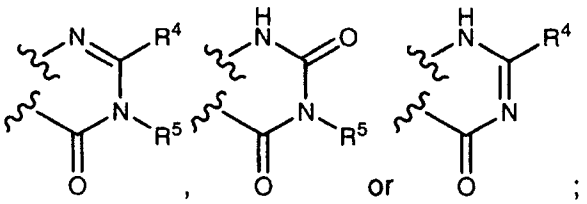
R^4 is -O-cycloalkyl, –O-alkynyl, -O-alkynylene-cycloalkyl, haloalkyl or –O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group, and wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy; and wherein the cycloalkyl portion of an –O-cycloalkyl group can be optionally substituted with an –alkylene-O-alkylene-aryl group; and

R^5 is –H, -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl; and

R^6 is alkoxy, -O-alkylene-O-alkyl, -O-arylalkyl or –O-haloalkyl.

10. The compound of claim 9, wherein

Q is:

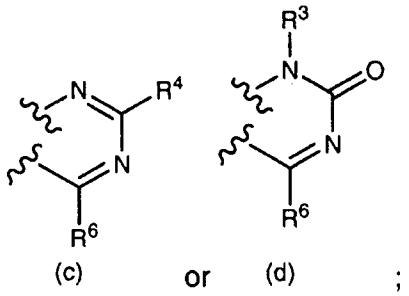


;

R^1 is alkyl, haloalkyl or -alkylene-cycloalkyl; R^2 is –H; and R^5 is –H or alkyl.

11. The compound of claim 9, wherein

Q is:

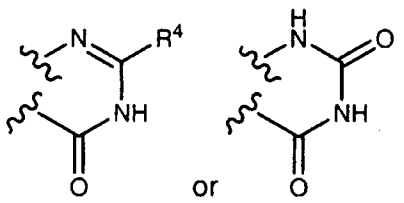


(c) or (d) ;

R^1 is alkyl, haloalkyl or -alkylene-cycloalkyl; and R^2 is –H.

12. The compound of claim 10, wherein

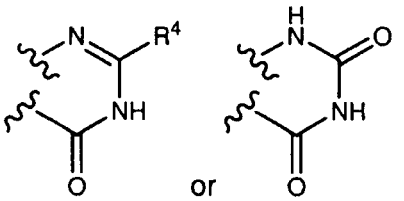
Q is:



and R^4 is –O-alkynyl or -O-alkynylene-cycloalkyl, wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy.

13. The compound of claim 10, wherein

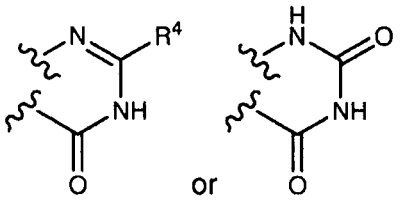
Q is:



and R^4 is haloalkyl.

14. The compound of claim 10, wherein

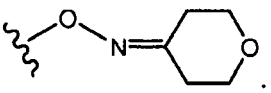
Q is:



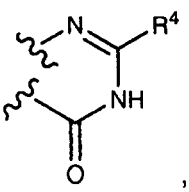
and R^4 is -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

15. The compound of claim 13, wherein R^4 is $-CH_2F$ or $-CH(F)_2$.

16. The compound of claim 14, wherein R^4 is:



17. The compound of claim 2, wherein Q is:



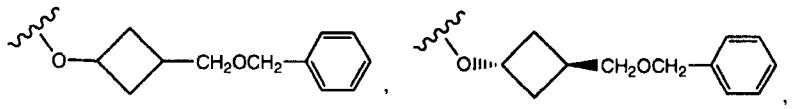
R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl, and R^2 is –H.

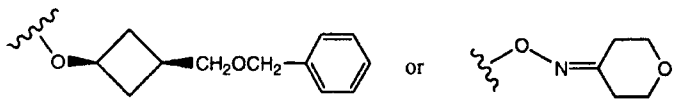
18. The compound of claim 17, wherein R^4 is –O-alkynyl or -O-alkynylene-cycloalkyl, wherein the alkynyl portion of an –O-alkynyl group can be optionally subsituted with –OH or alkoxy.

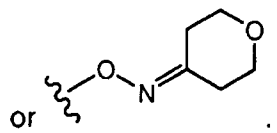
19. The compound of claim 17, wherein R^4 is haloalkyl.

20. The compound of claim 17, wherein R^4 is -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

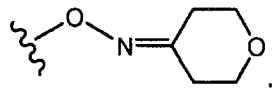
21. The compound of claim 17, wherein R^4 is –CH_2F, –$CH(F)_2$, –CF_3, –$OCH_2C{\equiv}CCH_2CH_3$, –$OCH_2C{\equiv}C(CH_2)_3CH_3$, –$OCH_2C{\equiv}CCH_2CH_2CH_3$, –$OCH_2C{\equiv}C$-cyclopropyl, –$OCH_2C{\equiv}CCH(OCH_3)CH_3$, –$OCH_2C{\equiv}CCH(OH)CH_3$, –$OCH_2C{\equiv}CCH(OH)CH_2CH_3$,–$OCH_2C{\equiv}CCH_2CH_2OCH_3$, –$OCH_2C{\equiv}CCH_2CH_2OH$, –$OCH_2C{\equiv}C(CH_2)_3OH$, –$OCH(CH_3)C{\equiv}CCH_2CH_3$, –$OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,



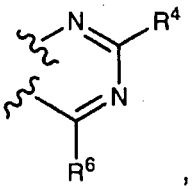




22. The compound of claim 21, wherein R^4 is –CH_2F, –$CH(F)_2$ or

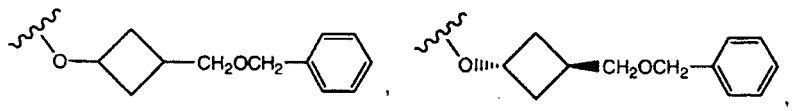


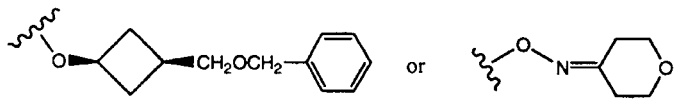
23. The compound of claim 2, wherein Q is:

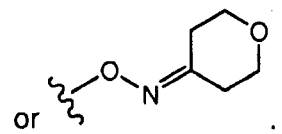


R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl, and R^2 is –H.

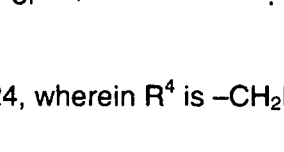
24. The compound of claim 23, wherein R^4 is $-CH_2F$, $-CH(F)_2$, $-CF_3$, $-OCH_2C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C(CH_2)_3CH_3$, $-OCH_2C{\equiv}CCH_2CH_2CH_3$, $-OCH_2C{\equiv}C$-cyclopropyl, $-OCH_2C{\equiv}CCH(OCH_3)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$,$-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,



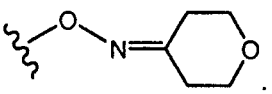




or



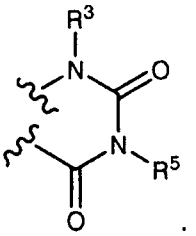
25. The compound of claim 24, wherein R^4 is $-CH_2F$, $-CH(F)_2$ or



26. The compound of claim 24, wherein R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

27. The compound of claim 24, wherein R^1 is $-(CH_2)_3$-cyclopropyl or $-(CH_2)_2$cyclobutyl.

28. The compound of claim 3, wherein Q is:



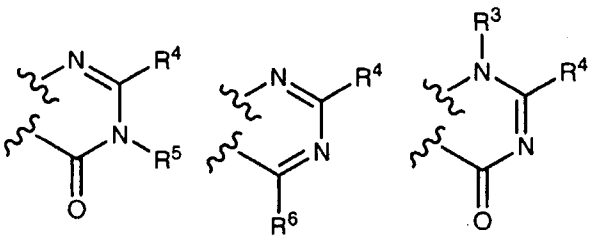
29. The compound of claim 28, wherein R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl; and R^2, R^3 and R^5 are each –H.

30. The compound of claim 28, wherein R^1 is alkyl, haloalkyl, or -alkylene-cycloalkyl; R^2 is –H and one, but not both of R^3 and R^5 are –H.

31. The compound of claim 29, wherein R^1 is a straight chain alkyl having from 1 to 6 carbon atoms.

32. The compound of claim 1, wherein

Q is:



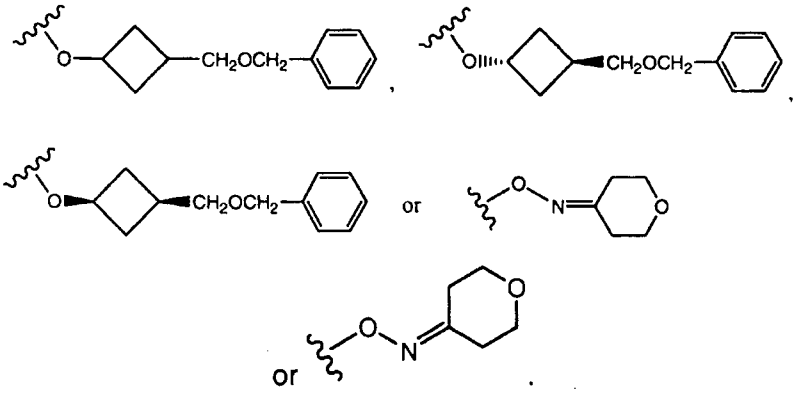
(a) (c) or (e) ,

R^1 is alkyl or -alkylene-cycloalkyl and R^2 is –H.

33. The compound of claim 32, wherein R^4 is haloalkyl or -O-N=C(R^{12})$_2$, wherein both R^{12} groups, together with the carbon atom to which they are attached, combine to form a heterocyclyl group.

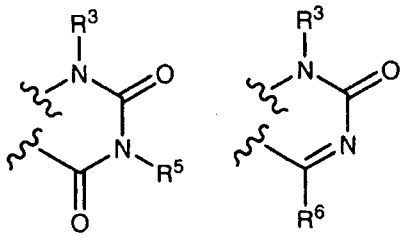
34. The compound of claim 33, wherein R^4 is $-CH_2F$ or $-CH(F)_2$.

35. The compound of claim 30, wherein R^1 is methyl, ethyl, n-butyl, n-phenyl, -$(CH_2)_3$-cyclopropyl or $-(CH_2)_2$-cyclobutyl, R^2 is –H, and R^4 is $-CH_2F$, $-CH(F)_2$, $-CF_3$, $-OCH_2C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C(CH_2)_3CH_3$, $-OCH_2C{\equiv}CCH_2CH_2CH_3$,$-OCH_2C{\equiv}C$-cyclopropyl, $-OCH_2C{\equiv}CCH(OCH_3)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$, $-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C$-cyclohexyl, –O-cyclobutyl,



36. The compound of claim 1, wherein

Q is:



(b) or (d) ,

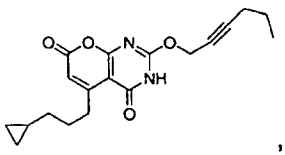
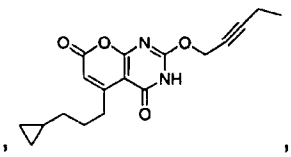
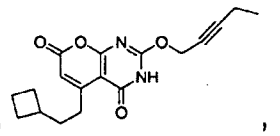
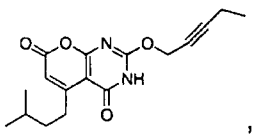
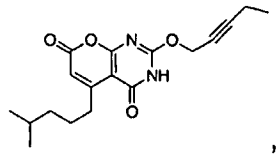
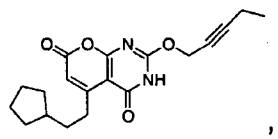
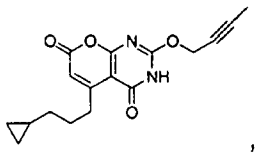
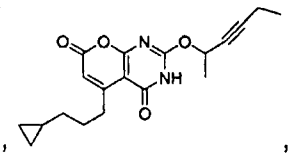
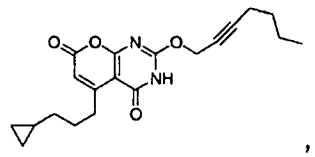
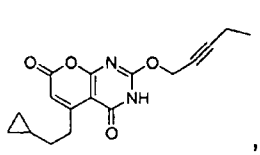
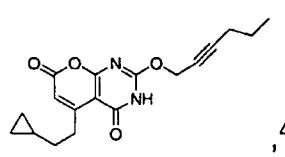
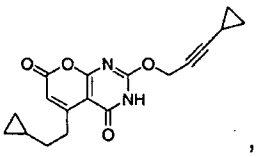
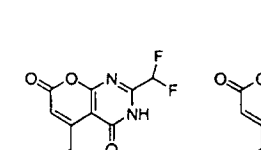
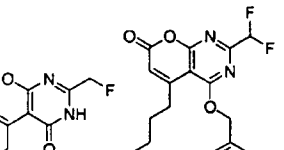
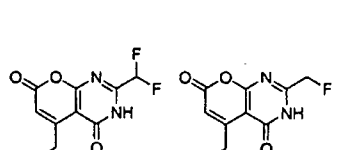
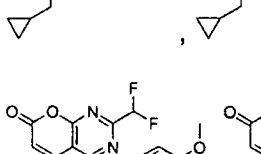
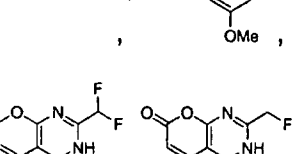
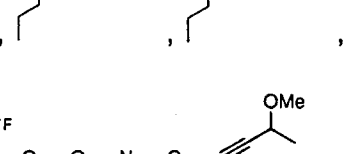
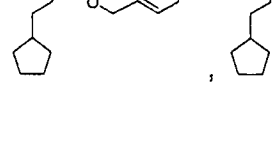
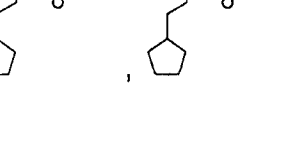
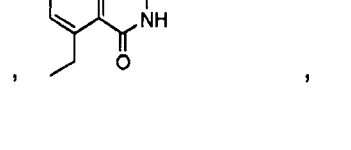
R^1 is alkyl or -alkylene-cycloalkyl and R^2 is –H.

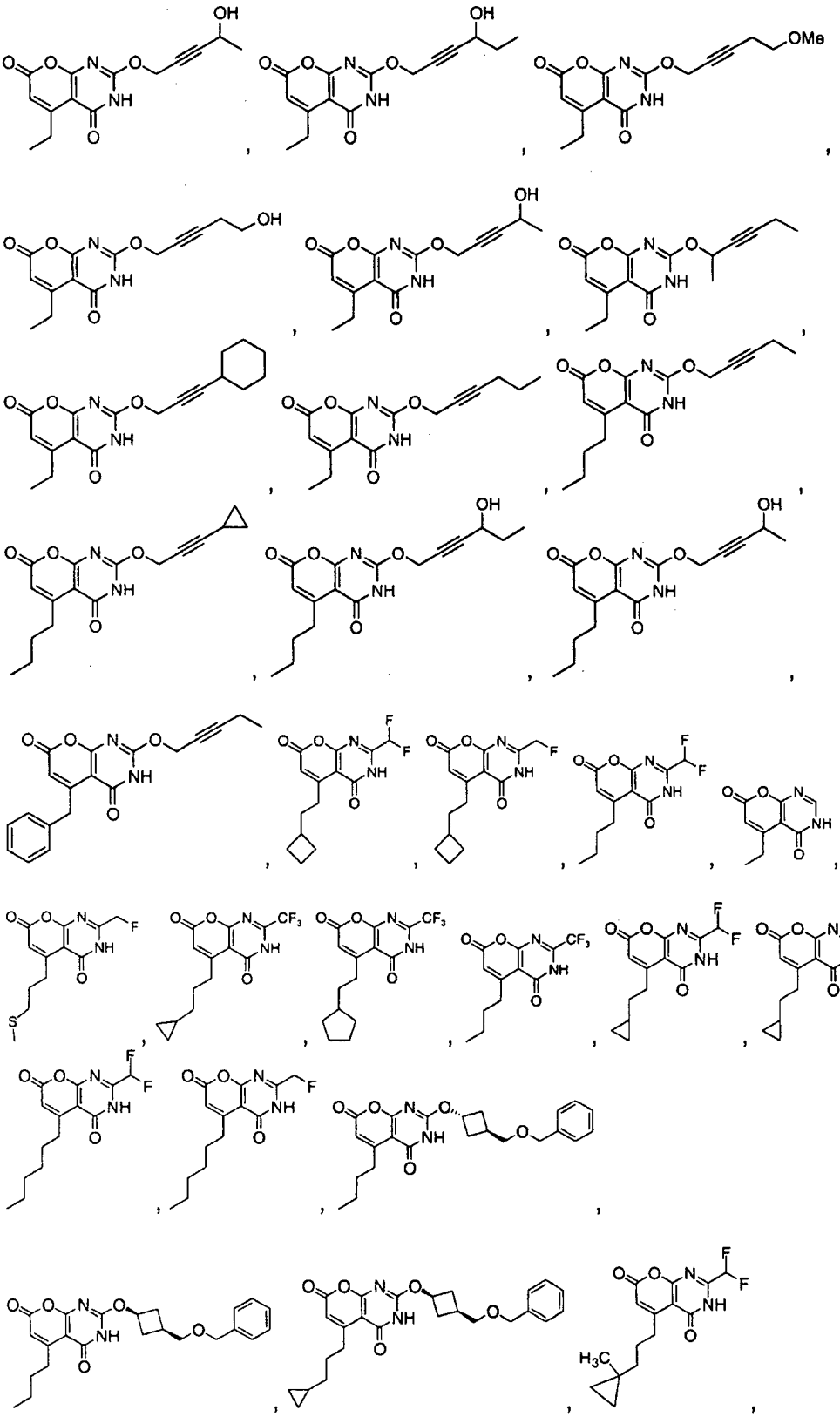
37. The compound of claim 36, wherein one, but not both, of R^3 and R^5 is –H.

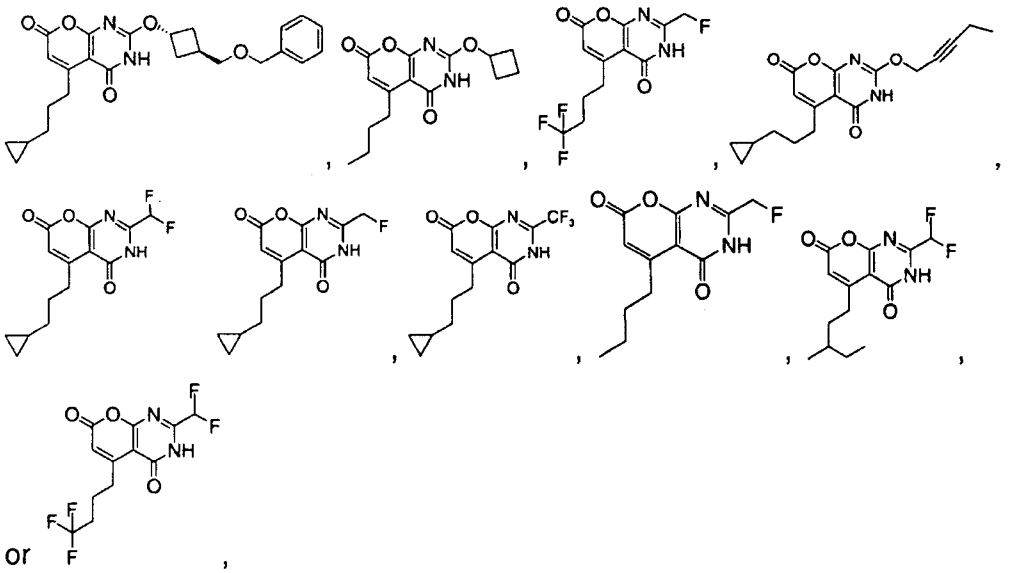
38. The compound of claim 37, wherein one of R^3 and R^5 is –H and the other is -OH, alkyl, haloalkyl, arylalkyl, -O-alkyl, -O-aryl, cycloalkyl, heterocyclyl, -O-cycloalkyl, -O-heterocyclyl, -O-arylalkyl or -alkylene-O-alkyl.

39. The compound of claim 38, wherein one of R^3 and R^5 is –H and the other is –OCH_3, cyclobutyl, ethyl, *N*-morpholinyl, –O-benzyl, –$CH_2CH_2OCH_3$, –OCH_2CH_3, –CH_2F, –CH_2CH_2F or –OH.

40. A compound having the structure:

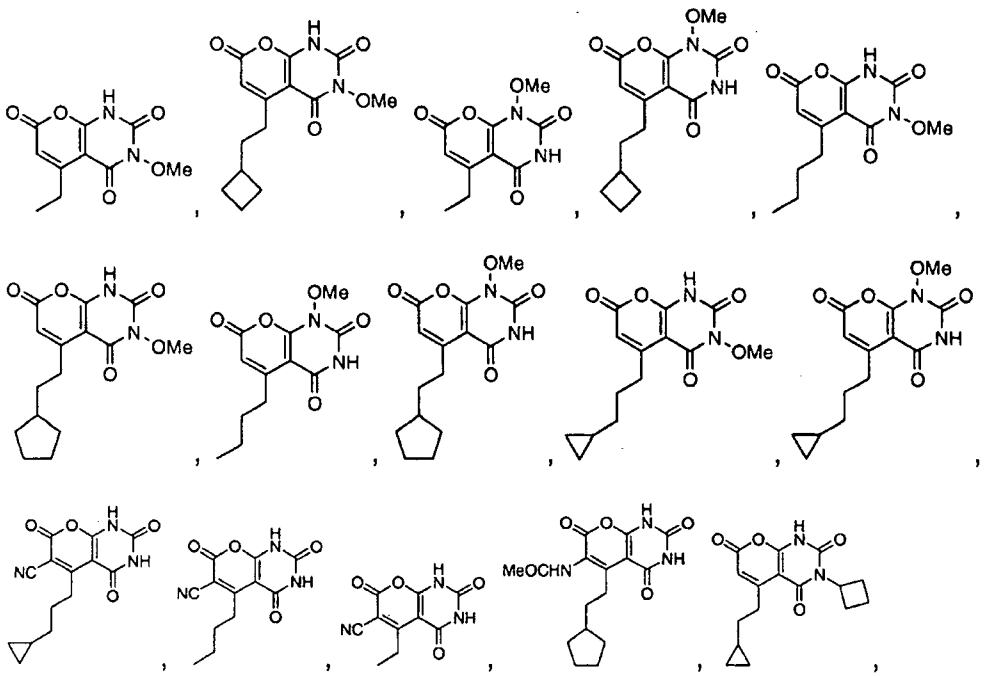






















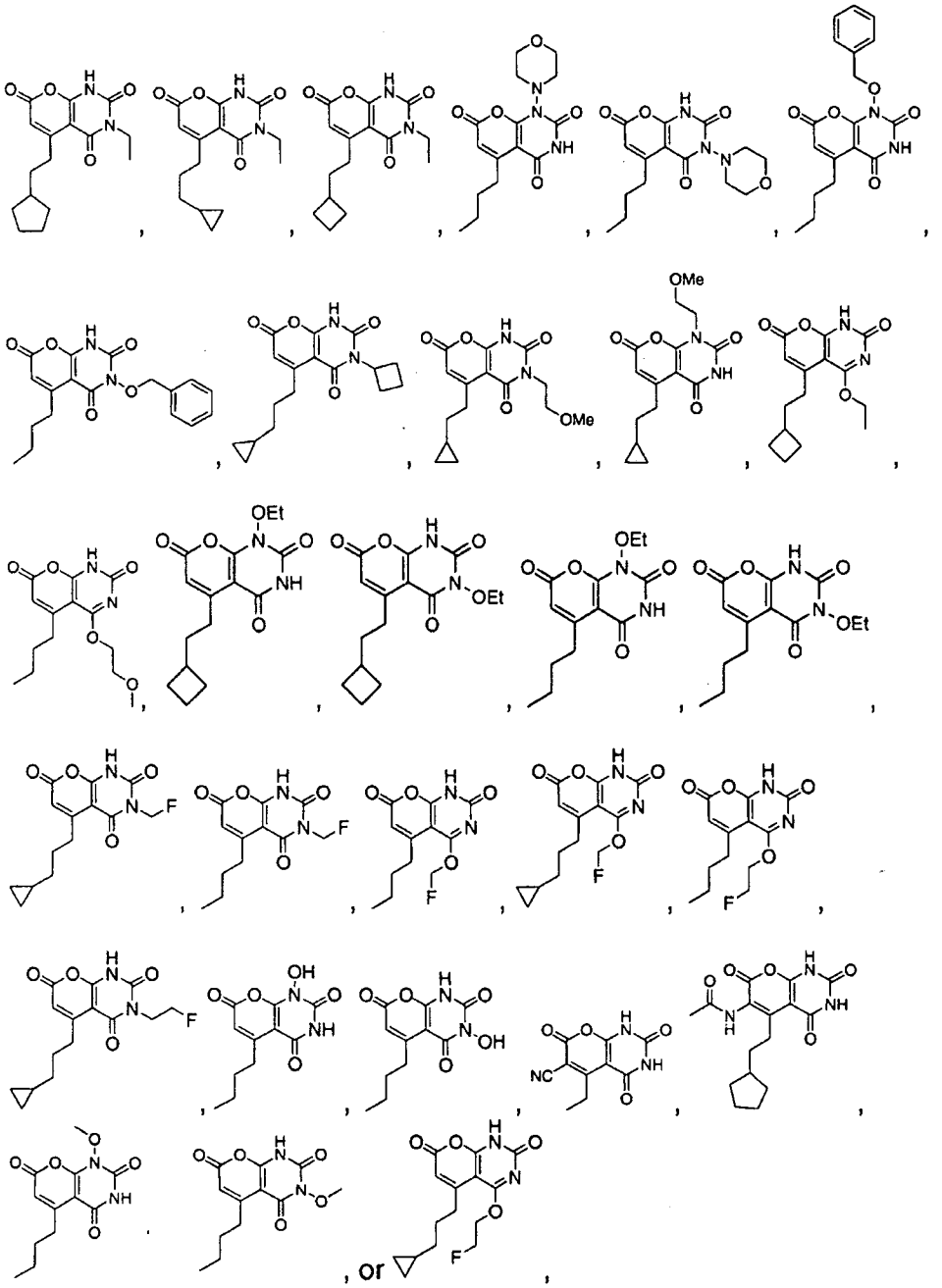




or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

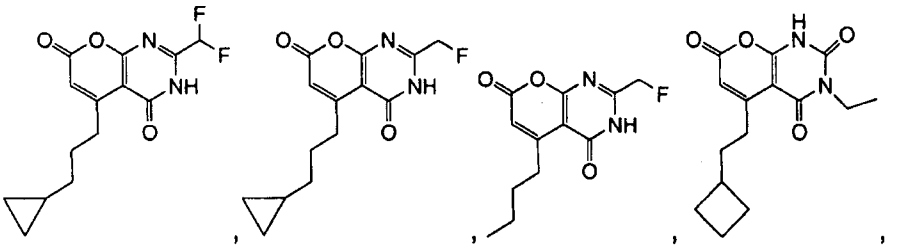
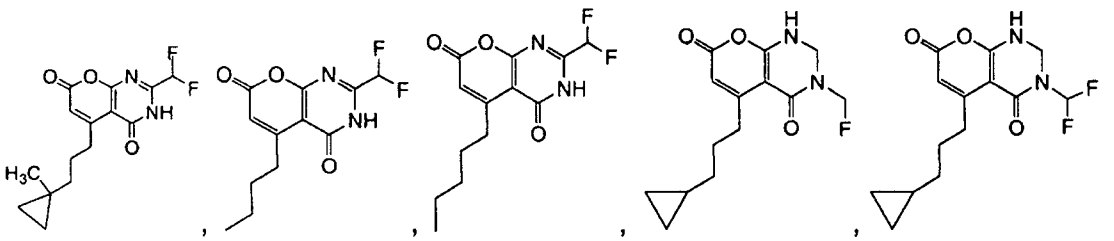
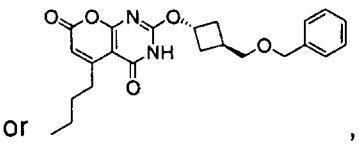
41. A compound having the structure:





or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

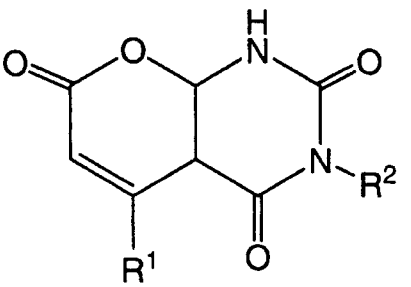
42. A compound having the structure:

or

or a pharmaceutically acceptable salt, solvate, ester, or tautomer thereof.

43. A compound having the formula:



(IV)

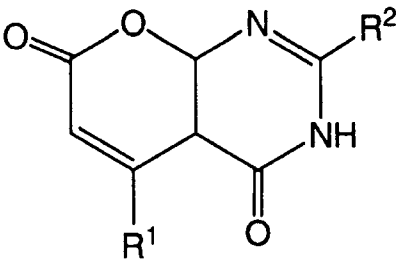
or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 is haloalkyl; and

R^2 is H or cycloalkyl.

44. A compound having the formula:



(V)

or a pharmaceutically acceptable salt or solvate thereof,

wherein:

R^1 and R^2 are each, independently, haloalkyl.

45. The compound of claim 43, wherein R^1 is fluoroalkyl.

46. The compound of claim 44, wherein R^1 is –alkylene-CF_2.

47. The compound of claim 44, wherein R^1 is –alkylene-F.

48. The compound of claim 46, wherein R^1 is $-(CH_2)_3-CF_2$, $-(CH_2)_4-CF_2$ or $-(CH_2)_5-CF_2$.

49. The compound of claim 43, wherein R^2 is H.

50. The compound of claim 43, wherein R^2 is cycloalkyl.

51. The compound of claim 50, wherein R^2 is cyclobutyl.

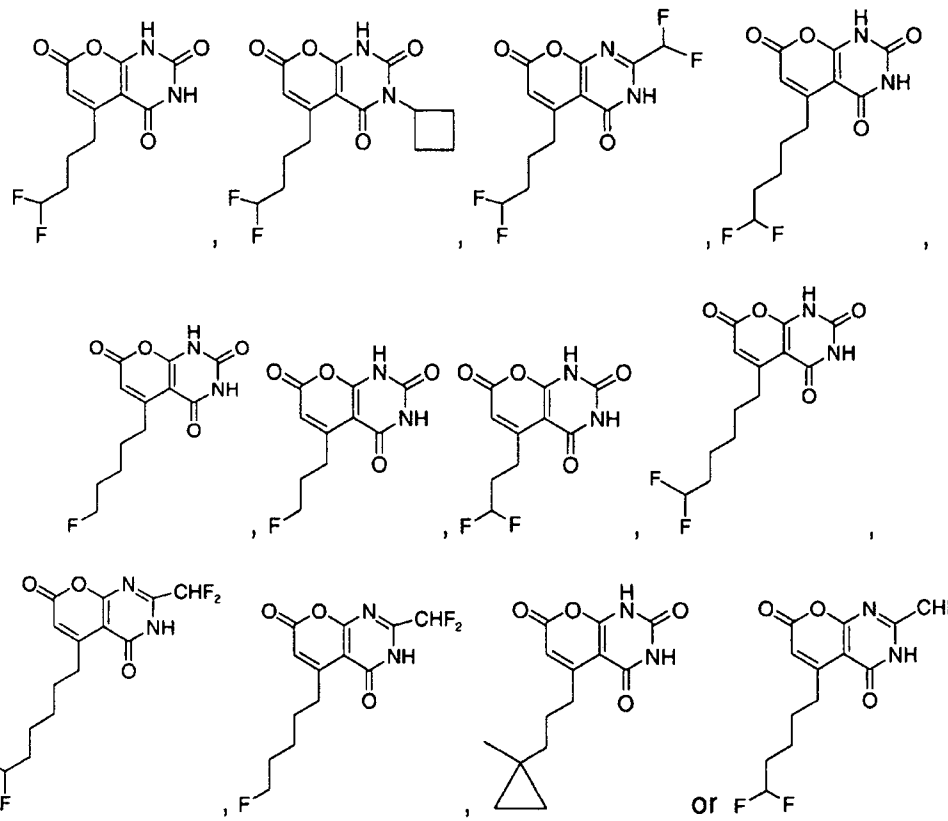
52. The compound of claim 44, wherein R^2 is H.

53. The compound of claim 45, wherein R^2 is H.

54. The compound of claim 44, wherein R^2 is cycloalkyl.

55. The compound of claim 45, wherein R^2 is cycloalkyl.

56. A compound having the structure:



or a pharmaceutically acceptable salt or solvate thereof.

57. A composition comprising at least one compound of claim 1 and a pharmaceutically acceptable carrier.

58. A composition comprising at least one compound of claim 40 and a pharmaceutically acceptable carrier.

59. A composition comprising at least one compound of claim 41 and a pharmaceutically acceptable carrier.

60. A composition comprising at least one compound of claim 42 and a pharmaceutically acceptable carrier.

61. A composition comprising at least one compound of claim 43 and a pharmaceutically acceptable carrier.

62. A composition comprising at least one compound of claim 44 and a pharmaceutically acceptable carrier.

63. A composition comprising at least one compound of claim 56 and a pharmaceutically acceptable carrier.

64. The composition of any one of claims 57-63, further comprising at least one additional therapeutic agent selected from the group consisting of anti-flushing agents, hydroxy-substituted azetidinone compounds, substituted β-lactam compounds, HMG CoA reductase inhibitor compounds, HMG CoA synthetase inhibitors, squalene synthesis inhibitors, squalene epoxidase inhibitors, sterol biosynthesis inhibitors, nicotinic acid derivatives, bile acid sequestrants, aspirin, NSAID agents, Vytorin®, ezetimibe, inorganic cholesterol sequestrants, AcylCoA:Cholesterol *O*-acyltransferaseinhibitors, cholesteryl ester transfer protein inhibitors, fish oils containing Omega 3 fatty acids, natural water soluble fibers, plant stanols and/or fatty acid esters of plant stanols, anti-oxidants, PPAR α agonists, PPAR γ-agonists, FXR receptor modulators, LXR receptor agonists, lipoprotein synthesis inhibitors, renin angiotensin inhibitors, microsomal triglyceride transport inhibitors, bile acid reabsorption inhibitors, PPAR δ agonists, triglyceride synthesis inhibitors, squalene epoxidase inhibitors, low density lipoprotein receptor inducers or activators, platelet aggregation inhibitors, 5-LO or FLAP inhibitors, PPAR δ partial agonists, niacin or niacin receptor agonists, 5HT transporter inhibitors, NE transporter inhibitors, CB_1 antagonists/inverse agonists, ghrelin antagonists, H_3 antagonists/inverse agonists, MCH1R antagonists, MCH2R agonists/antagonists, NPY1 antagonists, NPY5 antagonists, NPY2 agonists, NPY4 agonists, mGluR5 antagonists, leptins, leptin agonists/modulators, leptin derivatives, opioid antagonists, orexin receptor

antagonists, BRS3 agonists, CCK-A agonists, CNTF, CNTF derivatives, CNTF agonists/modulators, 5HT2c agonists, Mc4r agonists, monoamine reuptake inhibitors, serotonin reuptake inhibitors, GLP-1 mimetics, phentermine, topiramate, phytopharm compound 57, ghrelin antibodies, Mc3r agonists, ACC inhibitors, β3 agonists, DGAT1 inhibitors, DGAT2 inhibitors, FAS inhibitors, PDE inhibitors, thyroid hormone β agonists, UCP-1 activators, UCP-2 activators, UCP-3 activators, acyl-estrogens, glucocorticoid agonists/antagonists, 11β HSD-1 inhibitors, SCD-1 inhibitors, lipase inhibitors, fatty acid transporter inhibitors, dicarboxylate transporter inhibitors, glucose transporter inhibitors, phosphate transporter inhibitors, antidiabetic agents, anti-hypertensive agents, anti-dyslipidemic agents, DPP-IV inhibitors, apolipoprotein-B secretion/microsomal triglyceride transfer protein (apo-B/MTP) inhibitors, sympathomimetic agonists, dopamine agonists, melanocyte-stimulating hormone receptor analogs, melanin concentrating hormone antagonists, leptons, galanin receptor antagonists, bombesin agonists, neuropeptide-Y antagonists, thyromimetic agents, dehydroepiandrosterone, analogs of dehydroepiandrosterone, urocortin binding protein antagonists, glucagons-like peptide-1 receptor agonists, human agouti-related proteins (AGRP), neuromedin U receptor agonists, noradrenergic anorectic agents, appetite suppressants, hormone sensitive lipase antagonists, MSH-receptor analogs, α-glucosidase inhibitors, apo A1 milano reverse cholesterol transport inhibitors, fatty acid binding protein inhibitors (FABP), and fatty acid transporter protein inhibitors (FATP).

65. The composition of claim 64, wherein the at least one additional therapeutic agent is an HMG CoA reductase inhibitor selected from the group consisting of lovastatin, simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rivastatin, rosuvastatin calcium, and pitavastatin.

66. The composition of claim 65, wherein the at least one additional therapeutic agent is simvastatin.

67. The composition of claim 64, wherein the at least one additional therapeutic agent is a cholesteryl ester transfer protein inhibitor.

68. The composition of claim 67, wherein the at least one additional therapeutic agent is an anti-flushing agent.

69. The composition of claim 64, wherein the at least one additional therapeutic agent is Vytorin®, ezetimibe, aspirin, ibuprofen or acetaminophen or a combination thereof.

70. The composition of claim 64, wherein the at least one additional therapeutic agent is DPP-IV inhibitor or a GLP-1 mimetic.

COMPUESTOS HETEROCÍCLICOS QUE CONTIENEN NITRÓGENO Y MÉTODOS DE USO DE LOS MISMOS

Área de la invención

La presente invención se refiere a compuestos agonistas del receptor del ácido nicotínico útiles para el tratamiento de síndrome metabólico, dislipidemia, enfermedades cardiovasculares, trastornos del sistema nervioso central y periférico, enfermedades hematológicas, cáncer, inflamación, enfermedades respiratorias, enfermedades gastroenterológicas, diabetes y enfermedad de hígado graso no alcohólico; composiciones farmacéuticas que comprenden tales compuestos; composiciones farmacéuticas que comprenden compuestos agonistas del receptor del ácido nicotínico en combinación con otros agentes terapéuticos; y métodos de tratamiento utilizando los compuestos y composiciones para tratar afecciones tales como síndrome metabólico, dislipidemia, enfermedades cardiovasculares, trastornos del sistema nervioso central y periférico, enfermedades hematológicas, cáncer, inflamación, enfermedades respiratorias, enfermedades gastroenterológicas, diabetos, esteatosis hepática y enfermedad de hígado graso no alcohólico.

Antecedentes de la invención

Se ha estado utilizando el ácido nicotínico para tratar el síndrome metabólico y dislipidemia. De todos modos, el ácido nicotínico tiene efectos colaterales indeseables tales como rubor y diarrea. Es por lo tanto deseable proveer agonistas mejorados del receptor del ácido nicotínico que son más efectivos para el síndrome metabólico y la dislipidemia, aunque sin los efectos colaterales no deseados. Los compuestos de la presente invención proveen tales agonistas mejoradas del receptor del ácido nicotínico.

M. Ridi, Gazzetta Chim. Ital. (1950) vol. 80, p. 121 y M. Ridi, Gazzetta Chim. Ital. (1952) vol. 82, p. 23 revela la síntesis de derivados de ácido barbitúrico. En la FR 2563223 se revelan análogos de nucleótidos. T. Paterson et al., J. Chem. Soc., Perkins Trans. I (1972), vol. 8, pp. 1041-1050 revelan la síntesis de pirido[2,3-d]pirimidinas 8-sustituídas. Rao, Indian J. Chem. (1974), 12(10), pp. 1028-1030 revela la síntesis de pirano[2,3-d]pirimidinas. M. Skof, Heterocicles, (1999), 51(5), pp. 1051-1058 revela transformaciones en etapas de (S)-1-benzoil-3-[(E)-dimetilaminometiliden]-5-metoxicarbonil-pirrolidin-2-ona en derivados de alanina sustituidos con quinolizinilo y 2H-2-piranonilo. R. Toplak J. Heterociclic Chem. (1999), 36(1), pp. 225-235 revela la síntesis de piran-2-onas. De todos modos, los compuestos de las referencias anteriores difieren de aquellos de la presente invención.

WO 2004/110368 describe terapias combinadas para el tratamiento de hipertensión que comprende la combinación de un agente antiobesidad y un agente antihipertensivo. De todos modos, en la WO 2004/110368 no se describen agonistas del receptor del ácido nicotínico o combinaciones de uno o más agonistas del receptor del ácido nicotínico con un segundo agente terapéutico.

WO 2005/000217 describe terapias combinadas para el tratamiento de dislipidemia que comprende la administración de una combinación de un agente antiobesidad y un agente antidislipidémico. De todos modos, en la WO 2005/000217 no se describen agonistas del receptor del ácido nicotínico o combinaciones de uno o más agonistas del receptor del ácido nicotínico con un segundo agente terapéutico.

WO 2004/110375 describe terapias combinadas para el tratamiento de diabetes que comprende la administración de una combinación de un agente antiobesidad y un agente antidiabético. De todos modos, en la WO 2004/110375 no se describen agonistas del receptor del ácido nicotínico, o combinaciones de

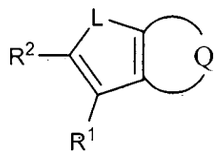
uno o más agonistas del receptor del ácido nicotínico con un segundo agente terapéutico.

La US 2004/0122033 describe terapias combinadas para el tratamiento de obesidad que comprende la administración de una combinación de un supresor de apetito y/o intensificadores de la velocidad del metabolismo y/o inhibidores de la absorción de nutrientes. De todos modos, en la US 2004/0122033 no se describen agonistas del receptor del ácido nicotínico, o combinaciones de uno o más agonistas del receptor del ácido nicotínico con un segundo agente terapéutico. En la US 2004/0229844 se describen terapias combinadas para el tratamiento de ateroesclerosis que comprende la administración de una combinación del ácido nicotínico u otro agonista del receptor del ácido nicotínico y un antagonista del receptor DP. De todos modos, Los agonistas del ácido nicotínico de US 2004/0229844 son bastante diferentes de aquellos de la presente invención.

En la WO2005/077950 se describen derivados de xantina que son agonistas del receptor del ácido nicotínico HM74A. De todos modos, los derivados de xantina de la WO2005/077950 son bastante diferentes de los compuestos de la presente invención.

Síntesis de la invención

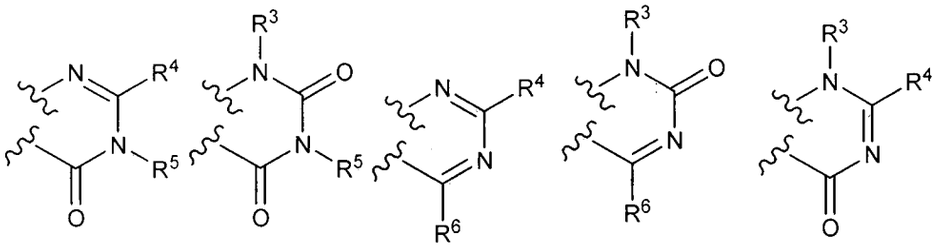
En una realización, la presente invención está dirigida a un compuesto de fórmula (I):



(I)

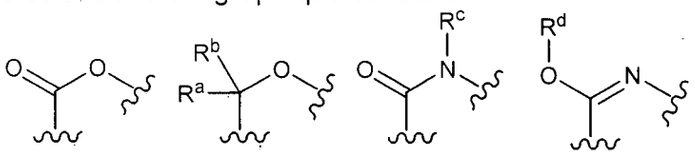
y sales aceptables para uso farmacéutico, solvatos, ésteres y tautómeros de los mismos, donde:

Q se seleccionó del grupo que consta de:



(a) , (b) , (c) , (d) y (e) ;

L se seleccionó del grupo que consta de:



(f) , (g) , (h) y (i) ;

R^1 se seleccionó del grupo que consta de H, alquilo, arilalquilo, -alquilen-S-alquilo, alquenilo, alquinilo, haloalquilo, donde un grupo alquilo puede estar sustituido con uno o más de los siguientes grupos, que pueden ser iguales o diferentes: -OH, cicloalquilo, -C(O)-alquilo, -alquilen-C(O)-O-alquilo, -O-R^{10}, -alquilen-O-alquilo, arilo, -alquilen-arilo, heteroarilo, -alquilen-heteroarilo, halógeno, -$(CH_2)_n$-$N(R^7)_2$, -alquilen-cicloalquilo, o -alquilen-cicloalquenilo,

donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^1 no está sustituida o está sustituida con uno o más grupos X, dicho arilo o la porción arilo de dicho -alquilen-arilo de R^1 no está sustituida o está sustituida con uno o más grupos Y y dicho heteroarilo o la porción heteroarilo de dicho –alquilen-heteroarilo de R^1 no está sustituida o está sustituida con uno o más grupos Y;

R^2 se seleccionó del grupo que consta de H, halógeno, alquilo, haloalquilo, alquilo sustituido con uno o más -OH, -C(O)-alquilo, -C(O)-O-alquilo, -C(O)-OH, -O-R^{10}, -alquilen-O-alquilo, arilo no sustituido, arilo sustituido con uno o más grupos Y, heteroarilo no sustituido, heteroarilo sustituido con uno o más grupos Y y halógeno; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo cicloalquenilo de 5 o 6 miembros o un anilo heterocíclico de 5 o 6 miembros que presenta 1 o 2 heteroátomos;

R^3 se seleccionó del grupo que consta de H, alquilo, alquilo sustituido con uno o más grupos hidroxilo, -alquilen-O-alquilo, cicloalquilo, -alquilen-cicloalquilo, -alquilen-C(O)-O-alquilo, -alquilen-O-C(O)-alquilo, alquenilo, arilo y heteroarilo,

donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^3 no está sustituida o está sustituida con uno o más grupos X, dicho arilo de R^3 no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo de R^3 no está sustituido o está sustituido con uno o más grupos Y;

R^4 se seleccionó del grupo que consta de H, halógeno, alquilo, haloalquilo, -O-cicloalquilo, -O-alquinilo, $-O-R^{10}$, -C(O)-O-alquilo, $-S(O)_m-R^9$, $-N(R^7)_2$, $-N(R^7)$-NH-C(O)-alquilo, $-N(R^7)$-NH-C(O)-O-alquilo, $-O-N=C(R^{12})_2$, $-N(R^7)-N=C(R^{12})_2$, -C(O)-alquilo, heterociclilo no sustituido, heterociclilo sustituido con uno o más grupos X, $-O-N(R^7)$-C(O)-O-alquilo, $-C(O)-N(R^7)_2$, -CN, $-N_3$ y -O-C(O)-alquilo;

R^5 se seleccionó del grupo que consta de H, alquilo, -OH, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo -alquilen-$C(O)-R^8$, -alquilen-$C(O)-N(R^{11})_2$, -alquilen-C(=N-O-alquil)-arilo, cicloalquilo, -alquilen-cicloalquilo, -alquilen-C(O)-O-alquilo, -alquilen-O-C(O)-alquilo, -alquilen-C(O)-heterociclilo y alquenilo,

donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^5 no está sustituida o está sustituida con uno o más grupos X y la porción arilo de dicho -alquilen-C(=N-O-alquil)-arilo de R^5 no está sustituido o está sustituido con uno o más grupos Y;

R^6 se seleccionó del grupo que consta de H, alquilo, alquenilo, alquilo sustituido con uno o más grupos hidroxilo, -alquilen-O-alquilo, -O-R^{10}, halógeno, arilo, heteroarilo y -N(R^7)$_2$,

donde el arilo de R^6 no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo de R^6 no está sustituido o está sustituido con uno o más grupos Z;

cada R^7 es seleccionado de manera independiente del grupo que consta de H, alquilo, cicloalquilo, arilo, -C(O)-alquilo y -C(O)-arilo,

donde el cicloalquilo de R^7 no está sustituido o está sustituido con uno o más grupos X y la porción arilo de dicho -C(O)-arilo o dicho arilo de R^7 no está sustituida o está sustituida con uno o más grupos Y;

dos grupos R^7 grupos, junto con el átomo N al que están unidos forman un heterociclilo;

R^8 se seleccionó del grupo que consta de arilo, -OH y heterociclilo,

donde el heterociclilo de R^8 no está sustituido o está sustituido con uno o más grupos X y dicho arilo de R^8 no está sustituido o está sustituido con uno o más grupos Y;

R^9 se seleccionó del grupo que consta de alquilo, -alquilen-cicloalquilo, alquenilo, -N(R^{11})$_2$ y -alquilen-arilo,

donde la porción cicloalquilo de dicho –alquilen-cicloalquilo de R^9 no está sustituida o está sustituida con uno o más grupos X y la porción arilo de dicho -alquilen-arilo de R^9 no está sustituida o está sustituida con uno o más grupos Y y

con la salvedad que cuando R^9 es -N(R^{11})$_2$, m es 1 o 2;

R^{10} se seleccionó del grupo que consta de H, alquilo, cicloalquilo, arilalquilo, haloalquilo, -alquilen-O-alquilo, -alquilen-arilo, -alquenilen-arilo, -alquilen-heteroarilo, alquenilo, -C(O)-alquilo, alquinilo y -alquilen-cicloalquilo,

donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con –OH o alcoxi; la porción cicloalquilo de un grupo -O-cicloalquilo

puede estar sustituida de manera opcional con un grupo -alquilen-O-alquilen-arilo; la porción cicloalquilo de dicho –alquilen-cicloalquilo de R^{10} no está sustituida o está sustituida con uno o más grupos X; la porción arilo de dicho -alquilen-arilo o -alquenilen-arilo de R^{10} no está sustituida o está sustituida con uno o más grupos Y; y la porción heteroarilo de dicho -alquilen-heteroarilo de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

R^{11} se seleccionó del grupo que consta de H, alquilo y arilo,

donde el arilo de R^{11} no está sustituido o está sustituido con uno o más grupos Y; o

dos grupos R^{11} junto con el átomo N al que están unidos, forman un heterociclilo;

cada R^{12} es seleccionado de manera independiente del grupo que consta de alquilo, arilo y heteroarilo,

donde el arilo de R^{12} no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo de R^{12} no está sustituido o está sustituido con uno o más grupos Z; o donde ambos grupos R^{12}, junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo;

R^a y R^b se seleccionaron cada uno de manera independiente del grupo que consta de H, alquilo, arilo y heteroarilo,

donde el arilo de R^a y R^b no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo de R^a y R^b no está sustituido o está sustituido con uno o más grupos Z;

R^c se seleccionó del grupo que consta de H, alquilo, alquilen-arilo y -C(O)-alquilo,

donde la porción arilo de dicho alquilen-arilo de R^c no está sustituido o está sustituido con uno o más grupos Y;

R^d se seleccionó del grupo que consta de H, alquilo y alquilen-arilo,

donde la porción arilo de dicho alquilen-arilo de R^d no está sustituida o está sustituida con uno o más grupos Y;

cada X es seleccionado de manera independiente del grupo que consta de halógeno, alquilo, haloalquilo, -O-alquilo, -O-haloalquilo y -OH;

cada Y es seleccionado de manera independiente del grupo que consta de halógeno, alquilo, haloalquilo, -O-alquilo, -O-haloalquilo, -CN, $-NO_2$, -OH, $-S(O_2)$-alquilo, $-S(O_2)$-arilo, $-S(O_2)-NH_2$, $-S(O_2)$-NH-alquilo, $-S(O_2)$-NH-arilo, $-S(O_2)-N(alquil)_2$, $-S(O_2)-N(aril)_2$, $-S(O_2)$-N(alquil)(arilo) y arilo;

cada Z es seleccionado de manera independiente del grupo que consta de alquilo, haloalquilo, halógeno, -O-alquilo, -O-haloalquilo, -CN, -OH, arilo y N-óxido;

n es 0, 1, 2, o 3;

m es 0, 1, o 2; y

con la salvedad que cuando L es (f) y R^2, R^3 y R^5 son cada uno H, entonces R^1 no es $-CH_3$.

En otra realización, la presente invención está dirigida a una composición farmacéutica que comprende una cantidad terapéuticamente efectiva de al menos un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo y al menos un vehículo aceptable para uso farmacéutico.

En otra realización, la presente invención está dirigida a un método para tratar una enfermedad o un trastorno en un paciente, tales como síndrome metabólico, dislipidemia, enfermedades cardiovasculares, trastornos del sistema nervioso central y periférico, enfermedades hematológicas, cáncer, inflamación, enfermedades respiratorias, enfermedades gastroenterológicas, diabetes y enfermedad de hígado graso no alcohólico. El método comprende administrar al paciente una cantidad efectiva de al menos un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo.

En otra realización, la presente invención está dirigida a un método para tratar una enfermedad o un trastorno en un paciente, tales como síndrome

metabólico, dislipidemia, enfermedades cardiovasculares, trastornos del sistema nervioso central y periférico, enfermedades hematológicas, cáncer, inflamación, enfermedades respiratorias, enfermedades gastroenterológicas, diabetos, esteatosis hepática y enfermedad de hígado graso no alcohólico. El método comprende administrar al paciente una cantidad efectiva de al menos un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo, en combinación con al menos un principio activo adicional seleccionado del grupo que consta de compuestos de azetidinona hidroxi-sustituidos, compuestos β-lactama sustituidos, compuestos inhibidores de HMG CoA reductasa, inhibidores de HMG CoA sintetasa, inhibidores de la síntesis de escualeno, inhibidores de la escualeno epoxidasa, inhibidores de la biosíntesis de ésteroles, derivados del ácido nicotínico, secuestrantes de ácidos biliares, secuestrantes inorgánicos de colesterol, inhibidores de AcilCoA:colesterol O-aciltransferasa, inhibidores de la proteína de transferencia de ésteres de colesterilo, aceites de pescado que contienen ácidos grasos Omega 3, fibras naturales solubles en agua, estanoles de plantas y/o ésteres de ácidos grasos de estanoles de plantas (p. ej., Omacor® de Pronova Biocare, Oslo, Noruega), activadores del receptor de lipoproteína de baja densidad, anti-oxidantes, agonistas de PPAR-α, agonistas de PPAR-γ, moduladores del receptor FXR, agonistas del receptor FXR, inhibidores de la síntesis de lipoproteína, inhibidores de la renin angiotensina, inhibidores de la proteína de transporte de triglicéridos microsomales, inhibidores de la recaptación de ácidos biliares, agonistas de PPAR-δ, inhibidores de la síntesis de triglicéridos, inhibidores de la escualeno epoxidasa, inductores del receptor de lipoproteína de baja densidad, inhibidores de la agregación plaquetaria, inhibidores 5-LO o FLAP, agonistas parciales de PPAR-δ, agonistas de niacina o del receptor de niacina, inhibidores de transportadores 5HT, inhibidores de transportadores de NE, antagonistas/

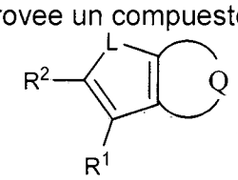
agonistas inversos de CB_1, antagonistas de grelina, antagonistas de H_3/agonistas inversos, antagonistas de MCH1R, agonistas/ antagonistas de MCH2R, antagonistas de NPY1, antagonistas de NPY5, agonistas de NPY2, agonistas de NPY4, antagonistas de mGluR5, leptinas, agonistas/moduladores de leptina, derivados de leptina, antagonistas de opioides, antagonistas del receptor de orexina, agonistas de BRS3, agonistas de CCK-A, CNTF, derivados de CNTF, agonistas/moduladores de CNTF, agonistas de 5HT2c, agonistas de Mc4r, inhibidores de la recaptación de monoamina, inhibidores de la recaptación de serotonina, agonistas GLP-1, fentermina, topiramato, fitofarm compuesto 57, anticuerpos de grelina, agonistas de Mc3r, inhibidores ACC2, agonistas β3, inhibidores DGAT1, inhibidores DGAT2, inhibidores FAS, inhibidores PDE, agonistas de la hormona ß tiroidea, activadores UCP-1, activadores UCP-2, activadores UCP-3, acil-estrógenos, agonistas/antagonistas de glucocorticoides, inhibidores 11β HSD-1, inhibidores SCD-1, inhibidores de lipasa, inhibidores de transportadores de ácido graso, inhibidores de transportadores de dicarboxilato, inhibidores de transportadores de glucosa, inhibidores de transportadores de fosfato, agentes antidiabéticos, agentes antihipertensivos, agentes antidislipidémicos, antagonistas del receptor DP, inhibidores de la secreción de apolipoproteína-B/ proteína de transferencia microsomal de triglicéridos (apo-B/MTP), agonistas simpatomiméticos, agonistas de dopamina, análogos del receptor de la hormona estimuladora de melanocitos, antagonistas de la hormona concentradora de melanina, leptonas, antagonistas del receptor de galanina, agonistas de bombesina, antagonistas de neuropéptidos Y, agentes tiromiméticos, dehidroepiandrosterona, análogos de dehidroepiandrosterona, antagonistas de la proteína de unión de urocortina, agonistas del receptor de péptidos-1 tipo glucágonos, proteínas humanas relacionadas con agouti (AGRP), agonistas del receptor de neuromedina U, agentes anoréxicos noradrenérgicos, supresores de

apetito, antagonistas de lipasas sensibles a hormonas, análogos del receptor de MSH, inhibidores de la α-glucosidasa, inhibidores del transporte inverso del colesterol apo A1 milano, inhibidores de la proteína de unión a ácidos grasos (FABP) y inhibidores de la proteínas transportadoras de ácidos graso (FATP).

Descripción detallada de la invención

Los compuestos agonistas del receptor del ácido nicotínico de la presente invención son útiles para el tratamiento de afecciones tales como síndrome metabólico, dislipidemia, enfermedades cardiovasculares, trastornos del sistema nervioso central y periférico, enfermedades hematológicas, cáncer, inflamación, enfermedades respiratorias, enfermedades gastroenterológicas, diabetos, esteatosis hepática y enfermedad de hígado graso no alcohólico y otras enfermedades aquí indicadas. Uno o más compuestos de la presente invención pueden administrarse solos o en combinación con uno o más agentes terapéuticos como se describió aquí.

La presente invención provee un compuesto de fórmula (I):



(I)

y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros del mismo, donde L, Q, R^1 y R^2 son como se definió antes para el compuesto de fórmula (I).

En una realización, R^1 es alquilo.

En otra realización, R^1 es haloalquilo.

En otra realización, R^1 es arilalquilo.

En aún otra realización, R^1 es -alquilen-S-alquilo.

En otra realización más, R^1 es -alquilen-cicloalquilo.

En otra realización, R^1 es -alquilen-ciclopropilo, -alquilen-ciclobutilo, -alquilen-ciclopentilo o -alquilen-ciclohexilo.

En una realización adicional, R^1 es -alquilen-cicloalquenilo.

En otra realización, R^1 es una cadena alquilo lineal que presenta de 1 a 6 átomos de carbono.

En una realización, R^1 es metilo.

En otra realización, R^1 es etilo.

En otra realización, R^1 es n-propilo.

En aún otra realización, R^1 es n-butilo.

En una realización, R^1 es n-pentilo.

En otra realización, R^1 es n-hexilo.

En otra realización más, R^1 es una cadena alquilo ramificada que presenta de 3 a 6 átomos de carbono.

En una realización adicional, R^1 es isopropilo.

En una realización, R^1 es isobutilo.

En otra realización, R^1 es isopentilo.

En otra realización, R^1 es sec-butilo.

En aún otra realización, R^1 es ter-butilo.

En otra realización más, R^1 es haloalquilo, que presenta de 1 a 3 átomos de F.

En otra realización, R^1 es $-(CH_2)_3CF_3$.

En una realización, R^2 es -H.

En otra realización, R^2 es -CN.

En otra realización, R^2 es -NHC(O)-alquilo.

En aún otra realización, R^2 es $-NHC(O)CH_3$.

En una realización, R^3 es -H.

En otra realización, R^3 es –OH.

En otra realización, R^3 es alquilo.

En otra realización, R^3 es haloalquilo.

En aún otra realización, R^3 es -O-alquilo.

En otra realización más, R^3 es cicloalquilo.

En una realización adicional, R^3 es heterociclilo.

En una realización, R^3 es -O-arilalquilo.

En otra realización, R^3 es -alquilen-O-alquilo.

En una realización, R^3 es $-OCH_3$.

En otra realización, R^3 es ciclobutilo.

En otra realización, R^3 es etilo.

En aún otra realización, R^3 es n-morfolinilo.

En una realización, R^3 es -O-bencilo.

En otra realización, R^3 es $-CH_2CH_2OCH_3$.

En otra realización más, R^3 es $-OCH_2CH_3$.

En otra realización, R^3 es $-CH_2F$.

En una realización, R^3 es $-CH_2CH_2F$.

En otra realización, R^3 es –OH.

En una realización, R^4 es $-CF_3$.

En otra realización, R^4 es -H.

En otra realización, R^4 es -O-cicloalquilo.

En otra realización, R^4–O-alquinilo.

En aún otra realización, R^4 es -O-alquinilen-cicloalquilo.

En otra realización más, R^4 es haloalquilo.

En una realización adicional, R^4 es $-O-N=C(R^7)_2$.

En una realización, R^4 es $-CH_2F$.

En otra realización, R^4 es $-CH(F)_2$.

En otra realización, R^4 es $-CF_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}C(CH_2)_3CH_3$.

En aún otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_2CH_3$.

En otra realización más, R^4 es $-OCH_2C{\equiv}C$-ciclopropilo.

En una realización adicional, R^4 es $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

En una realización, R^4 es $-OCH_2C{\equiv}CCH(OH)CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

En aún otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_2OH$.

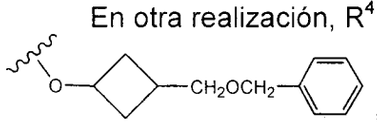
En otra realización más, R^4 es $-OCH_2C{\equiv}C(CH_2)_3OH$.

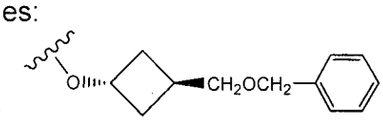
En una realización adicional, R^4 es $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}C$-ciclohexilo.

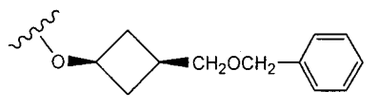
En una realización, R^4 es -O-ciclobutilo.

En otra realización, R^4 es:



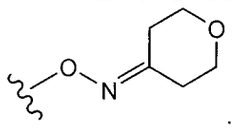
,


or



o

En una realización, R^4 es:



En una realización, R^5 es -H.

En otra realización, R^5 es –OH.

En otra realización, R^5 es alquilo.

En otra realización, R^5 es haloalquilo.

En aún otra realización, R^5 es -O-alquilo.

En otra realización más, R^5 es cicloalquilo.

En una realización adicional, R^5 es heterociclilo.

En una realización, R^5 es -O-arilalquilo.

En otra realización, R^5 es -alquilen-O-alquilo.

En una realización, R^5 es $-OCH_3$.

En otra realización, R^5 es ciclobutilo.

En otra realización, R^5 es etilo.

En aún otra realización, R^5 es n-morfolinilo.

En una realización, R^5 es -O-bencilo.

En otra realización, R^5 es $-CH_2CH_2OCH_3$.

En otra realización más, R^5 es $-OCH_2CH_3$.

En otra realización, R^5 es $-CH_2F$.

En una realización, R^5 es $-CH_2CH_2F$.

En otra realización, R^5 es –OH.

En una realización, R^6 es alcoxi.

En otra realización, R^6 es -O-alquilen-O-alquilo.

En otra realización, R^6 es -O-arilalquilo.

En aún otra realización, R^6 es -O-haloalquilo.

En otra realización más, R^6 es $-OCH_2$-(4-metoxifenilo).

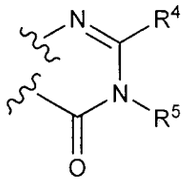
En una realización, R^6 es $-OCH_2F$.

En otra realización, R^6 es $-OCH_2CH_2F$.

En otra realización, R^6 es $-OCH_2CH_3$

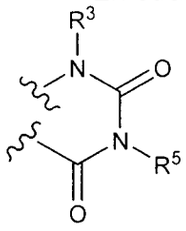
En aún otra realización, R^6 es $-OCH_2CH_2OCH_3$.

En una realización, Q es:



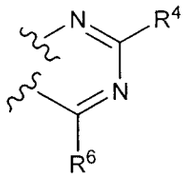
(a)

En otra realización, Q es:



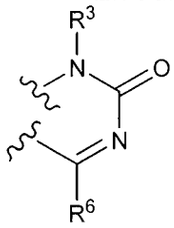
(b)

En otra realización, Q es:



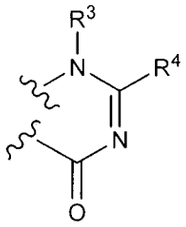
(c)

En aún otra realización, Q es:



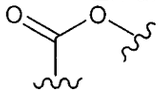
(d)

En otra realización más, Q es:



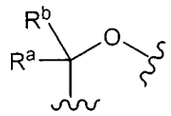
(e)

En una realización, L es:



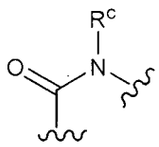
(f)

En otra realización, L es:



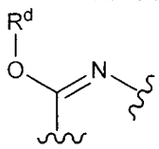
(g)

En otra realización, L es:



(h)

En aún otra realización, L es:



(i)

En otra realización de los compuestos de fórmula (I),

R^1 se seleccionó del grupo que consta de -alquilo (C_1-C_6), -alquenilo (C_1-C_6), -alquinilo (C_1-C_6), -haloalquilo (C_1-C_6), -alquilo (C_1-C_6) sustituido con un grupo hidroxilo, -cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6), -$(CH_2)_n$-$N(R^7)_2$, -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) y -alquilen-(C_1-C_6)-cicloalquenilo (C_3-C_7)

donde la porción -cicloalquilo (C_3-C_7) o la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) no está sustituida o está sustituida con uno o más grupos X, la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) no está sustituida o está sustituida con uno o más grupos Y y la porción heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) no está sustituida o está sustituida con uno o más grupos Z;

R^2 es H, halógeno, arilo no sustituido, arilo sustituido con uno o más grupos Y seleccionados de manera independiente, heteroarilo no sustituido, heteroarilo sustituido con uno o más grupos Y seleccionados de manera independiente; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo cicloalquenilo de 5 o 6 miembros;

R^3 se seleccionó del grupo que consta de H, alquilo (C_1-C_6), -alquilen-(C_3-C_6)-O-alquilo (C_1-C_6), cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-C(O)-O-alquilo y alquenilo (C_1-C_6),

donde la porción cicloalquilo (C_3-C_7) o la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_3-C_6)-cicloalquilo (C_3-C_7) de R^3 no está sustituida o está sustituida con uno o más grupos X;

R^4 se seleccionó del grupo que consta de halógeno, -O-R^{10}, -C(O)-O-alquilo (C_1-C_6), -$S(O)_m$-R^9, -$N(R^7)_2$, -O-N=$C(R^{12})_2$, -$N(R^7)$-NH-C(O)-O-alquilo (C_1-C_6) y -C(O)-alquilo (C_1-C_6);

R^5 se seleccionó del grupo que consta de H, -alquilo (C_1-C_6), -alquilen-(C_1-C_6)-C(O)-R^8, -alquilen-(C_1-C_6)-C(=N-O-alquil-(C_1-C_6)-arilo (C_6-C_{10}), cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6) y alquenilo (C_2-C_6)

donde la porción cicloalquilo (C_3-C_7) o la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) de R^5 no está sustituida o está sustituida con uno o más grupos X y la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-C(=N-O-alquil-(C_1-C_6)-arilo (C_6-C_{10}) de R^5 no está sustituido o está sustituido con uno o más grupos Y;

R^6 se seleccionó del grupo que consta de –O-R^{10}, halógeno y -$N(R^7)_2$;

cada R^7 es seleccionado de manera independiente del grupo que consta de H, alquilo (C_1-C_6), cicloalquilo (C_3-C_7) y arilo (C_6-C_{10}),

donde el cicloalquilo (C_3-C_7) de R^7 no está sustituido o está sustituido con uno o más grupos X y dicho arilo (C_6-C_{10}) de R^7 no está sustituido o está sustituido con uno o más grupos Y;

R^8 se seleccionó del grupo que consta de arilo (C_6-C_{10}) no sustituido, arilo (C_6-C_{10}) sustituido con uno o más grupos Y, -OH, heterociclilo (C_2-C_{10}) no sustituido y heterociclilo (C_2-C_{10}) sustituido con uno o más grupos X;

R^9 se seleccionó del grupo que consta de alquilo (C_1-C_6), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7), alquenilo (C_2-C_6) y -alquilen-(C_1-C_6)-arilo (C_6-C_{10}),

donde la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) de R^9 no está sustituida o está sustituida con uno o más grupos X y la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^9 no está sustituida o está sustituida con uno o más grupos Y;

R^{10} se seleccionó del grupo que consta de H, alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquenilen-(C_2-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}), alquenilo (C_2-C_6), alquinilo (C_2-C_6) y -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7),

donde la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) de R^{10} no está sustituida o está sustituida con uno o más grupos X y la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) o -alquenilen-(C_2-C_6)-arilo (C_6-C_{10}) de R^{10} no está sustituida o está sustituida con uno o más grupos Y y la porción heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

cada R^{12} es de manera independiente un alquilo (C_1-C_6);

R^a y R^b son cada uno independientemente un alquilo (C_1-C_6);

R^c es H;

R^d se seleccionó del grupo que consta de H, alquilo (C_1-C_6) y -alquilen-(C_1-C_6)-arilo (C_6-C_{10}),

donde la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^d no está sustituida o está sustituida con uno o más grupos Y;

cada X es seleccionado de manera independiente del grupo que consta de F, Cl, Br, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-haloalquilo (C_1-C_6) y –OH;

cada Y es seleccionado de manera independiente del grupo que consta de F, Br, Cl, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-haloalquilo (C_1-C_6), -CN, $-NO_2$, -OH,, $-S(O_2)$-alquilo (C_1-C_6), $-S(O_2)$-arilo (C_6-C_{10}), $-S(O_2)-NH_2$, $-S(O_2)$-NH-alquilo (C_1-C_6), $-S(O_2)$-NH-arilo (C_6-C_{10}), $-S(O_2)$-N(alquil-(C_1-C_6)$_2$, $-S(O_2)$-N(arilo (C_6-C_{10}))$_2$, $-S(O_2)$-N(alquil-(C_1-C_6)(arilo (C_6-C_{10})) y arilo (C_6-C_{10}); y

cada Z es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), haloalquilo (C_1-C_6), F, Br y Cl, -O-alquilo (C_1-C_6), -CN, -OH, arilo (C_6-C_{10}) y N-óxido.

En otra realización de los compuestos de fórmula (I),

R^1 se seleccionó del grupo que consta de $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, $-CH_2$-OH, $-CH(CH_3)$-OH, ciclobutilo, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CF_3$, $-CHBrCH_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$,, $-CH_2$-(2-tiofenilo), $-CH_2CH_2CH_2$-(2-tiofenilo), $-CH_2$-ciclopropilo, $-CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2CH_2$-ciclopropilo, $-CH_2$-ciclobutilo, $-CH_2CH_2$-ciclobutilo, $-CH_2CH_2CH_2$-ciclobutilo, $-CH_2CH_2CH_2CH_2$-ciclobutilo, $-CH_2$-ciclopentilo, $-CH_2CH_2$-ciclopentilo, $-CH_2CH_2CH_2$-ciclopentilo, $-CH_2CH_2CH_2CH_2$-ciclopentilo, $-CH_2$-ciclohexilo, $-CH_2$-(4-metilciclohexilo), $-CH_2CH_2$-ciclohexilo, $-CH_2$-cicloheptilo, $-CH_2$-(2-ciclopentenilo, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-fenilo, $-CH_2$-(2-fluorofenilo), $-CH_2$-(3-fluorofenilo) y $-CH_2$-NH(3-metoxifenil);

R^2 se seleccionó del grupo que consta de H, F, Cl, Br, arilo no sustituido, arilo sustituido con uno o más grupos Y, heteroarilo no sustituido, heteroarilo sustituido con uno o más grupos Y; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo ciclopentenilo o ciclohexenilo;

R^3 se seleccionó del grupo que consta de H, $-CH_2$-ciclopropilo, $-CH_2-C(O)-O-CH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentilo, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH=CH_2$ y $-CH_2-O-CH_3$;

R^4 se seleccionó del grupo que consta de Cl, $-O-R^{10}$, $-C(O)-O-CH_3$, $-S(O)_2-CH_3$, $-S(O)-CH_3$, $-S(O)-CH_2CH_3$, $-S(O)-CH(CH_3)_2$, $-S(O)-C(CH_3)_3$, $-S(O)-CH_2$-ciclopropilo, $-S(O)-CH_2$-fenilo, $-S(O)-CH(CH_3)$-fenilo, $-S-CH_2-CH=CH_2$, $-N(R^7)_2$, $-O-N=C(CH_3)_2$, $-NH-NH-C(O)-O-CH_3$ y $-C(O)-CH_3$,

donde la porción fenilo de dicho $-S(O)-CH_2$-fenilo, o $-S(O)-CH(CH_3)$-fenilo de R^4 no está sustituida o está sustituida con uno o más grupos Y;

R^5 se seleccionó del grupo que consta de H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2-C(O)$-fenilo, $-CH_2-C(O)-OH$, $-CH_2-C(=N-O-CH_3)$-fenilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_2-C(O)$-piperidilo, $-CH_2$-ciclopropilo, $-CH_2-C(O)-O-CH_3$ y $-CH_2-CH=CH_3$,

donde la porción fenilo de dicho $-CH_2-C(O)$-fenilo no está sustituida o está sustituida con uno o más grupos Y;

R^6 se seleccionó del grupo que consta de $-OR^{10}$, Cl y $-N(R^7)_2$;

cada R^7 es seleccionado de manera independiente del grupo que consta de H, ciclobutilo, fenilo no sustituido, y fenilo sustituido con uno o más grupos Y;

R^{10} se seleccionó del grupo que consta de H, $-CH_3$, $-CH_2$-ciclopropilo, $-CH_2-CH=CH_3$, $-CH_2C\equiv C-CH_3$, $-CH_2$-fenilo, $-CH(CH_3)$-fenilo, $-CH(CH_2CH_3)$-fenilo, $-CH(CH_2CH_2CH_3)$-fenilo, $-CH(CH(CH_3)_2)$-fenilo, $-CH(CH_2CH=CH_2)$-fenilo, $-CH_2$-piridilo, $-CH(CH_3)$-tiazolilo y $-CH_2$-pirimidinilo,

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donde la porción fenilo de dicho -CH_2-fenilo, -$CH(CH_3)$-fenilo, -$CH(CH_2CH_3)$-fenilo, -$CH(CH_2CH_2CH_3)$-fenilo, $CH(CH(CH_3)_2)$-fenilo, o -$CH(CH_2CH{=}CH_2)$-fenilo de R^{10} no está sustituida o está sustituida con uno o más grupos Y y la porción piridilo, tiazolilo, o pirimidinilo de dicho -CH_2-piridilo, -CH_2-tiazolilo, o -CH_2-pirimidinilo de R^{10} no está sustituido o está sustituido con uno o más grupos Z;

R^a y R^b son cada uno $-CH_3$;

R^c es H;

R^d se seleccionó del grupo que consta de H, $-CH_3$ y $-CH_2$-fenilo,

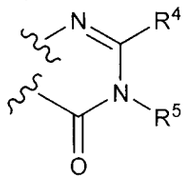
donde la porción fenilo de dicho $-CH_2$-fenilo de R^d no está sustituida o está sustituida con uno o más grupos Y;

cada Y es seleccionado de manera independiente del grupo que consta de F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, -CN, -OH y fenilo; y

cada Z es seleccionado de manera independiente del grupo que consta de $-CH_3$, $-CF_3$, F, Br y Cl, $-O-CH_3$, -CN, -OH, fenilo, y N-óxido.

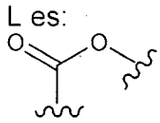
En otra realización de los compuestos de fórmula (I),

Q es:



(a) ;

L es:



(f) ;

R^1 se seleccionó del grupo que consta de -alquilo (C_1-C_6), -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6), arilo (C_6-C_{10}) no sustituido y arilo (C_6-C_{10}) sustituido con uno o más sustituyentes Y;

R^2 es H o halógeno;

R^4 se seleccionó del grupo que consta de halógeno, -O-R^{10}, -C(O)-O-alquilo (C_1-C_6), -$S(O)_m$-R^9, -$N(R^7)_2$, -O-N=$C(R^{12})_2$, -$N(R^7)$-NH-C(O)-O-alquilo (C_1-C_6) y -C(O)-alquilo (C_1-C_6);

R^5 es H o alquilo (C_1-C_6);

cada R^7 es seleccionado de manera independiente del grupo que consta de H, alquilo (C_1-C_6), cicloalquilo (C_3-C_6), arilo (C_6-C_{10}) no sustituido y arilo (C_6-C_{10}) sustituido con uno o más grupos Y;

R^9 se seleccionó del grupo que consta de alquilo (C_1-C_6), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6), alquenilo (C_2-C_6) y -alquilen-(C_1-C_6)-arilo (C_6-C_{10}),

donde el arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^9 no está sustituido o está sustituido con uno o más grupos Y;

R^{10} se seleccionó del grupo que consta de H, alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquenilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}), alquenilo (C_2-C_6), alquinilo (C_2-C_6) y -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6)

donde el arilo de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) o -alquenilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^{10} no está sustituido o está sustituido con uno o más grupos Y y el heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) de R^{10} no está sustituido o está sustituido con uno o más grupos Z;

cada R^{12} es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), arilo (C_6-C_{10}) y heteroarilo (C_2-C_{10}),

donde el arilo (C_6-C_{10}) no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo (C_2-C_{10}) no está sustituido o está sustituido con uno o más grupos Z;

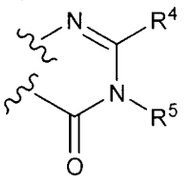
cada Y es seleccionado de manera independiente del grupo que consta de halógeno, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -CN, -NO_2, -OH, -$S(O_2)$-alquilo (C_1-C_6), -$S(O_2)$-arilo (C_6-C_{10}), -$S(O_2)$-NH_2, -$S(O_2)$-NH-

alquilo (C_1-C_6), -$S(O_2)$-NH-arilo (C_6-C_{10}), -$S(O_2)$-N(alquil-(C_1-C_6)$_2$, -$S(O_2)$-N(arilo (C_6-C_{10}))$_2$, -$S(O_2)$-N(alquil-(C_1-C_6)(arilo (C_6-C_{10})) y arilo (C_6-C_{10}); y

cada Z es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), haloalquilo (C_1-C_6), halógeno, -O-alquilo, -O-haloalquilo (C_1-C_6), -CN, -OH, arilo (C_6-C_{10}), y y N-óxido.

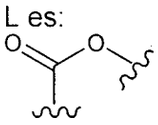
En otra realización de los compuestos de fórmula (I),

Q es:



(a) ;

L es:



(f) ;

R^1 es -CH_2CH_3, butilo, pentilo, -CH_2-CH_2-CH_2-ciclopropilo;

R^2 es H, Br, arilo no sustituido, arilo sustituido con uno o más grupos Y, heteroarilo no sustituido, heteroarilo sustituido con uno o más grupos Y;

R^4 se seleccionó del grupo que consta de Cl, -O-R^{10}, -C(O)-O-CH_3, -S(O)-CH_3, -S(O)-CH_2CH_3, -S(O)-$CH(CH_3)_2$, -S(O)-$C(CH_3)_3$, -S(O)-CH_2-ciclopropilo, -S-CH_2-CH=CH_2, -S(O)-CH_2-fenilo, -S(O)-$CH(CH_3)$-fenilo, -N(R^7)$_2$, -O-N=$C(CH_3)_2$, -NH-NH-C(O)-O-CH_3 y -C(O)-CH_3,

donde la porción fenilo de dicho -S(O)-CH_2-fenilo, o -S(O)-$CH(CH_3)$-fenilo de R^4 no está sustituida o está sustituida con uno o más grupos Y;

R^5 es H o –CH_2CH_3;

cada R^7 es seleccionado de manera independiente del grupo que consta de H y ciclobutilo;

R^{10} se seleccionó del grupo que consta de H, $-CH_3$, $-CH_2$-ciclopropilo, $-CH_2-CH=CH_2$, $-CH_2C\equiv C-CH_3$, $-CH_2$-fenilo, $-CH(CH_3)$-fenilo, $-CH(CH_2CH_3)$-fenilo, $-CH(CH(CH_3)_2)$-fenilo, $-CH(CH_2CH_2CH_3)$-fenilo, $-CH(CH_2CH=CH_2)$-fenilo, $-CH_2$-piridilo, $-CH(CH_3)$-tiazolilo, $-CH_2$-pirimidinilo,

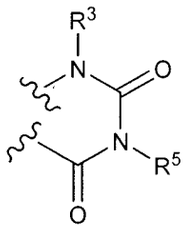
donde la porción fenilo de dicho $-CH_2$-fenilo, $-CH(CH_3)$-fenilo, $-CH(CH_2CH_3)$-fenilo, $-CH(CH(CH_3)_2)$-fenilo, $-CH(CH_2CH=CH_2)$-fenilo, o $-CH(CH_2CH_2CH_3)$-fenilo, de R^{10} no está sustituida o está sustituida con uno o más grupos Y y la porción piridilo, tiazolilo o pirimidinilo de dicho $-CH_2$-piridilo, $-CH(CH_3)$-tiazolilo, o $-CH_2$-pirimidinilo de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

cada Y es seleccionado de manera independiente del grupo que consta de F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$ y fenilo; y

cada Z es seleccionado de manera independiente del grupo que consta de $-CH_3$, fenilo, y N-óxido.

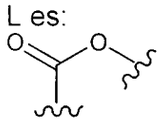
En otra realización de los compuestos de fórmula (I),

Q es:



(b) ;

L es:



(f) ;

se seleccionó del grupo que consta de -alquilo (C_1-C_6), -alquenilo (C_1-C_6), -alquinilo (C_1-C_6), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-

heteroarilo (C_2-C_{10}), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-cicloalquenilo (C_3-C_7), alquilo (C_1-C_6) sustituido con uno o más grupos hidroxilo, -$(CH_2)_n$-$N(R^7)_2$ y -haloalquilo (C_1-C_6)

donde la porción -cicloalquilo (C_3-C_7) o la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) no está sustituida o está sustituida con uno o más grupos X, la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) no está sustituida o está sustituida con uno o más grupos Y y la porción heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) no está sustituida o está sustituida con uno o más grupos Z;

R^2 es H;

R^3 se seleccionó del grupo que consta de H, alquilo (C_1-C_6), cicloalquilo (C_3-C_6), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6), alquenilo (C_2-C_6) y -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6);

R^5 se seleccionó del grupo que consta de H, -alquilo (C_1-C_6), alquenilo (C_2-C_6), -alquilen-(C_1-C_6)-C(O)-R^8, -alquilen-(C_1-C_6)-C(=N-O-alquil-(C_1-C_6)-arilo (C_6-C_{10}), cicloalquilo (C_3-C_6), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6) y -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6);

cada R^7 es seleccionado de manera independiente del grupo que consta de H y arilo, donde el arilo de R^7 no está sustituido o está sustituido con uno o más grupos Y;

R^8 se seleccionó del grupo que consta de arilo (C_6-C_{10}) no sustituido, arilo (C_6-C_{10}) sustituido con uno o más grupos Y, -OH, heterociclilo (C_2-C_{10}) no sustituido y heterociclilo (C_2-C_{10}) sustituido con uno o más grupos X;

cada X es seleccionado de manera independiente del grupo que consta de halógeno, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-haloalquilo (C_1-C_6) y –OH;

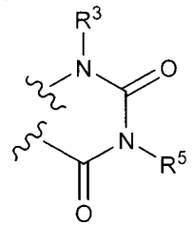
cada Y es seleccionado de manera independiente del grupo que consta de halógeno, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -CN,

$-NO_2$, -OH, $-S(O_2)$-alquilo (C_1-C_6), $-S(O_2)$-arilo (C_6-C_{10}), $-S(O_2)-NH_2$, $-S(O_2)$-NH-alquilo (C_1-C_6), $-S(O_2)$-NH-arilo (C_6-C_{10}), $-S(O_2)$-N(alquil-(C_1-C_6)$_2$, $-S(O_2)$-N(arilo (C_6-C_{10}))$_2$, $-S(O_2)$-N(alquil-(C_1-C_6)(arilo (C_6-C_{10})) y arilo (C_6-C_{10}); y

cada Z es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), haloalquilo (C_1-C_6), F, Br y Cl, -O-alquilo (C_1-C_6), -CN, -OH, arilo (C_6-C_{10}) y N-óxido.

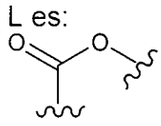
En otra realización de los compuestos de fórmula (I),

Q es:



(b) ;

L es:



(f) ;

R^1 se seleccionó del grupo que consta de $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3, $-CH_2CF_3$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, $-CH_2OH$, $-CH(CH_3)OH$, $-CH_2N(R^7)_2$, ciclobutilo, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$,, $-CH_2$-(2-tiofenilo), $-CH_2CH_2CH_2$-(2-tiofenilo), $-CH_2$-ciclopropilo, $-CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2CH_2$-ciclopropilo, $-CH_2$-ciclopentilo, $-CH_2CH_2$-ciclopentilo, $-CH_2$-ciclohexilo, $-CH_2$-(4-metilciclohexilo), $-CH_2CH_2$-ciclohexilo, $-CH_2$-cicloheptilo, $-CH_2$-(2-ciclopentenilo, $-CH_2CH_2C\equiv CH$,

$-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-fenilo, $-CH_2$-(2-fluorofenilo), $-CH_2$-(3-fluorofenilo) y $-CHBrCH_3$;

R^2 es H; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo ciclopentenilo o ciclohexenilo;

R^3 se seleccionó del grupo que consta de H, $-CH_2$-ciclopropilo, $-CH_2-C(O)-O-CH_3$, -ciclopropilo, ciclobutilo, ciclopentilo, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH=CH_2$ y $-CH_2-O-CH_3$;

R^5 se seleccionó del grupo que consta de H, $-CH_2$-ciclopropilo, $-CH_2-C(O)-O-CH_3$, $-CH_2-C(O)-R^8$, $-CH_2-C(=N-O-CH_3)$-fenilo, ciclopropilo, ciclobutilo, ciclopentilo, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$ y $-CH_2CH=CH_2$;

cada R^7 es de manera independiente H o fenilo,

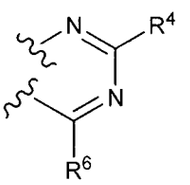
donde el fenilo de R^7 no está sustituido o está sustituido con uno o más grupos Y;

R^8 se seleccionó del grupo que consta de fenilo no sustituido, fenilo sustituido con uno o más grupos Y, -OH y piperidilo; y

cada Y es seleccionado de manera independiente del grupo que consta de F, $-CF_3$, $-OCH_3$, -CN y –OH.

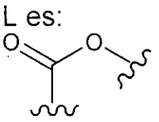
En otra realización de los compuestos de fórmula (I),

Q es:



(c) ;

L es:



(f) ;

R^1 se seleccionó del grupo que consta de -alquilo (C_1-C_6), -alquenilo (C_1-C_6), -alquinilo (C_1-C_6), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6), -cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7), -alquilen-(C_1-C_6)-cicloalquenilo (C_3-C_7), -alquilo (C_1-C_6) sustituido con uno o más grupos hidroxilo, $-(CH_2)_n-N(R^7)_2$ y -haloalquilo (C_1-C_6)

donde la porción -cicloalquilo (C_3-C_7) o la porción cicloalquilo (C_3-C_7) de dicho -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_7) no está sustituida o está sustituida con uno o más grupos X, la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) no está sustituida o está sustituida con uno o más grupos Y y la porción heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) no está sustituida o está sustituida con uno o más grupos Z;

R^2 es H; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo cicloalquenilo de 5 o 6 miembros;

R^4 se seleccionó del grupo que consta de halógeno, $-O-R^{10}$, -C(O)-O-alquilo (C_1-C_6), $-S(O)_m-R^9$, $-N(R^7)_2$, $-O-N=C(R^{12})_2$, $-N(R^7)-NH-C(O)-O$-alquilo (C_1-C_6) y -C(O)-alquilo (C_1-C_6);

R^6 se seleccionó del grupo que consta de $-O-R^{10}$, halógeno y $-N(R^7)_2$;

cada R^7 es seleccionado de manera independiente del grupo que consta de H, alquilo (C_1-C_6), cicloalquilo (C_3-C_6), arilo (C_6-C_{10}) no sustituido y arilo (C_6-C_{10}) sustituido con uno o más grupos Y;

R^9 se seleccionó del grupo que consta de alquilo (C_1-C_6), -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6), alquenilo (C_2-C_6) y -alquilen-(C_1-C_6)-arilo (C_6-C_{10}),

donde la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^9 no está sustituida o está sustituida con uno o más grupos Y;

R^{10} se seleccionó del grupo que consta de H, alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquenilen-(C_1-C_6)-arilo (C_6-C_{10}), -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}), alquenilo (C_2-C_6), alquinilo (C_2-C_6) y -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6),

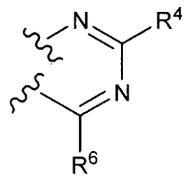
donde la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) o -alquenilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^{10} no está sustituida o está sustituida con uno o más grupos Y y la porción heteroarilo (C_2-C_{10}) de dicho -alquilen-(C_1-C_6)-heteroarilo (C_2-C_{10}) de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

cada Y es seleccionado de manera independiente del grupo que consta de F, Br, Cl, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-haloalquilo (C_1-C_6), -CN, -NO_2, -OH,, -$S(O_2)$-alquilo (C_1-C_6), -$S(O_2)$-arilo (C_6-C_{10}), -$S(O_2)$-NH_2, -$S(O_2)$-NH-alquilo (C_1-C_6), -$S(O_2)$-NH-arilo (C_6-C_{10}), -$S(O_2)$-N(alquil-(C_1-C_6)$_2$, -$S(O_2)$-N(arilo (C_6-C_{10}))$_2$, -$S(O_2)$-N(alquil-(C_1-C_6)(arilo (C_6-C_{10})) y arilo (C_6-C_{10}); y

cada Z es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), haloalquilo (C_1-C_6), F, Br y Cl, -O-alquilo (C_1-C_6), -CN, -OH, arilo (C_6-C_{10}) y N-óxido.

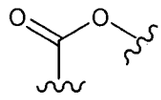
En otra realización de los compuestos de fórmula (I),

Q es:



(c) ;

L es:



(f) ;

R^1 se seleccionó del grupo que consta de $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH(CH_3)_2$, $-CH_2$-C(O)-O-CH_2CH_3,

$-CH_2$-OH, $-CH(CH_3)$-OH, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, ciclobutilo, $-CH_2CH_2CH_2$-O-CH_3, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$,, $-CH_2$-(2-tiofenilo), $-CH_2CH_2CH_2$-(2-tiofenilo), $-CH_2$-ciclopropilo, $-CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2CH_2$-ciclopropilo, $-CH_2$-ciclopentilo, $-CH_2CH_2$-ciclopentilo, $-CH_2$-ciclohexilo, $-CH_2$-(4-metilciclohexilo), $-CH_2CH_2$-ciclohexilo, $-CH_2$-cicloheptilo, $-CH_2$-(2-ciclopentenilo, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-fenilo, $-CH_2$-(2-fluorofenilo), $-CH_2$-(3-fluorofenilo), $-CHBrCH_3$ y $-CH_2CF_3$;

R^2 es H; o

R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra, forman un anilo ciclopentenilo o ciclohexenilo

R^4 se seleccionó del grupo que consta de Cl, -O-R^{10}, $-C(O)-O-CH_3$, $-S(O)_2-CH_3$, $-S(O)-CH_3$, $-S(O)-CH_2CH_3$, $-S(O)-CH(CH_3)_2$, $-S(O)-C(CH_3)_3$, $-S(O)-CH_2$-ciclopropilo, $-S-CH_2-CH=CH_2$, $-S(O)-CH_2$-fenilo, $-S(O)-CH(CH_3)$-fenilo, $-N(R^7)_2$, $-O-N=C(CH_3)_2$, $-NH-NH-C(O)-O-CH_3$ y $-C(O)-CH_3$,

donde la porción fenilo de dicho $-S(O)-CH_2$-fenilo, o $-S(O)-CH(CH_3)$-fenilo de R^4 no está sustituida o está sustituida con uno o más grupos Y;

R^6 se seleccionó del grupo que consta de -O-R^{10}, $-N(R^7)_2$ y Cl;

cada R^7 es seleccionado de manera independiente del grupo que consta de H, fenilo no sustituido, fenilo sustituido con uno o más grupos Y y ciclobutilo;

R^{10} se seleccionó del grupo que consta de H, CH_3, $-CH_2$-ciclopropilo, $-CH_2-C\equiv C-CH_3$, $-CH_2-CH=CH_2$, $-CH_2$-fenilo, $-CH(CH_3)$-fenilo, $-CH(CH_2CH_3)$-fenilo, $-CH(CH(CH_3)_2)$-fenilo, $-CH(CH_2CH_2CH_3)$-fenilo, $-CH(CH_2CH=CH_2)$-fenilo, $-CH_2$-piridilo, $-CH(CH_3)$-tiazolilo, $-CH_2$-pirimidinilo,

donde la porción fenilo de dicho $-CH_2$-fenilo, $-CH(CH_3)$-fenilo, $-CH(CH_2CH_3)$-fenilo, $-CH(CH_2CH=CH_2)$-fenilo, o $-CH(CH_2CH_2CH_3)$-fenilo de R^{10} no está sustituido o

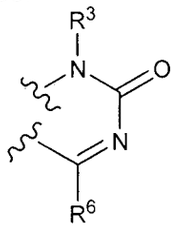
está sustituido con uno o más grupos Y y la porción piridilo, tiazolilo, o pirimidinilo de dicho $-CH_2$-piridilo, $-CH(CH_3)$-tiazolilo, o $-CH_2$-pirimidinilo de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

cada Y es seleccionado de manera independiente del grupo que consta de F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, -CN, -OH y fenilo; y

cada Z es seleccionado de manera independiente del grupo que consta de $-CH_3$, F, Br y Cl, $-O-CH_3$, -CN, -OH, fenilo, y N-óxido.

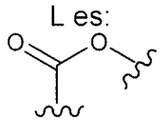
En otra realización de los compuestos de fórmula (I),

Q es:



(d) ;

L es:



(f) ;

R^1 es -alquilo (C_1-C_6);

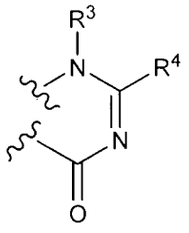
R^2 es H;

R^3 es H o -alquenilo (C_2-C_6); y

R^6 es -OH o -O-alquilen-(C_1-C_6)-cicloalquilo (C_1-C_6).

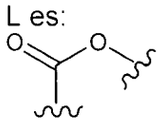
En otra realización de los compuestos de fórmula (I),

Q es:



(e) ;

L es:



(f) ;

R^1 es -alquilo (C_1-C_6) o -haloalquilo (C_1-C_6);

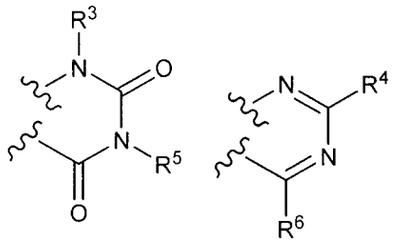
R^2 es H;

R^3 se seleccionó del grupo que consta de H, -alquilen-(C_1-C_6)-cicloalquilo (C_1-C_6), -alquilen-(C_1-C_6)-C(O)-O-alquilo (C_1-C_6), -cicloalquilo (C_1-C_6), alquilo (C_1-C_6), alquenilo (C_2-C_6) y -alquilen-(C_1-C_6)-O-alquilo (C_1-C_6); y

R^4 es -O-N=C(alquil-(C_1-C_6)$_2$.

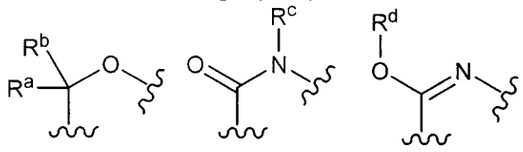
En otra realización de los compuestos de fórmula (I),

Q es:



(b) o (c) ;

L se seleccionó del grupo que consta de:



(g) , (h) y (i) ;

R^a y R^b se seleccionaron cada uno de manera independiente del grupo que consta de H, alquilo (C_1-C_6), arilo (C_6-C_{10}) y heteroarilo (C_2-C_{10}),

donde el arilo (C_6-C_{10}) de R^a y R^b no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo (C_2-C_{10}) de R^a y R^b no está sustituido o está sustituido con uno o más grupos Z;

R^c se seleccionó del grupo que consta de H, alquilo (C_1-C_6), -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) y -C(O)-alquilo (C_1-C_6),

donde la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^c no está sustituida o está sustituida con uno o más grupos Y;

R^d se seleccionó del grupo que consta de H, alquilo (C_1-C_6) y -alquilen-(C_1-C_6)-arilo (C_6-C_{10}),

donde la porción arilo (C_6-C_{10}) de dicho -alquilen-(C_1-C_6)-arilo (C_6-C_{10}) de R^d no está sustituida o está sustituida con uno o más grupos Y;

R^1 es alquilo (C_1-C_6) o o -haloalquilo (C_1-C_6);

R^2 es H;

R^3 es H;

R^4 es -O-R^{10};

R^5 es H o -alquilen-(C_1-C_6)-cicloalquilo (C_3-C_6);

R^6 es -O-R^{10};

R^{10} es H, alquilo (C_1-C_6), o -alquilen-(C_1-C_6)-arilo (C_6-C_{10}); y

cada Y es seleccionado de manera independiente del grupo que consta de F, Br, Cl, alquilo (C_1-C_6), haloalquilo (C_1-C_6), -O-alquilo (C_1-C_6), -O-haloalquilo (C_1-C_6), -CN, -NO_2, -OH,, -$S(O_2)$-alquilo (C_1-C_6), -$S(O_2)$-arilo (C_6-C_{10}), -$S(O_2)$-NH_2, -$S(O_2)$-NH-alquilo (C_1-C_6), -$S(O_2)$-NH-arilo (C_6-C_{10}), -$S(O_2)$-N(alquil-(C_1-C_6)$_2$, -$S(O_2)$-N(arilo (C_6-C_{10}))$_2$, -$S(O_2)$-N(alquil-(C_1-C_6)(arilo (C_6-C_{10})) y arilo (C_6-C_{10}); y

cada Z es seleccionado de manera independiente del grupo que consta de alquilo (C_1-C_6), haloalquilo (C_1-C_6), F, Br y Cl, -O-alquilo (C_1-C_6), -CN, -OH, arilo (C_6-C_{10}) y N-óxido.

En otra realización de fórmula (I), R^1 es $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH(CH_3)_2$, $-CH_2-C(O)-O-CH_2CH_3$, $-CH_2CF_3$, $-CH_2-OH$, $-CH(CH_3)OH$, $-CH_2-N(R^7)_2$, $-CH_2-NH$(3-metoxifenilo), $-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH=CH_2$, $-CH_2CH_2CH=CHCH_3$, $-CH_2CH_2CH_2CH_2CH=CH_2$, $-CH_2CH_2CH_2CH=CH_2$, ciclobutilo, $-CH_2CH_2CH_2-O-CH_3$, $-CH_2CF_3$, $-CHBrCH_3$, $-CH_2CH_2CF_3$, $-CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2CH_2CF_3$, $-CH_2CH_2CH_2Cl$,, $-CH_2$-(2-tiofenilo), $-CH_2CH_2CH_2$-(2-tiofenilo), $-CH_2$-ciclopropilo, $-CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2$-ciclopropilo, $-CH_2CH_2CH_2CH_2$-ciclopropilo, $-CH_2$-ciclopentilo, $-CH_2CH_2$-ciclopentilo, $-CH_2$-ciclohexilo, $-CH_2$-(4-metilciclohexilo), $-CH_2CH_2$-ciclohexilo, $-CH_2$-cicloheptilo, $-CH_2$-(2-ciclopentenilo, $-CH_2CH_2C\equiv CH$, $-CH_2CH_2CH_2C\equiv CH$, $-CH_2$-fenilo, $-CH_2$-(2-fluorofenilo), $-CH_2$-(3-fluorofenilo), o $-CHBrCH_3$.

En otra realización de fórmula (I), R^2 es H.

En otra realización de fórmula (I), R^2 es Br.

En otra realización, R^1 y R^2 junto con los átomos de carbono anulares al que están unidos según se muestra en Formula (I), forman un anilo ciclopentenilo o ciclohexenilo.

En otra realización de fórmula (I), R^3 es H, $-CH_2$-ciclopropilo, $-CH_2-C(O)-O-CH_3$, -ciclopropilo, ciclobutilo, ciclopentilo, $-CH_3$, $-CH_2CH_3$, $-CH_2-CH_2CH_3$, $-CH_2CH=CH_2$, o $-CH_2-O-CH_3$.

En otra realización de fórmula (I), R^4 es Cl, -OH, $-O-CH_3$, $-O-CH_2$-ciclopropilo, $-CH_2-C\equiv C-CH_3$, $-O-CH_2$-fenilo, $-O-CH(CH_3)$-fenilo, $-O-CH(CH_2CH_3)$-fenilo, $-O-CH(CH_2CH_2CH_3)$-fenilo, $-O-CH(CH(CH_3)_2)$-fenilo,

-O-CH($CH_2CH=CH_2$)-fenilo, -O-CH_2-piridilo, -O-CH_2-tiazolilo, -O-CH(CH_3)-tiazolilo, -O-CH_2-pirimidinilo, -C(O)-O-CH_3, -S(O_2) -CH_3, -S(O)-CH_3, -S(O)-CH_2CH_3, -S(O)-$CH(CH_3)_2$, -S(O)-$C(CH_3)_3$, -S(O)-CH_2-ciclopropilo, -S(O)-CH_2-fenilo, -S(O)-$CH(CH_3)$-fenilo, -S(O)-$N(R^{11})_2$, -$S(O_2)$-$N(R^{11})_2$, -S-CH_2-$CH=CH_2$, -N(H)ciclobutilo, -N(H)fenilo, -NH-NH-C(O)-O-CH_3, -O-CH_2-$CH=CH_2$, -O-$N=C(CH_3)_2$, o -C(O)-CH_3, donde los fenilos de cualquiera de estos grupos pueden estar insustituidos o sustituidos con uno o más grupos Y como se definió aquí, las porciones ciclobutilo de cualquiera de estos grupos pueden estar no sustituidos o sustituido con uno o más grupos X como se definió aquí y las porciones piridilo, tiazolilo, o pirimidinilo de cualquiera de estos grupos puede estar no sustituido o sustituido con uno o más grupos Z como se definió aquí.

En otra realización del compuesto de fórmula (I), R^5 es H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, -CH_2-C(O)-fenilo, -CH_2-C(O)-OH, -CH_2-C(=N-O-CH_3)-fenilo, ciclopropilo, ciclobutilo, ciclopentilo, -CH_2-C(O)-piperidilo, -CH_2-ciclopropilo, -CH_2-C(O)-O-CH_3, o -CH_2-$CH=CH_3$, donde el fenilo de dicho -CH_2-C(O)-fenilo de R^5 no está sustituido o está sustituido con uno o más grupos Y como se definió aquí, dicho ciclopropilo, el ciclopropilo de dicho -CH_2-ciclopropilo, ciclobutilo, ciclopentilo, o el piperidilo de dicho -CH_2-C(O)-piperidilo de R^5 no están sustituidos o están sustituidos con uno o más grupos X como se definió aquí.

En otra realización del compuesto de fórmula (I), R^6 es -OH, Cl, -O-CH_3, -O-CH_2-ciclopropilo, -O-CH_2-$CH=CH_3$, -O-CH_2-fenilo, -O-CH(CH_3)-fenilo, -O-CH(CH_2CH_3)-fenilo, -O-CH($CH_2CH_2CH_3$)-fenilo, -O-CH(CH(CH_3)$_2$)-fenilo, -O-CH($CH_2CH=CH_2$)-fenilo, -O-CH_2-piridilo, -O-CH_2-tiazolilo, -O-CH_2-pirimidinilo, y -N(H)ciclobutilo, -N(H)fenilo, -NH-NH-C(O)-O-CH_3, donde el fenilo de dicho -O-CH_2-fenilo, -O-CH(CH_3)-fenilo, -O-CH(CH_2CH_3)-fenilo, -O-CH($CH_2CH_2CH_3$)-fenilo, -O-CH(CH(CH_3)$_2$)-fenilo, o -O-CH($CH_2CH=CH_2$)-fenilo de R^6 no está sustituido o está sustituido con uno o más grupos Y como se

definió aquí y el piridilo, tiazolilo o pirimidinilo de dicho -O-CH_2-piridilo, -O-CH_2-tiazolilo, o -O-CH_2-pirimidinilo de R^6 no está sustituido o está sustituido con uno o más grupos Z como se definió aquí.

En otra realización del compuesto de fórmula (I), cada R^7 es de manera independiente H, -CH_3, -CH_2CH_3, -$CH_2CH_2CH_3$, fenilo no sustituido, fenilo sustituido con uno o más grupos Y, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, -C(O)-CH_3 y -C(O)-fenilo. Alternativamente, dos grupos R^7, junto con el átomo N al que están unidos, forman un anilo azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinonilo, triazolilo o pirrolilo.

En otra realización del compuesto de fórmula (I), R^8 es -CH_3, fenilo no sustituido, fenilo sustituido con uno o más grupos Y, piperidilo y -OH.

En otra realización del compuesto de fórmula (I), R^9 es -CH_3, -CH_2CH_3, -$CH(CH_3)_2$, -$C(CH_3)_3$, -CH_2-ciclopropilo, -CH_2-CH=CH_2 (alilo), -CH_2-fenilo, y -$CH(CH_3)$-fenilo.

En otra realización del compuesto de fórmula (I), R^{10} es H, -$CH_2C{\equiv}CCH_3$, -CH_2-ciclopropilo, -$CH_2CH{=}CH_2$, -CH_2-fenilo, -$CH(CH_3)$-fenilo, -$CH(CH_2CH_3)$-fenilo, -$CH(CH(CH_3)_2)$-fenilo, -CH_2-piridilo, -CH_2-tiazolilo, -$CH(CH_3)$-tiazolilo, -CH_2-pirimidilo, -$CH(CH_2CH{=}CH_2)$-fenilo, -$CH(CH_2CH_2CH_3)$-fenilo, donde la porción fenilo de -CH_2-fenilo, -$CH(CH_3)$-fenilo, -$CH(CH_2CH_3)$-fenilo, -$CH(CH(CH_3)_2)$-fenilo, -$CH(CH_2CH{=}CH_2)$-fenilo, y -$CH(CH_2CH_2CH_3)$-fenilo de R^{10} no están sustituidos o están sustituidos con uno o más grupos Y y la porción piridilo, tiazolilo y pirimidilo de dicho -CH_2-piridilo, -CH_2-tiazolilo, -$CH(CH_3)$-tiazolilo, -CH_2-pirimidilo no están sustituidos o están sustituidos con uno o más grupos Z.

En otra realización del compuesto de fórmula (I), R^{11} es H, -CH_3, o fenilo, donde el fenilo no está sustituido o está sustituido con uno o más grupos Y. Alternativamente, dos grupos R^{11}, junto con el átomo N al que están unidos,

forman un anilo azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, pirrolidinonilo, triazolilo, o pirrolilo.

En otra realización del compuesto de fórmula (I), R^{12} es H, $-CH_3$, $-CH_2CH_3$, o piridilo no sustituido o piridilo sustituido con uno o más grupos Z.

En otra realización del compuesto de fórmula (I), R^a es H o $-CH_3$.

En otra realización del compuesto de fórmula (I), R^b es H o $-CH_3$.

En otra realización del compuesto de fórmula (I), R^a y R^b son ambos $-CH_3$.

En otra realización del compuesto de fórmula (I), R^c es H o $-CH_3$.

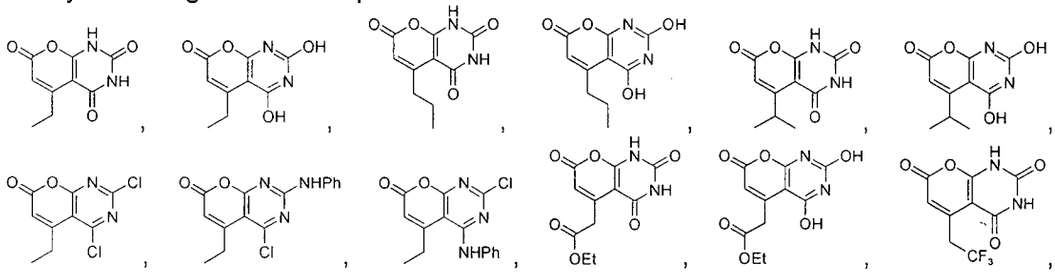
En otra realización del compuesto de fórmula (I), R^d es H, $-CH_3$, o $-CH_2$-fenilo, donde la porción fenilo de dicho $-CH_2$-fenilo de R^d no está sustituido o está sustituido con uno o más grupos Y como se definió aquí.

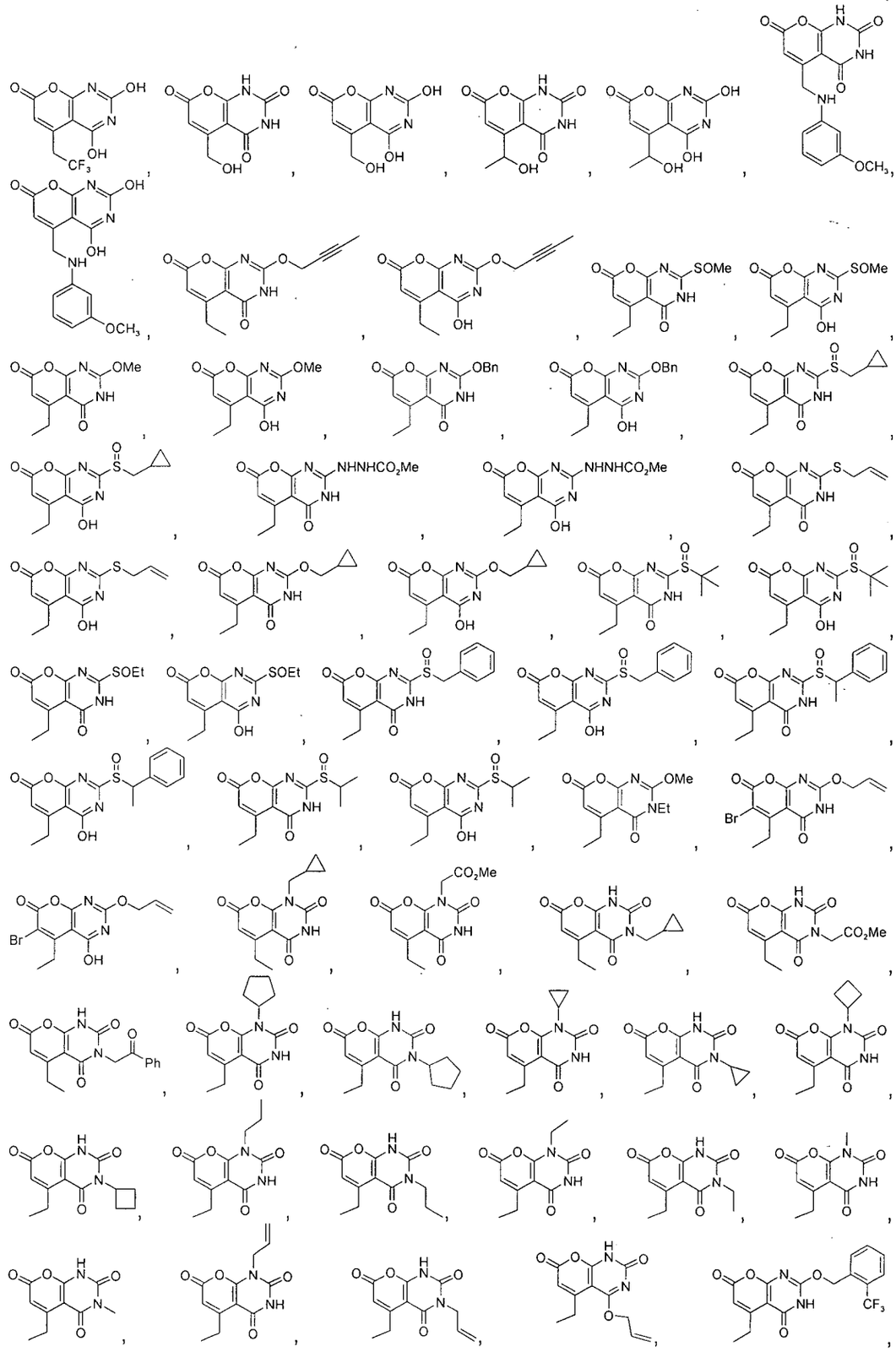
En otra realización del compuesto de fórmula (I), cada X es seleccionado de manera independiente del grupo que consta de $-CH_3$, $-CF_3$, F, Br y Cl, $-O-CH_3$,, $-O-CF_3$, -CN, -OH, fenilo, y N-óxido;

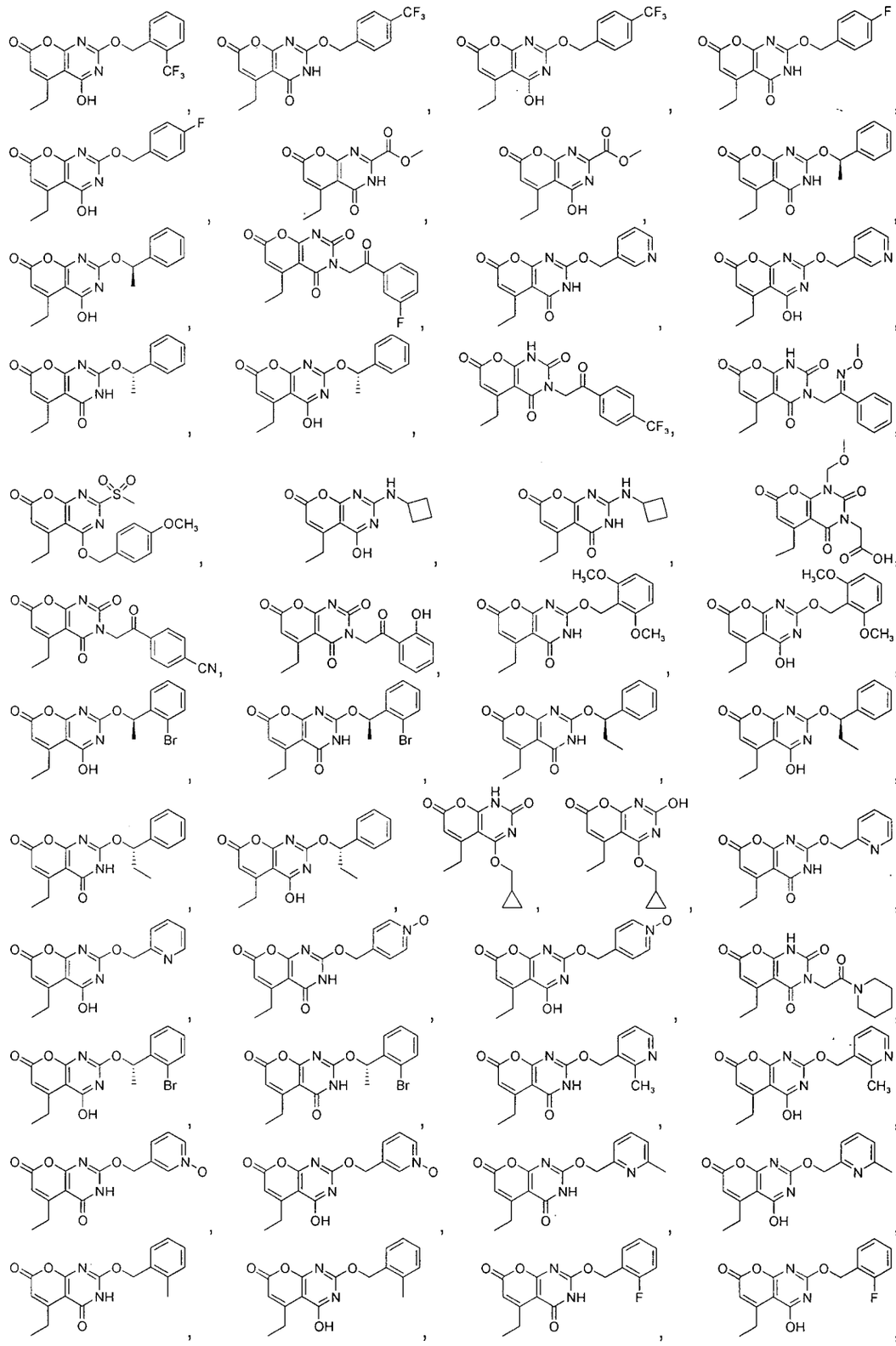
En otra realización del compuesto de fórmula (I), cada Y es seleccionado de manera independiente del grupo que consta de F, Cl, Br, $-CH_3$, $-CF_3$, $-O-CH_3$, $-O-CF_3$, -CN, -OH y fenilo; y

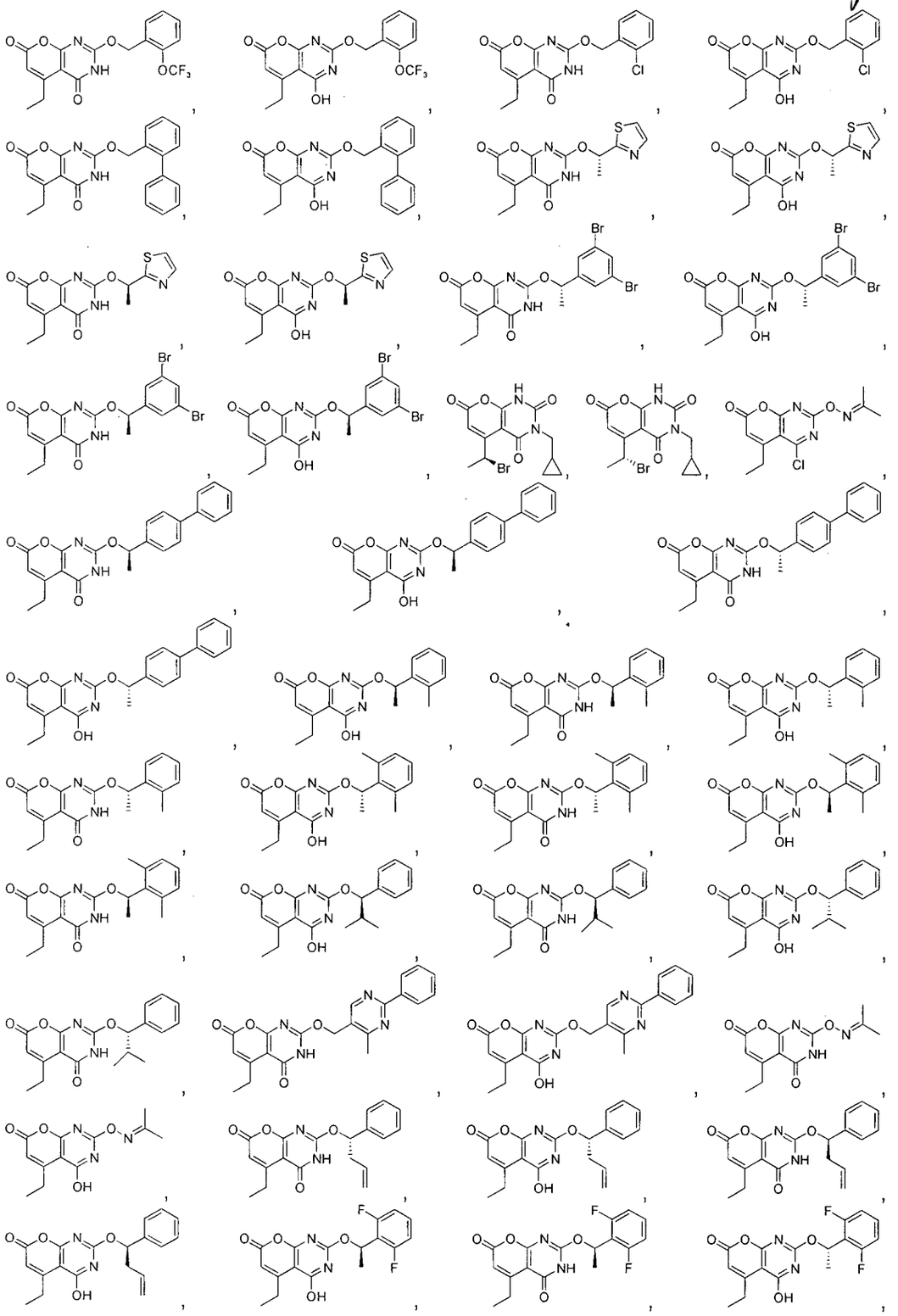
En otra realización del compuesto de fórmula (I), cada Z es seleccionado de manera independiente del grupo que consta de $-CH_3$, $-CF_3$, F, Br y Cl, $-O-CH_3$, $-O-CF_3$, -CN, -OH, fenilo, y N-óxido.

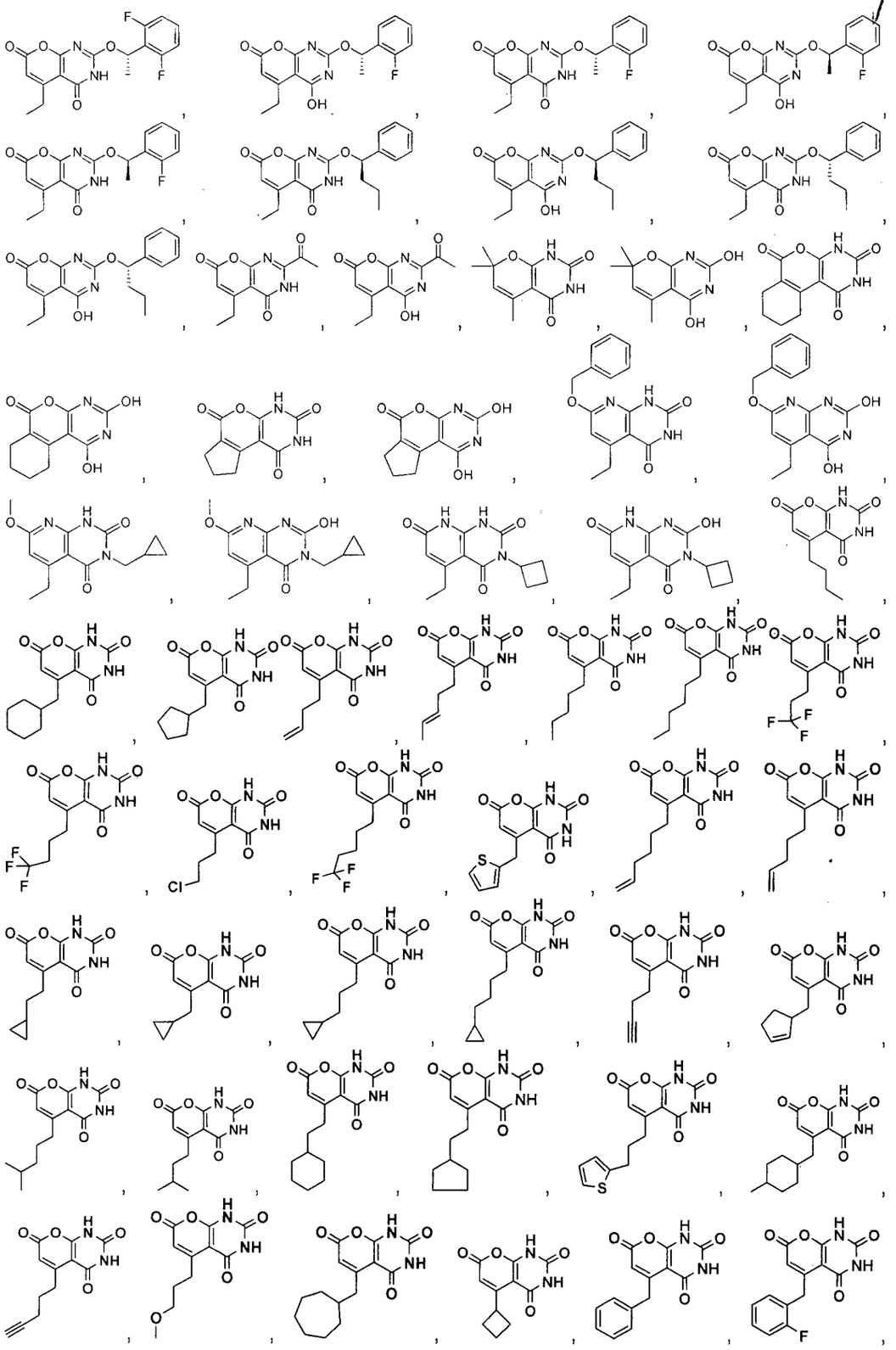
Los ejemplos ilustrativos no limitantes de los compuestos de fórmula (I), incluyen los siguientes compuestos:

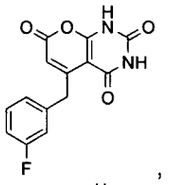
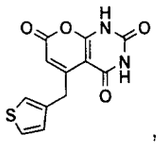
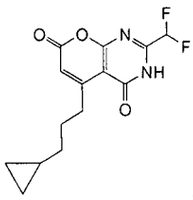
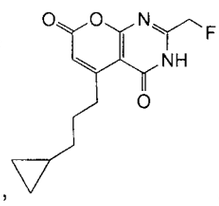
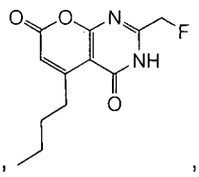
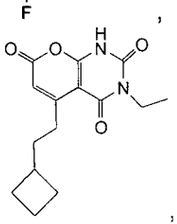
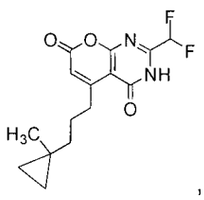
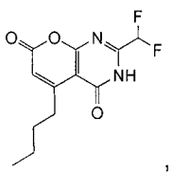
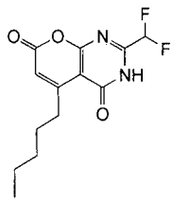
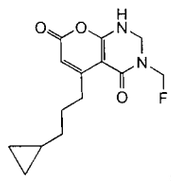
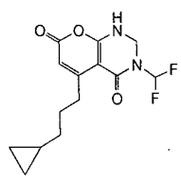
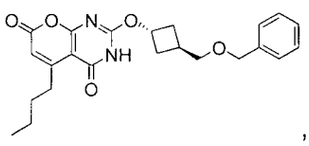
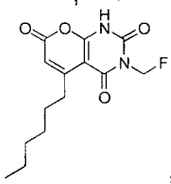
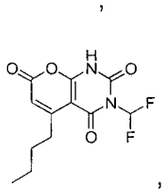
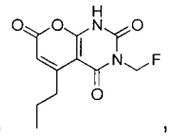
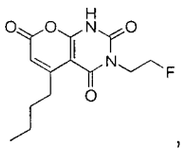
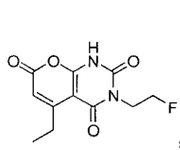
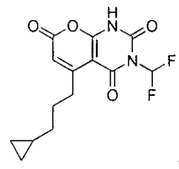
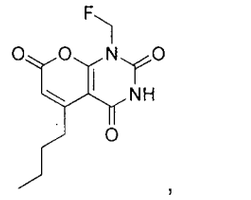
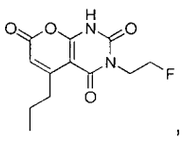
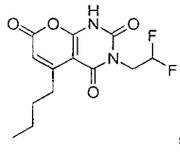
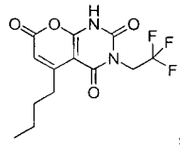
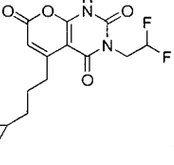
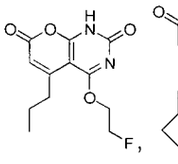
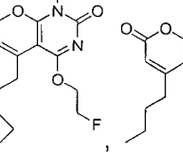
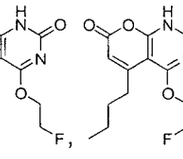
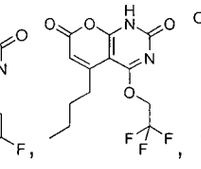
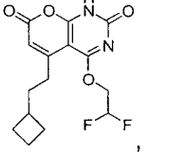











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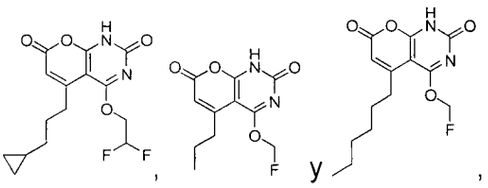
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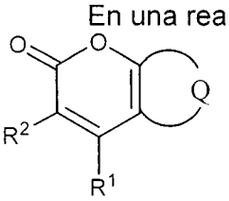
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y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros de los mismos.

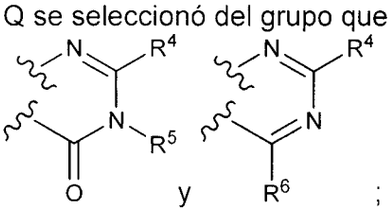
En una realización, los compuestos de fórmula (I) presentan la fórmula (II):



(II)

y sales aceptables para uso farmacéutico, solvatos, ésteres y tautómeros de los mismos, donde:

Q se seleccionó del grupo que consta de:



R^1 es -H, alquilo, haloalquilo, arilalquilo, -alquilen-S-alquilo o -alquilen-cicloalquilo;

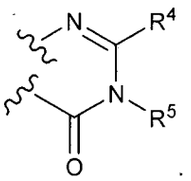
R^2 es -H, -CN, o -NHC(O)-alquilo;

R^4 es -O-cicloalquilo, –O-alquinilo, -O-alquinilen-cicloalquilo, haloalquilo o –O-N=C(R^{12})$_2$, donde ambos grupos R^{12} grupos, junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo y donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituido de manera opcional con –OH o alcoxi; y donde la porción cicloalquilo de un grupo -O-cicloalquilo puede estar sustituido de manera opcional con un grupo -alquilen-O-alquilen-arilo;

R^5 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo; y

R^6 es alcoxi, -O-alquilen-O-alquilo, -O-arilalquilo o –O-haloalquilo.

Las siguientes realizaciones se refieren a los compuestos de fórmula (II), donde Q es:



En una realización, R^1 es alquilo.

En otra realización, R^1 es haloalquilo.

En otra realización, R^1 es arilalquilo.

En aún otra realización, R^1 es -alquilen-S-alquilo.

En otra realización más, R^1 es -alquilen-cicloalquilo.

En otra realización, R^1 es -alquilen-ciclopropilo, -alquilen-ciclobutilo, -alquilen-ciclopentilo o -alquilen-ciclohexilo.

En una realización adicional, R^1 es -alquilen-cicloalquenilo.

En otra realización, R^1 es una cadena alquilo lineal que presenta de 1 a 6 átomos de carbono.

En una realización, R^1 es metilo.

En otra realización, R^1 es etilo.

En otra realización, R^1 es n-propilo.

En aún otra realización, R^1 es n-butilo.

En una realización, R^1 es n-pentilo.

En otra realización, R^1 es n-hexilo.

En otra realización más, R^1 es una cadena alquilo ramificada que presenta de 3 a 6 átomos de carbono.

En una realización adicional, R^1 es isopropilo.

En una realización, R^1 es isobutilo.

En otra realización, R^1 es isopentilo.

En otra realización, R^1 es sec-butilo.

En aún otra realización, R^1 es ter-butilo.

En otra realización más, R^1 es haloalquilo, que presenta de 1 a 3 átomos de F.

En otra realización, R^1 es $-(CH_2)_3CF_3$.

En una realización, R^4 es $-CF_3$.

En otra realización, R^4 es -H.

En otra realización, R^4 es -O-cicloalquilo.

En otra realización, R^4–O-alquinilo.

En aún otra realización, R^4 es -O-alquinilen-cicloalquilo.

En otra realización más, R^4 es haloalquilo.

En una realización adicional, R^4 es $-O-N=C(R^7)_2$.

En una realización, R^4 es $-CH_2F$.

En otra realización, R^4 es $-CH(F)_2$.

En otra realización, R^4 es $-CF_3$.

En otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C\equiv C(CH_2)_3CH_3$.

En aún otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_2CH_3$.

En otra realización más, R^4 es $-OCH_2C\equiv C$-ciclopropilo.

En una realización adicional, R^4 es $-OCH_2C\equiv CCH(OCH_3)CH_3$.

En una realización, R^4 es $-OCH_2C\equiv CCH(OH)CH_3$.

En otra realización, R^4 es $-OCH_2C\equiv CCH(OH)CH_2CH_3$.

En otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_2OCH_3$.

En aún otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_2OH$.

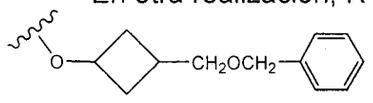
En otra realización más, R^4 es $-OCH_2C{\equiv}C(CH_2)_3OH$.

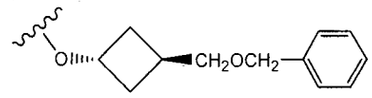
En una realización adicional, R^4 es $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}C$-ciclohexilo.

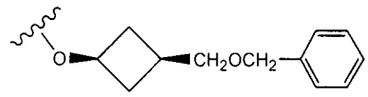
En una realización, R^4 es -O-ciclobutilo.

En otra realización, R^4 es:

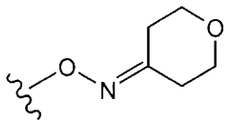


,


or



En una realización, R^4 es:



En una realización, R^5 es -H.

En otra realización, R^5 es –OH.

En otra realización, R^5 es alquilo.

En otra realización, R^5 es haloalquilo.

En aún otra realización, R^5 es -O-alquilo.

En otra realización más, R^5 es cicloalquilo.

En una realización adicional, R^5 es heterociclilo.

En una realización, R^5 es -O-arilalquilo.

En otra realización, R^5 es -alquilen-O-alquilo.

En una realización, R^5 es $-OCH_3$.

En otra realización, R^5 es ciclobutilo.

En otra realización, R^5 es etilo.

En aún otra realización, R^5 es n-morfolinilo.

En una realización, R^5 es -O-bencilo.

En otra realización, R^5 es $-CH_2CH_2OCH_3$.

En otra realización más, R^5 es $-OCH_2CH_3$.

En otra realización, R^5 es $-CH_2F$.

En una realización, R^5 es $-CH_2CH_2F$.

En otra realización, R^5 es –OH.

En una realización, R^1 es alquilo y R^5 es -H.

En otra realización, R^1 es haloalquilo y R^5 es -H.

En otra realización, R^1 es arilalquilo y R^5 es -H.

En aún otra realización, R^1 es -alquilen-S-alquilo y R^5 es -H.

En otra realización más, R^1 es -alquilen-cicloalquilo y R^5 es -H.

En una realización, R^1 es alquilo y R^5 es -H.

En otra realización, R^1 es haloalquilo y R^5 es -H

En otra realización, R^1 es arilalquilo y R^5 es -H.

En aún otra realización, R^1 es -alquilen-S-alquilo y R^5 es -H.

En otra realización más, R^1 es -alquilen-cicloalquilo y R^5 es -H.

En una realización, R^1 es alquilo, R^5 es -H y R^4 es -O-alquinilo.

En otra realización, R^1 es alquilo, R^5 es -H y R^4 es -O-alquinilen-cicloalquilo.

En otra realización, R^1 es alquilo, R^5 es -H y R^4 es haloalquilo.

En aún otra realización, R^1 es alquilo, R^5 es -H y R^4 es $-O-N=C(R^7)_2$.

En una realización, R^1 es haloalquilo, R^5 es -H y R^4 es -O-alquinilo.

En otra realización, R^1 es haloalquilo, R^5 es -H y R^4 es -O-alquinilen-cicloalquilo.

En otra realización, R^1 es haloalquilo, R^5 es -H y R^4 es haloalquilo.

En aún otra realización, R^1 es haloalquilo, R^5 es -H y R^4 es $-O-N=C(R^7)_2$.

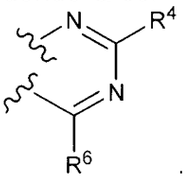
En una realización, R^1 es -alquilen-cicloalquilo, R^5 es -H y R^4 es -O-alquinilo.

En otra realización, R^1 es -alquilen-cicloalquilo, R^5 es -H y R^4 es -O-alquinilen-cicloalquilo.

En otra realización más, R^1 es -alquilen-cicloalquilo, R^5 es -H y R^4 es haloalquilo.

En aún otra realización, R^1 es -alquilen-cicloalquilo, R^5 es -H y R^4 es -O-N=C(R^7)$_2$.

Las siguientes realizaciones se refieren a los compuestos de fórmula (II), donde Q es:



En una realización, R^1 es alquilo.

En otra realización, R^1 es haloalquilo.

En otra realización, R^1 es arilalquilo.

En aún otra realización, R^1 es -alquilen-S-alquilo.

En otra realización más, R^1 es -alquilen-cicloalquilo.

En otra realización, R^1 es -alquilen-ciclopropilo, -alquilen-ciclobutilo, -alquilen-ciclopentilo o -alquilen-ciclohexilo.

En una realización adicional, R^1 es -alquilen-cicloalquenilo.

En otra realización, R^1 es una cadena alquilo lineal que presenta de 1 a 6 átomos de carbono.

En una realización, R^1 es metilo.

En otra realización, R^1 es etilo.

En otra realización, R^1 es n-propilo.

En aún otra realización, R^1 es n-butilo.

En una realización, R^1 es n-pentilo.

En otra realización, R^1 es n-hexilo.

En otra realización más, R^1 es una cadena alquilo ramificada que presenta de 3 a 6 átomos de carbono.

En una realización adicional, R^1 es isopropilo.

En una realización, R^1 es isobutilo.

En otra realización, R^1 es isopentilo.

En otra realización, R^1 es sec-butilo.

En aún otra realización, R^1 es ter-butilo.

En otra realización más, R^1 es haloalquilo, que presenta de 1 a 3 átomos de F.

En otra realización, R^1 es $-(CH_2)_3CF_3$.

En una realización, R^2 es -H.

En otra realización, R^2 es -CN.

En otra realización, R^2 es -NHC(O)-alquilo.

En aún otra realización, R^2 es $-NHC(O)CH_3$.

En una realización, R^4 es $-CF_3$.

En otra realización, R^4 es -H.

En otra realización, R^4 es -O-cicloalquilo.

En otra realización, R^4–O-alquinilo.

En aún otra realización, R^4 es -O-alquinilen-cicloalquilo.

En otra realización más, R^4 es haloalquilo.

En una realización adicional, R^4 es $-O-N=C(R^7)_2$.

En una realización, R^4 es $-CH_2F$.

En otra realización, R^4 es $-CH(F)_2$.

En otra realización, R^4 es $-CF_3$.

En otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C\equiv C(CH_2)_3CH_3$.

En aún otra realización, R^4 es $-OCH_2C\equiv CCH_2CH_2CH_3$.

En otra realización más, R^4 es $-OCH_2C{\equiv}C$-ciclopropilo.

En una realización adicional, R^4 es $-OCH_2C{\equiv}CCH(OCH_3)CH_3$.

En una realización, R^4 es $-OCH_2C{\equiv}CCH(OH)CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_2OCH_3$.

En aún otra realización, R^4 es $-OCH_2C{\equiv}CCH_2CH_2OH$.

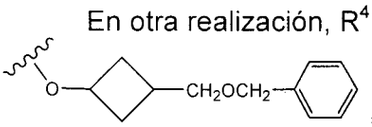
En otra realización más, R^4 es $-OCH_2C{\equiv}C(CH_2)_3OH$.

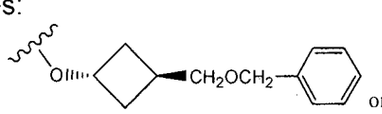
En una realización adicional, R^4 es $-OCH(CH_3)C{\equiv}CCH_2CH_3$.

En otra realización, R^4 es $-OCH_2C{\equiv}C$-ciclohexilo.

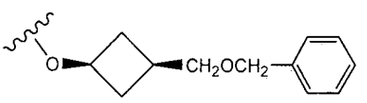
En una realización, R^4 es -O-ciclobutilo.

En otra realización, R^4 es:



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or



En una realización, R^4 es:



En una realización, R^6 es alcoxi.

En otra realización, R^6 es -O-alquilen-O-alquilo.

En otra realización, R^6 es -O-arilalquilo.

En aún otra realización, R^6 es -O-haloalquilo.

En otra realización más, R^6 es $-OCH_2$-(4-metoxifenilo).

En una realización, R^6 es $-OCH_2F$.

En otra realización, R^6 es $-OCH_2CH_2F$.

En otra realización, R^6 es $-OCH_2CH_3$

En aún otra realización, R^6 es $-OCH_2CH_2OCH_3$.

En una realización, R^1 es alquilo y R^4 es -O-alquinilo.

En otra realización, R^1 es alquilo y R^4 es -O-alquinilen-cicloalquilo.

En otra realización, R^1 es alquilo y R^4 es haloalquilo.

En aún otra realización, R^1 es alquilo y R^4 es -O-N=C(R^7)$_2$.

En una realización, R^1 es haloalquilo y R^4 es -O-alquinilo.

En otra realización, R^1 es haloalquilo y R^4 es -O-alquinilen-cicloalquilo.

En otra realización, R^1 es haloalquilo y R^4 es haloalquilo.

En aún otra realización, R^1 es haloalquilo y R^4 es -O-N=C(R^7)$_2$.

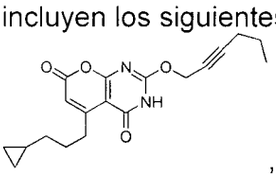
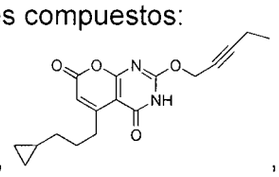
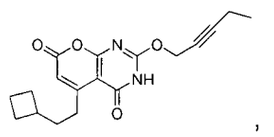
En una realización, R^1 es -alquilen-cicloalquilo y R^4 es -O-alquinilo.

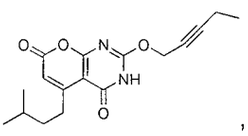
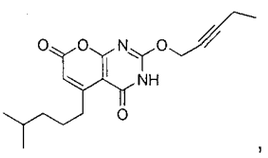
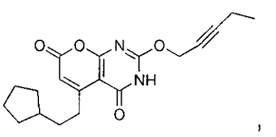
En otra realización, R^1 es -alquilen-cicloalquilo y R^4 es -O-alquinilen-cicloalquilo.

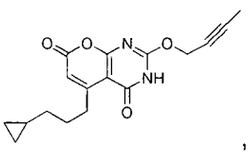
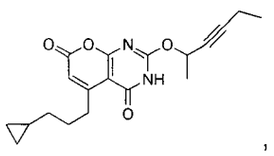
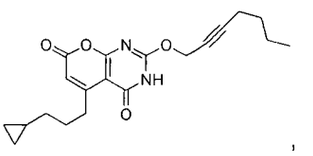
En otra realización más, R^1 es -alquilen-cicloalquilo y R^4 es haloalquilo.

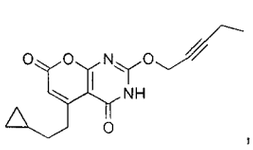
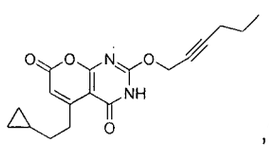
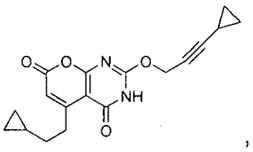
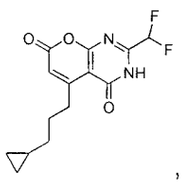
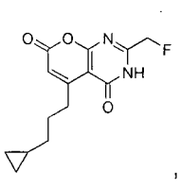
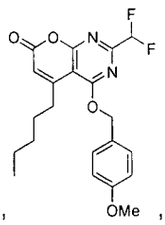
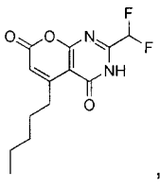
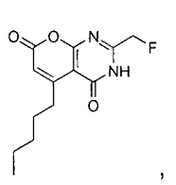
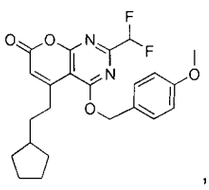
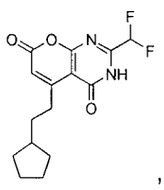
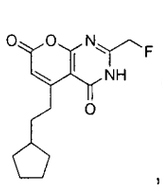
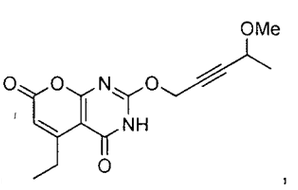
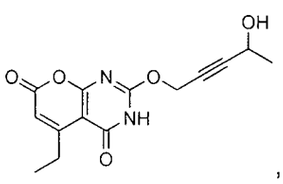
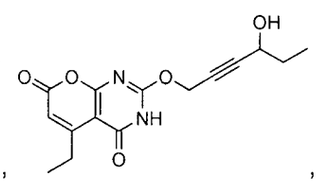
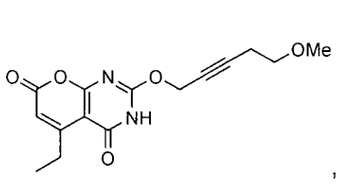
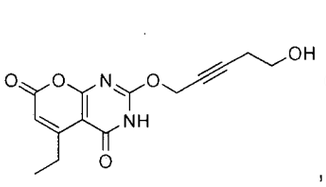
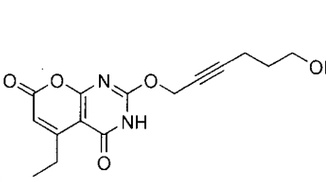
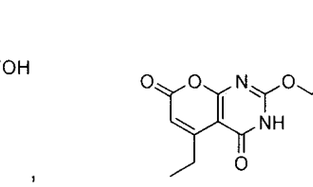
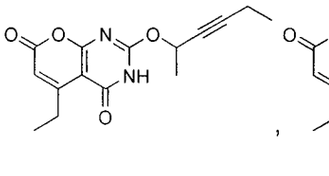
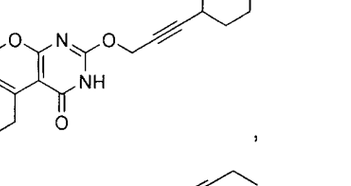
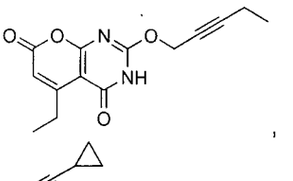
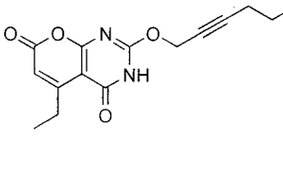
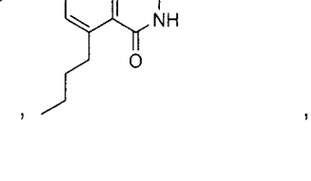
En aún otra realización, R^1 es -alquilen-cicloalquilo y R^4 es -O-N=C(R^7)$_2$.

Los ejemplos ilustrativos no limitantes de los compuestos de fórmula (II), incluyen los siguientes compuestos:


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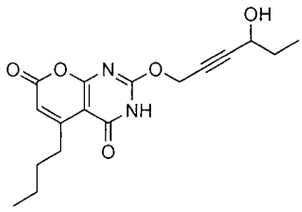
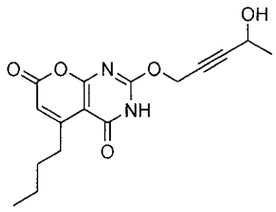
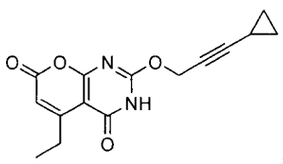
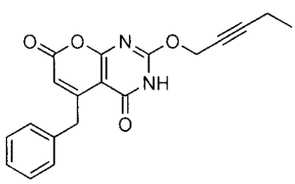
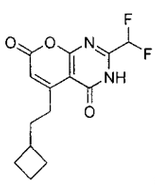
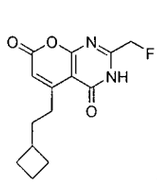
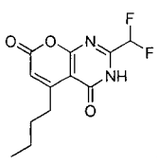
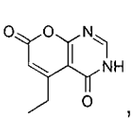
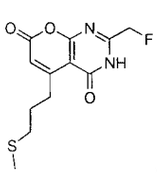
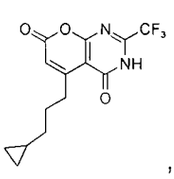
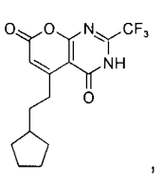
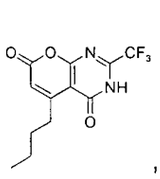
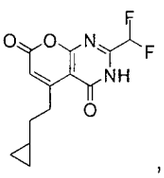
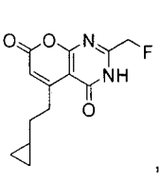
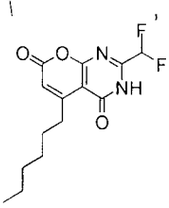
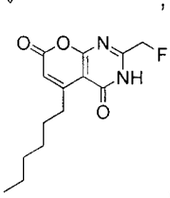
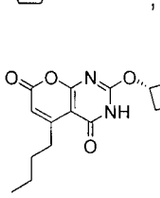
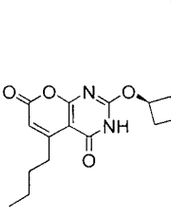
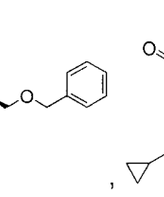
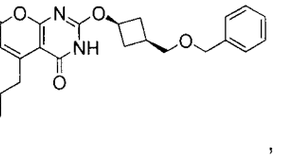
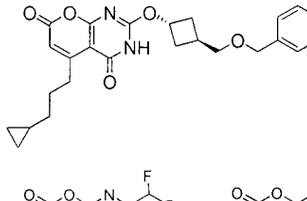
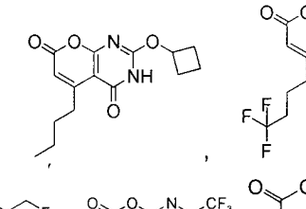
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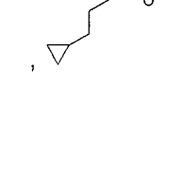
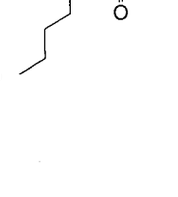
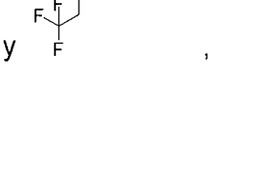
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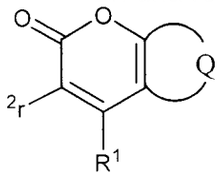
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y

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y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros de los mismos.

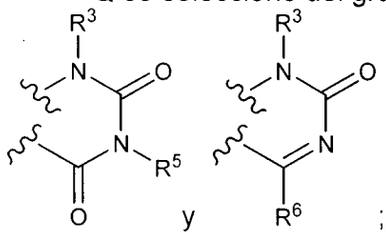
En una realización, los compuestos de fórmula (I) presentan la fórmula (III):



(III)

y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros de los mismos, donde:

Q se seleccionó del grupo que consta de:



y ;

R^1 es -H, alquilo, haloalquilo, arilalquilo, -alquilen-S-alquilo o -alquilen-cicloalquilo;

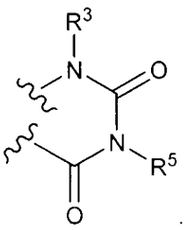
R^2 es -H, -CN, o -NHC(O)-alquilo;

R^3 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo;

R^5 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo; y

R^6 es alcoxi, -O-alquilen-O-alquilo, -O-arilalquilo o –O-haloalquilo.

Las siguientes realizaciones se refieren a los compuestos de fórmula (III), donde Q es:



En una realización, R^1 es alquilo.

En otra realización, R^1 es haloalquilo.

En otra realización, R^1 es -alquilen-S-alquilo.

En aún otra realización, R^1 es -arilalquilo.

En otra realización más, R^1 es -alquileno.

En una realización adicional, R^1 es –cicloalquilo.

En una realización, R^1 es -alquilen-cicloalquenilo.

En otra realización, R^1 es una cadena alquilo lineal que presenta de 1 a 6 átomos de carbono.

En una realización, R^1 es metilo.

En otra realización, R^1 es etilo.

En otra realización, R^1 es n-propilo.

En aún otra realización, R^1 es n-butilo.

En una realización, R^1 es n-pentilo.

En otra realización, R^1 es n-hexilo.

En otra realización más, R^1 es una cadena alquilo ramificada que presenta de 3 a 6 átomos de carbono.

En una realización adicional, R^1 es isopropilo.

En una realización, R^1 es isobutilo.

En otra realización, R^1 es isopentilo.

En otra realización, R^1 es sec-butilo.

En aún otra realización, R^1 es ter-butilo.

En otra realización más, R^1 es haloalquilo, que presenta de 1 a 3 átomos de F.

En otra realización, R^1 es $-(CH_2)_3CF_3$.

En una realización, R^2 es -H.

En otra realización, R^2 es -CN.

En otra realización, R^2 es -NHC(O)-alquilo.

En aún otra realización, R^2 es $-NHC(O)CH_3$.

En una realización, R^3 es -H.

En otra realización, R^3 es –OH.

En otra realización, R^3 es alquilo.

En otra realización, R^3 es haloalquilo.

En aún otra realización, R^3 es -O-alquilo.

En otra realización más, R^3 es cicloalquilo.

En una realización adicional, R^3 es heterociclilo.

En una realización, R^3 es -O-arilalquilo.

En otra realización, R^3 es -alquilen-O-alquilo.

En una realización, R^3 es $-OCH_3$.

En otra realización, R^3 es ciclobutilo.

En otra realización, R^3 es etilo.

En aún otra realización, R^3 es n-morfolinilo.

En una realización, R^3 es -O-bencilo.

En otra realización, R^3 es $-CH_2CH_2OCH_3$.

En otra realización más, R^3 es $-OCH_2CH_3$.

En otra realización, R^3 es $-CH_2F$.

En una realización, R^3 es $-CH_2CH_2F$.

En otra realización, R^3 es –OH.

En una realización, R^5 es -H.

En otra realización, R^5 es –OH.

En otra realización, R^5 es alquilo.

En otra realización, R^5 es haloalquilo.

En aún otra realización, R^5 es -O-alquilo.

En otra realización más, R^5 es cicloalquilo.

En una realización adicional, R^5 es heterociclilo.

En una realización, R^5 es -O-arilalquilo.

En otra realización, R^5 es -alquilen-O-alquilo.

En una realización, R^5 es $-OCH_3$.

En otra realización, R^5 es ciclobutilo.

En otra realización, R^5 es etilo.

En aún otra realización, R^5 es n-morfolinilo.

En una realización, R^5 es -O-bencilo.

En otra realización, R^5 es $-CH_2CH_2OCH_3$.

En otra realización más, R^5 es $-OCH_2CH_3$.

En otra realización, R^5 es $-CH_2F$.

En una realización, R^5 es $-CH_2CH_2F$.

En otra realización, R^5 es –OH.

En una realización, R^1 es alquilo y cada uno de R^2, R^3 y R^5 es -H.

En otra realización, R^1 es alquilo, R^2 es -H y uno, pero no ambos de R^3 y R^5 es -H.

En otra realización, R^1 es alquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es alquilo.

En aún otra realización, R^1 es alquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es -O-alquilo.

En otra realización más, R^1 es alquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es –cicloalquilo.

En una realización, R^1 es alquilo, $R^{2\ es\ -H}$ y uno de R^3 y R^5 es -H y el otro es –heterociclilo.

En una realización, R^1 es alquilo, $R^{2\ es\ -H}$ y uno de R^3 y R^5 es -H y el otro es –alquilen-O-alquilo.

En una realización, R^1 es –alquilen-cicloalquilo y cada uno de R^2, R^3 y R^5 es -H.

En otra realización, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno, pero no ambos de R^3 y R^5 es -H.

En otra realización, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es alquilo.

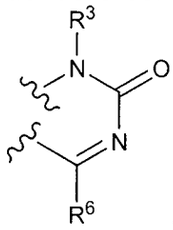
En aún otra realización, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es -O-alquilo.

En otra realización más, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es –cicloalquilo.

En una realización, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es –heterociclilo.

En una realización, R^1 es –alquilen-cicloalquilo, R^2 es -H y uno de R^3 y R^5 es -H y el otro es –alquilen-O-alquilo.

Las siguientes realizaciones se refieren a los compuestos de fórmula (III), donde Q es:



En una realización, R^6 es alcoxi.

En otra realización, R^6 es -O-alquilen-O-alquilo.

En otra realización, R^6 es -O-arilalquilo.

En aún otra realización, R^6 es -O-haloalquilo.

En otra realización más, R^6 es $–OCH_2$-(4-metoxifenil).

En una realización, R^6 es $–OCH_2F$.

En otra realización, R^6 es $-OCH_2CH_2F$.

En otra realización, R^6 es $-OCH_2CH_3$

En aún otra realización, R^6 es $-OCH_2CH_2OCH_3$.

En una realización, R^1 es alquilo.

En otra realización, R^1 es haloalquilo.

En otra realización, R^1 es -alquilen-S-alquilo.

En aún otra realización, R^1 es -arilalquilo.

En otra realización más, R^1 es -alquileno.

En una realización adicional, R^1 es –cicloalquilo.

En una realización, R^1 es -alquilen-cicloalquenilo.

En otra realización, R^1 es una cadena alquilo lineal que presenta de 1 a 6 átomos de carbono.

En una realización, R^1 es metilo.

En otra realización, R^1 es etilo.

En otra realización, R^1 es n-propilo.

En aún otra realización, R^1 es n-butilo.

En una realización, R^1 es n-pentilo.

En otra realización, R^1 es n-hexilo.

En otra realización más, R^1 es una cadena alquilo ramificada que presenta de 3 a 6 átomos de carbono.

En una realización adicional, R^1 es isopropilo.

En una realización, R^1 es isobutilo.

En otra realización, R^1 es isopentilo.

En otra realización, R^1 es sec-butilo.

En aún otra realización, R^1 es ter-butilo.

En otra realización más, R^1 es haloalquilo, que presenta de 1 a 3 átomos de F.

En otra realización, R^1 es $-(CH_2)_3CF_3$.

En una realización, R^2 es -H.

En otra realización, R^2 es -CN.

En otra realización, R^2 es -NHC(O)-alquilo.

En aún otra realización, R^2 es $-NHC(O)CH_3$.

En una realización, R^3 es -H.

En otra realización, R^3 es –OH.

En otra realización, R^3 es alquilo.

En otra realización, R^3 es haloalquilo.

En aún otra realización, R^3 es -O-alquilo.

En otra realización más, R^3 es cicloalquilo.

En una realización adicional, R^3 es heterociclilo.

En una realización, R^3 es -O-arilalquilo.

En otra realización, R^3 es -alquilen-O-alquilo.

En una realización, R^3 es $-OCH_3$.

En otra realización, R^3 es ciclobutilo.

En otra realización, R^3 es etilo.

En aún otra realización, R^3 es n-morfolinilo.

En una realización, R^3 es -O-bencilo.

En otra realización, R^3 es $-CH_2CH_2OCH_3$.

En otra realización más, R^3 es $-OCH_2CH_3$.

En otra realización, R^3 es $-CH_2F$.

En una realización, R^3 es $-CH_2CH_2F$.

En otra realización, R^3 es –OH.

En una realización, R^6 es alcoxi, R^1 es alquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es alcoxi, R^1 es alquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es alcoxi, R^1 es alquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es alcoxi, R^1 es alquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es alcoxi, R^1 es alquilo, R^2 es -H y R^3 es –heterociclilo.

En una realización, R^6 es alcoxi, R^1 es alquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –heterociclilo.

En una realización, R^6 es alcoxi, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo, R^2 es -H y y R^3 es –heterociclilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es alquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –heterociclilo.

En una realización, R^6 es -O-alquilen-O-alquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es -O-arilalquilo, R^1 es alquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es -O-arilalquilo, R^1 es alquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-arilalquilo, R^1 es alquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-arilalquilo, R^1 es alquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es -O-arilalquilo, R^1 es alquilo, R^2 es -H y y R^3 es –heterociclilo.

En una realización, R^6 es -O-arilalquilo, R^1 es alquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –heterociclilo.

En una realización, R^6 es -O-arilalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

En una realización, R^6 es -O-haloalquilo, R^1 es alquilo y cada uno de R^2 y R^3 es -H.

En otra realización, R^6 es -O-haloalquilo, R^1 es alquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-haloalquilo, R^1 es alquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-haloalquilo, R^1 es alquilo, R^2 es -H y R^3 es –cicloalquilo.

En una realización, R^6 es -O-haloalquilo, R^1 es alquilo, R^2 es -H y R^3 es –heterociclilo.

En una realización, R^6 es -O-haloalquilo, R^1 es alquilo, R^2 es -H y R^3 es –alquilen-O-alquilo.

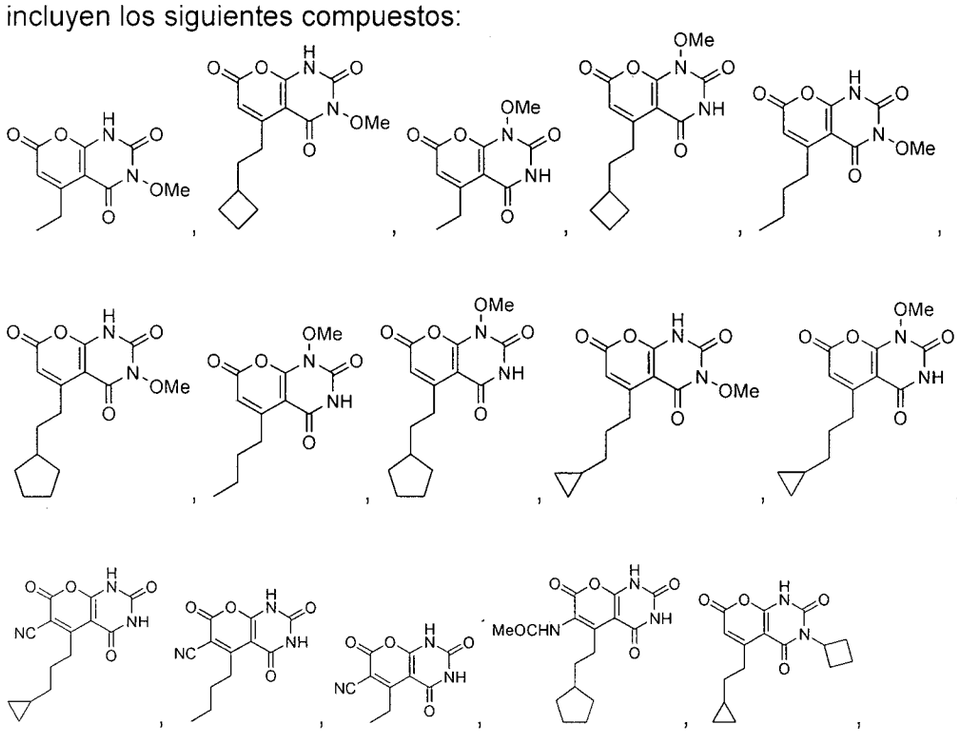
En una realización, R^6 es -O-haloalquilo, R^1 es –alquilen-cicloalquilo y cada uno de R^2 y R^3 es -H.

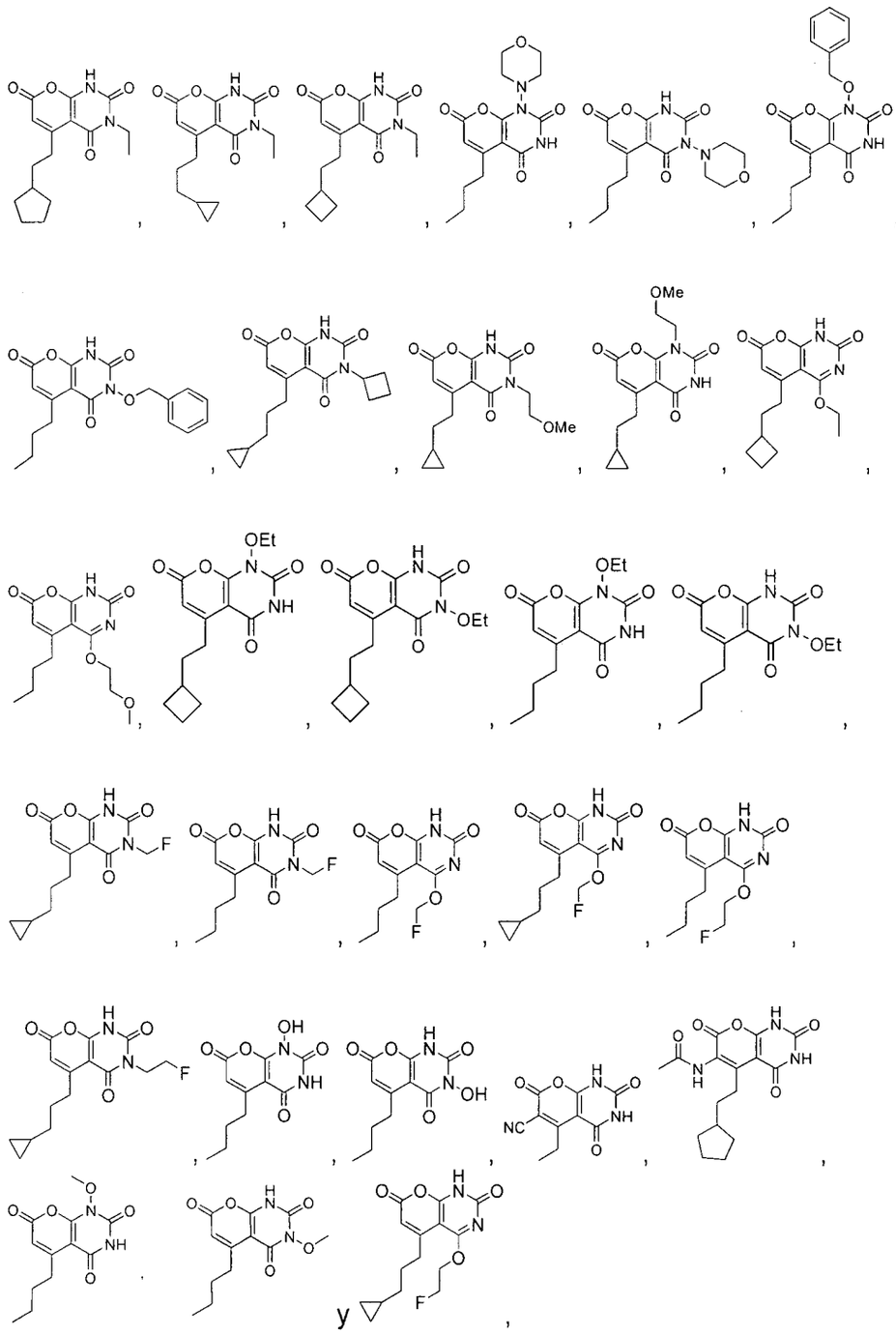
En otra realización, R^6 es -O-haloalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es alquilo.

En aún otra realización, R^6 es -O-haloalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es -O-alquilo.

En otra realización más, R^6 es -O-haloalquilo, R^1 es –alquilen-cicloalquilo, R^2 es -H y R^3 es –cicloalquilo.

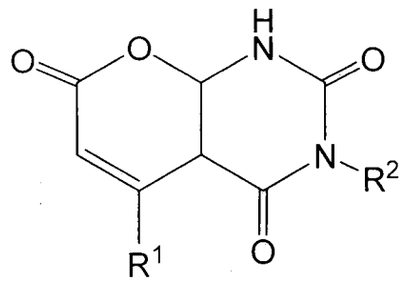
Los ejemplos ilustrativos no limitantes de los compuestos de fórmula (III), incluyen los siguientes compuestos:





y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros de los mismos.

En una realización, los compuestos de fórmula (I) son compuestos de fórmula (IV):



(IV)

y y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros del mismo,

donde:

R^1 es haloalquilo; y

R^2 es H o cicloalquilo.

En una realización, R^1 es fluoroalquilo.

En otra realización, R^1 es –alquilen-F.

En otra realización, R^1 es $^-$alquilen-CF_2.

En aún otra realización, R^1 es $^-(CH_2)_2$-CF_2.

En otra realización, R^1 es $^-(CH_2)_3$-CF_2.

En otra realización, R^1 es $^-(CH_2)_4$-CF_2.

En otra realización más, R^1 es $^-(CH_2)_5$-CF_2.

En aún otra realización, R^1 es $^-(CH_2)_3$-F.

En otra realización, R^1 es $^-(CH_2)_4$-F.

En otra realización, R^1 es $^-(CH_2)_5$-F.

En otra realización más, R^1 es $^-(CH_2)_6$-F.

En una realización, R^2 es H.

En otra realización, R^2 es ciclopropilo.

En otra realización, R^2 es ciclobutilo.

En aún otra realización, R^2 es ciclopentilo.

En otra realización, R^2 es ciclohexilo.

En una realización, R^1 es fluoroalquilo y R^2 es H.

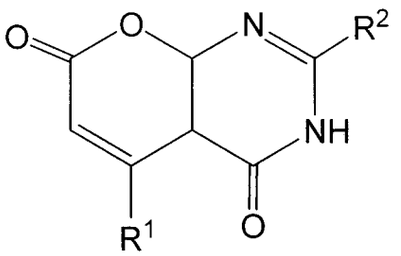
En otra realización, R^1 es fluoroalquilo y R^2 es cicloalquilo.

En otra realización, R^1 es –alquilen-CF_2 y R^2 es H.

En otra realización, R^1 es –alquilen-CF_2 y R^2 es cicloalquilo.

Los ejemplos no limitantes de compuestos de fórmula (IV) incluyen compuestos **834**, **835** y **837-841** como se detallan en las sección de Ejemplos a continuación y sales aceptables para uso farmacéutico, solvatos, ésteres y tautómeros de los mismos.

En otra realización, los compuestos de fórmula (I) son compuestos de fórmula (V):



(V)

y y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros del mismo,

donde:

R^1 y R^2 son ambos, de manera independiente, haloalquilo.

En una realización, R^1 es fluoroalquilo.

En otra realización, R^1 es –alquilen-F.

En otra realización, R^1 es ¯alquilen-CF_2.

En aún otra realización, R^1 es ¯$(CH_2)_2$-CF_2.

En otra realización, R^1 es ¯$(CH_2)_3$-CF_2.

En otra realización, R^1 es –$(CH_2)_4$-CF_2.

En otra realización más, R^1 es ¯$(CH_2)_5$-CF_2.

En aún otra realización, R^1 es ¯$(CH_2)_3$-F.

En otra realización, R^1 es ¯$(CH_2)_4$-F.

En otra realización, R^1 es $-(CH_2)_5$-F.

En otra realización más, R^1 es $-(CH_2)_6$-F.

En una realización, R^2 es fluoroalquilo.

En otra realización, R^2 es -CHF_2.

En una realización, R^1 es fluoroalquilo y R^2 es fluoroalquilo.

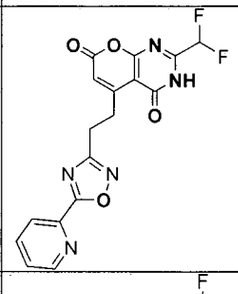
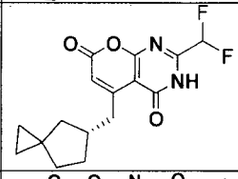
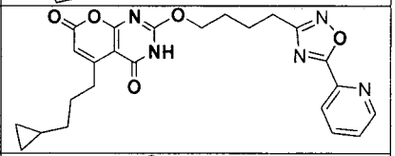
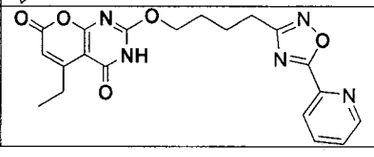
En otra realización, R^1 es fluoroalquilo y R^2 es -CHF_2.

En otra realización, R^1 es –alquilen-CF_2 y R^2 es fluoroalquilo.

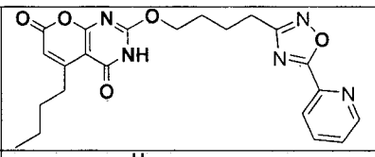
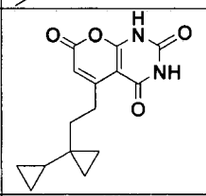
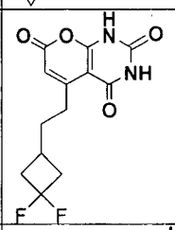
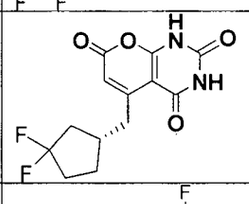
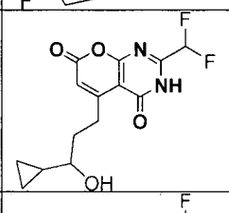
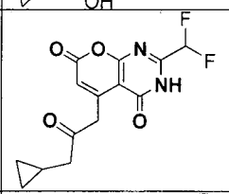
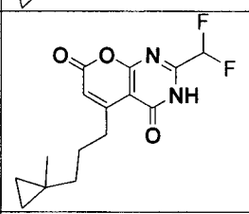
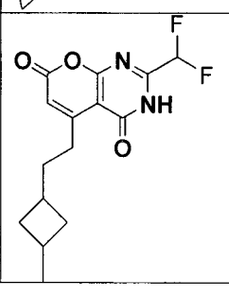
En aún otra realización, R^1 es –alquilen-CF_2 y R^2 es -CHF_2.

Los ejemplos no limitantes de compuestos de fórmula (V) incluyen compuestos **836** y **842-844** como se describió en la sección de Ejemplos a continuación y sales aceptables para uso farmacéutico, solvatos, ésteres y tautómeros de los mismos.

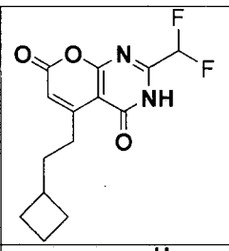
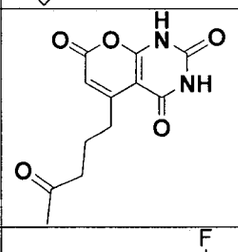
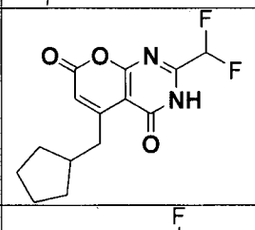
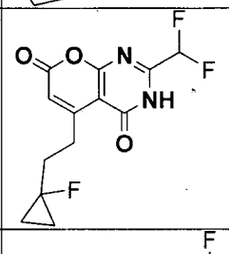
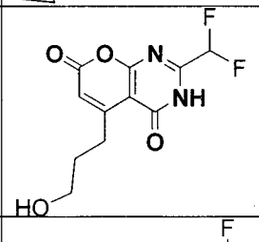
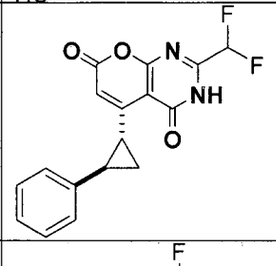
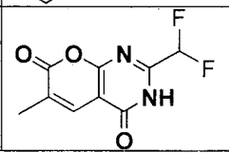
Los ejemplos adicionales no limitantes de compuestos de fórmula (I) incluyen compuestos **845-911** como se describió en la siguiente tabla:

Compuesto Nº	**Estructura**
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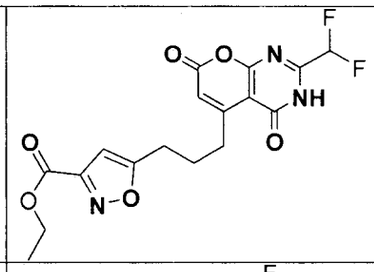
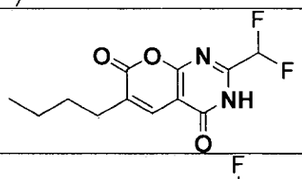
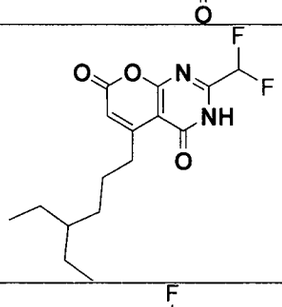
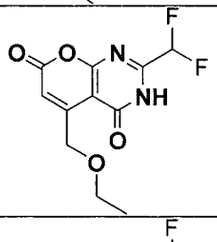
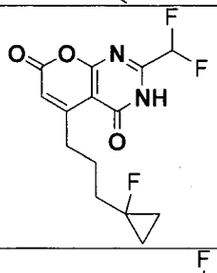
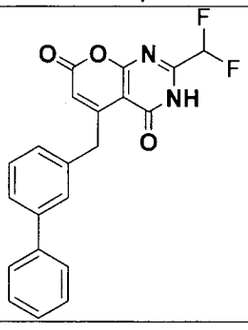
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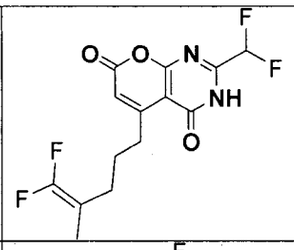
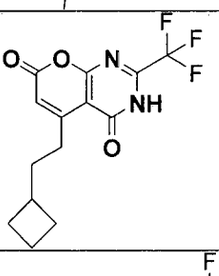
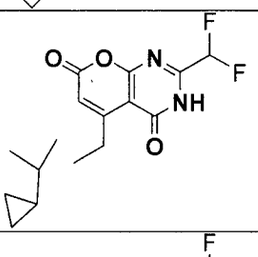
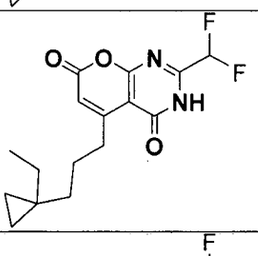
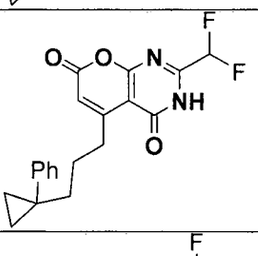
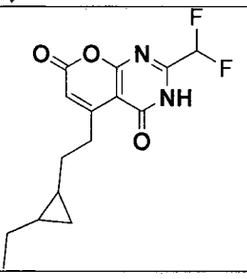
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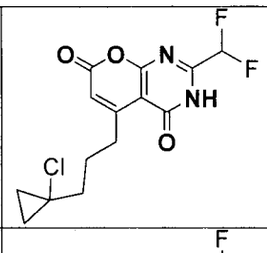
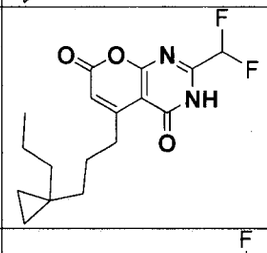
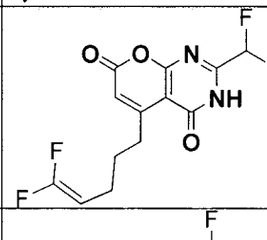
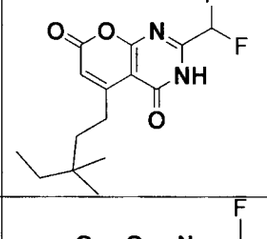
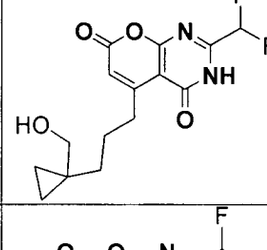
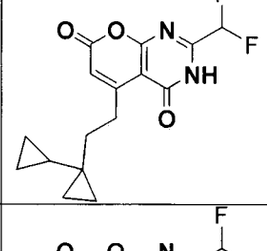
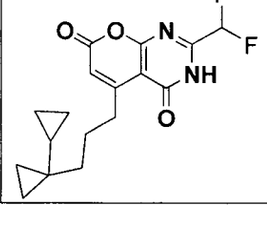
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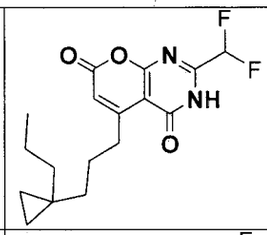
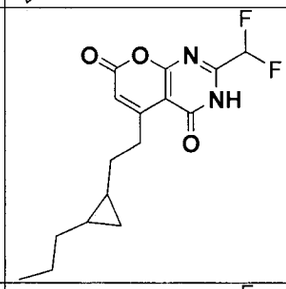
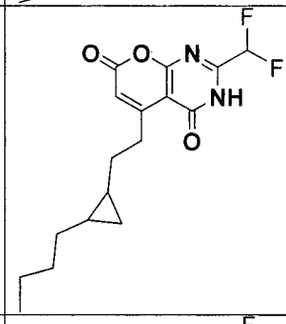
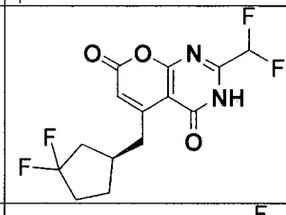
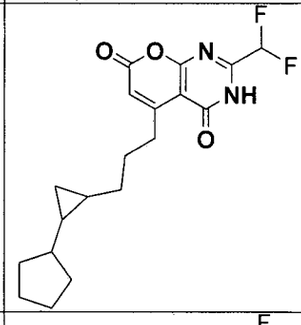
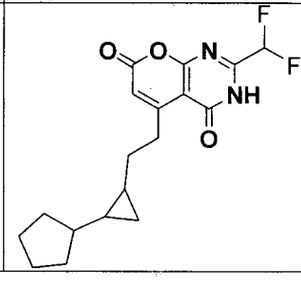
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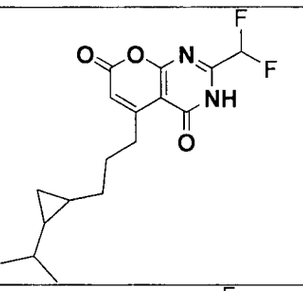
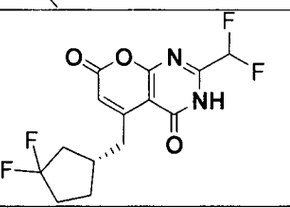
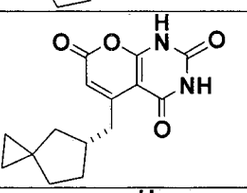
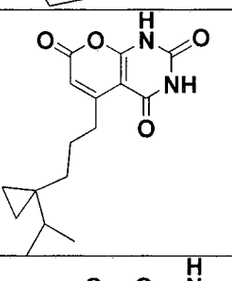
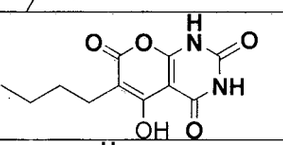
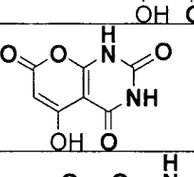
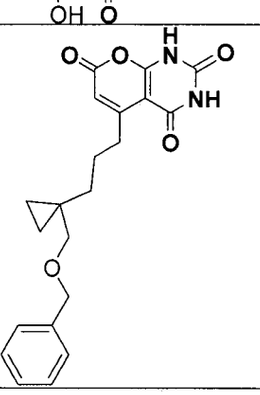
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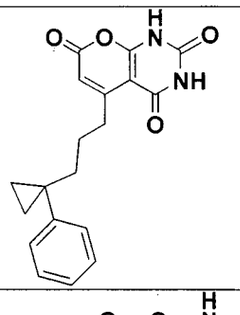
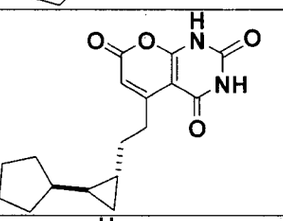
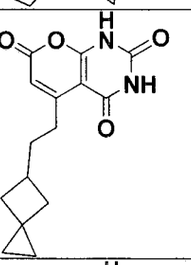
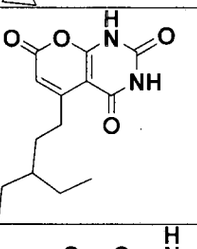
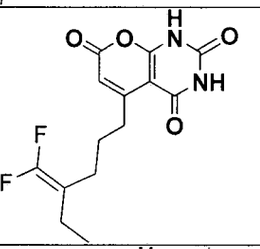
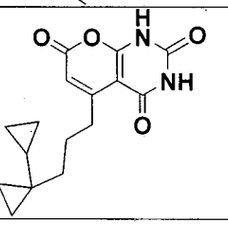
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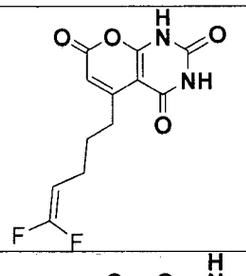
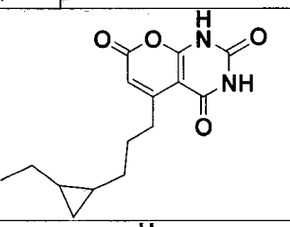
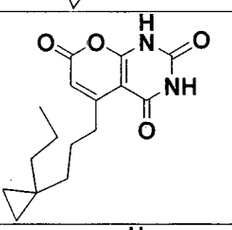
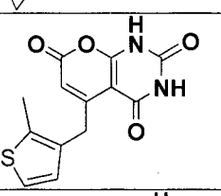
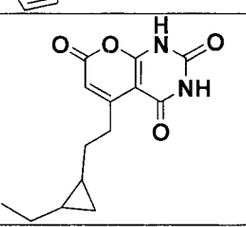
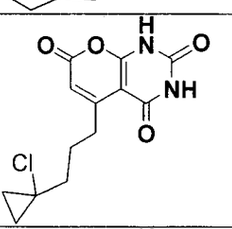
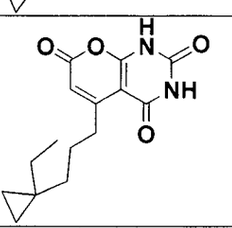
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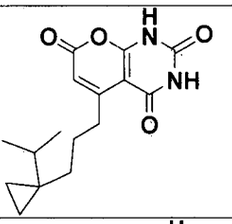
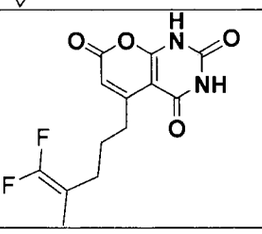
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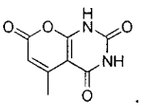
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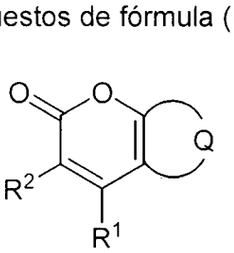
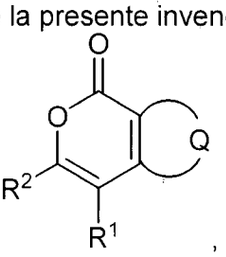
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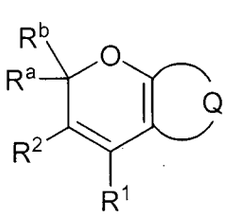
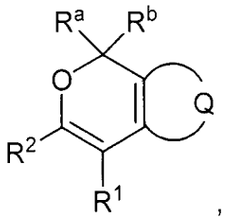
y y sales aceptables para uso farmacéutico, solvatos, ésteres o tautómeros del mismo.

En todas las realizaciones de la presente invención, cuando L es (f) y R^2, R^3 y R^5 son cada uno H, entonces R^1 no es $-CH_3$. Un especialista en el arte será capaz de recnocer que la presente invención no incluye el siguiente compuesto, o las formas tautoméricas del mismo:

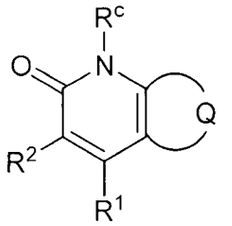
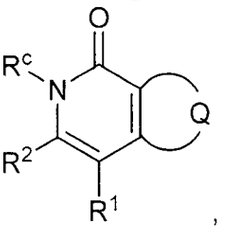


El resto L de fórmula (I) de la presente invención puede tener cualquier orientación químicamente estable. Ello significa que cuando L es (f), los compuestos de fórmula (I) de la presente invención pueden incluir los siguientes:

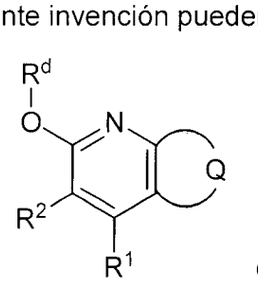
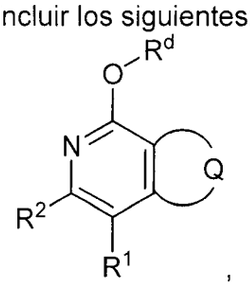
 o  , o sales, solvatos, ésteres o tautómeros del mismo. Cuando L es (g), los compuestos de fórmula (I) de la presente invención pueden incluir los siguientes:

o , o sales, solvatos, ésteres o tautómeros de los mismos. Cuando L es (h), los compuestos de fórmula (I) de la presente invención pueden incluir los siguientes:

o , o sales, solvatos, ésteres o tautómeros de los mismos. Cuando L es (i), los compuestos de fórmula (I) de la presente invención pueden incluir los siguientes:

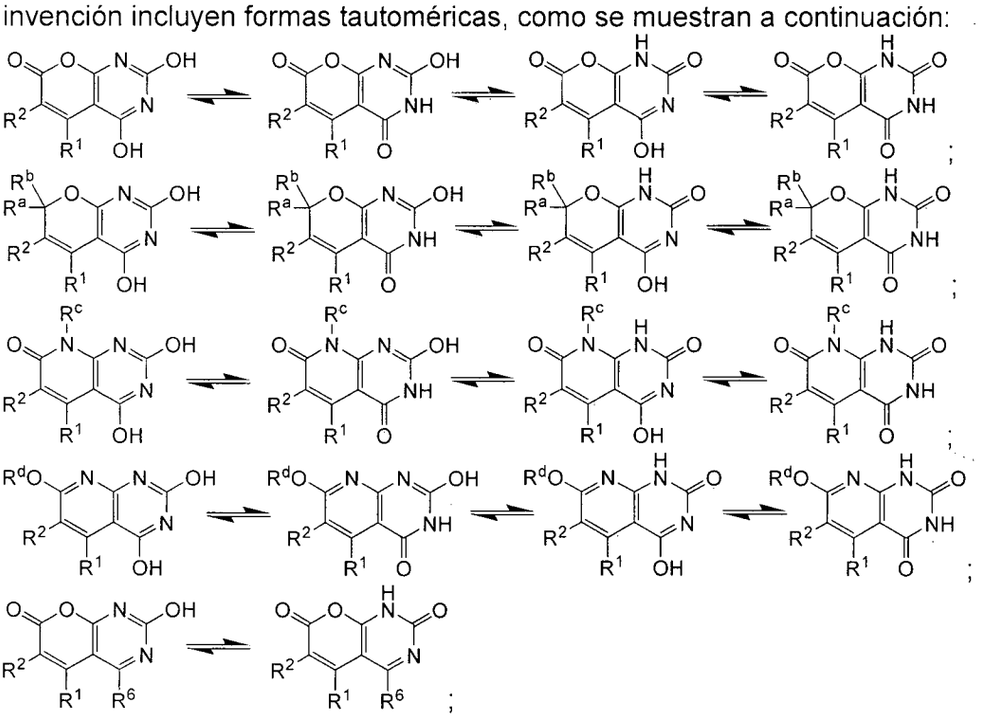
o , o sales, solvatos, ésteres o tautómeros de los mismos.

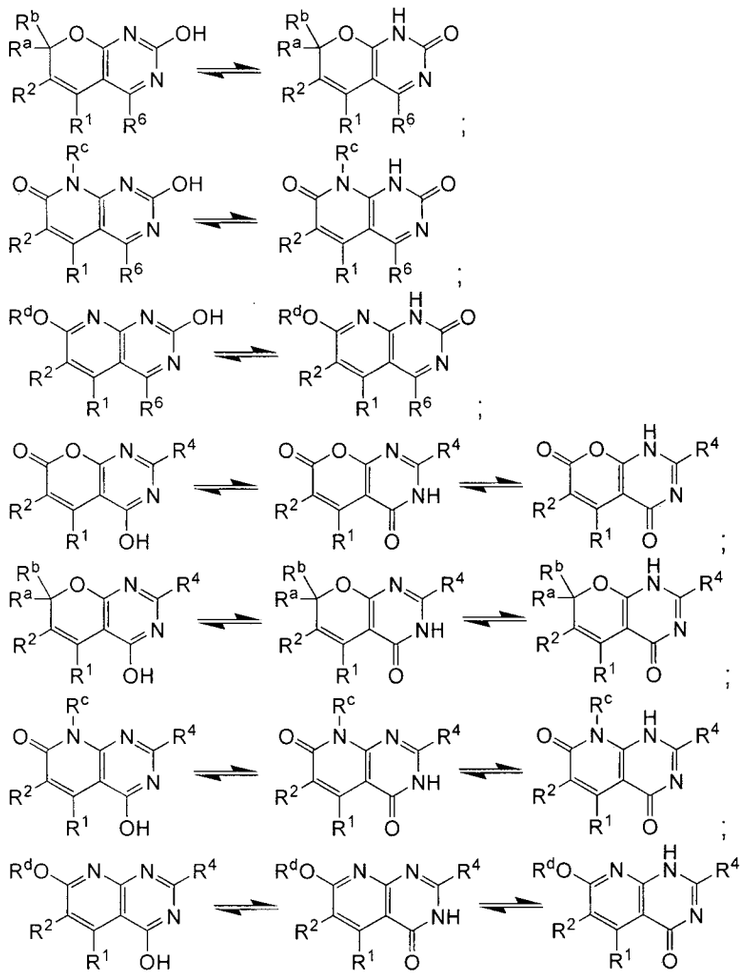
Los compuestos de fórmula (I) pueden estar purificados a un grado adecuado para su uso como una sustancia farmacéuticamente activa. Ello significa, que los compuestos de fórmula (I) pueden ser de una pureza de 95% en peso o más (excluyendo adyuvantes tales como vehículos, solventes aceptables para uso farmacéutico etc., que se utilizan para formular el compuesto de fórmula (I) en una forma convencional, tal como un comprimido, una cápsula, solución IV etc. adecuada para la administración al paciente). La pureza puede ser de 97% en peso o más o 99% en peso o más. Un compuesto purificado de fórmula (I) incluye un isómero individual que presenta una pureza, como se indicó

previamente, de 95% en peso o más, de 97% en peso o más, o de 99% en peso o más como se indicó antes.

Alternativamente, el compuesto purificado de fórmula (I) puede incluir una mezcla de isómeros, presentando cada uno una estructura de acuerdo con la fórmula (I), en la que la suma de impurezas (es decir, compuestos u otros contaminantes, salvo los adyuvantes que se indicaron previamente) es de 5% en peso o inferior, de 3% en peso o inferior, o de 1% en peso o menos. Por ejemplo, el compuesto purificado de fórmula (I) puede ser una mezcla isomérica de compuestos de la Estructura (I), donde la proporción de las cantidades de los isómeros es aproximadamente 1:1 y la cantidad combinada de los dos isómeros es de 95% en peso o más, de 97% en peso o más o de 99% en peso o más.

Los compuestos de fórmula (I) y las sales, solvatos, ésteres y profármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o un iminoéter). Todas aquellas formas tautoméricas se incluyen aquí como parte de la presente invención. Por ejemplo, los compuestos de la presente invención incluyen formas tautoméricas, como se muestran a continuación:





Tales formas tautoméricas se consideran equivalentes.

Como se utilizó previamente y a través de esta revelación, los siguientes términos, salvo indicación en contrario, deben entenderse con los siguientes significados:

"AcOH" significa ácido acético.

"Bn" significa bencilo.

"BnBr" significa bromuro de bencilo.

"BnOH" significa alcohol bencílico.

"CDI" significa carbodiimida.

"DCM" significa diclorometano (CH_2Cl_2).

"DIAD" significa diisopropil azodicarboxilato.

"DIEA" significa N,N-diisopropiletilamina.

"DMF" significa dimetilformamida.

"Et" significa etilo.

"EtO_2" significa dietiléter.

"EtOAc" significa etilacetato.

"HATU" significa O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametilamonio hexafluorophosphate.

"HOAc" significa ácido acético.

"IBMX" significa 3-isobutil-1-metilxantina.

"*m*-CPBA" significa ácido m-cloroperoxibenzoico.

"Me" significa metilo.

"MeCN" significa acetonitrilo.

"MeI" significa yodometano.

"Me_2S" significa azufre de dimetilo.

"MeOH" significa metanol.

"NaOEt" significa etóxido de sodio.

"NaOMe" significa metóxido de sodio.

"NBS" significa *N*-bromosuccinimida.

"NEt_3" significa trietilamina.

"NIS" significa *N*-yodosuccinimida.

"*t*-Bu" significa butilo terciario.

"*t*-BuOK" significa ter-butóxido de potasio.

"TFA" significa ácido trifluoroacético.

"TfOH" significa ácido trifluorometansulfónico.

"THF" significa tetrahidrofurano.

"TLC" significa cromatografía de capa fina.

"PMBOH" significa alcohol 4-metoxi bencílico.

"PMBCl" significa cloruro de 4-metoxibencilo.

"TLC prep" significa cromatografía preparativa de capa fina.

"Paciente" incluye a ambos, humanos y animales.

"Mamífero" significa humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarburo alifático que puede ser lineal o ramificado y comprende aproximadamente 1 a aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 a aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo de mayor preferencia contienen aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior, tales como metilo, etilo o propilo, están unidos a una cadena lineal alquilo. "Alquilo inferior" significa un grupo que presenta aproximadamente 1 a aproximadamente 6 átomos de carbono en la cadena que puede ser lineal o ramificada. "Alquilo" puede estar no sustituido o sustituido opcionalmente con uno o más sustituyentes que pueden ser iguales o diferentos, siendo cada sustituyente independientemente seleccionado del grupo que consta de halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -$N(alquil)_2$, carboxi y –C(O)O-alquilo. Los ejemplos no limitantes de grupos alquilo adecuados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquenilo" significa un grupo hidrocarburo alifático que contiene al menos un doble enlace carbono-carbono y que puede ser lineal o ramificado y comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y de mayor preferencia aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a la cadena lineal alquenilo. "Alquenilo inferior" significa

aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena que puede ser lineal o ramificada. "Alquenilo" puede estar no sustituido o sustituido opcionalmente con uno o más sustituyentes que pueden ser iguales o diferentos, siendo cada sustituyente independientemente seleccionado del grupo que consta de halo, alquilo. arilo, cicloalquilo, ciano, alcoxi y –S(alquilo). Los ejemplos no limitantes de grupos alquenilo adecuados incluyen etenilo, propenilo, n-butenilo, 3-metilbut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquileno" significa un grupo disfuncional obtenido por remoción de un átomo de hidrogeno de un grupo alquilo que se definió previamente. Los ejemplos no limitantes de alquileno incluyen metileno, etileno y propileno.

"Alquenileno" significa un grupo disfuncional obtenido por remoción de un átomo de hidrogeno de un grupo alquenilo que se definió previamente. Los ejemplos no limitantes de alquenileno incluyen –CH=CH-, $-C(CH_3)=CH-$ y $-CH=CHCH_2-$.

"Alquilen-arilo" (o aril-alquilen-) significa un grupo, en el que el arilo y el alquileno son como se describieron previamente. La unión con el resto precursor es a través del alquileno. El resto alquileno puede estar unido a uno o más restos arilo. Los alquilen-arilos pueden comprende un grupo alquileno inferior. Los ejemplos no limitantes de grupos alquilen-arilo adecuados incluyen bencilo, 2-fenetilo, 2,2-difeniletileno y naftalenilmetilo.

"Alquinilo" significa un grupo hidrocarburo alifático que contiene al menos un triple enlace carbono-carbono y que puede ser lineal o ramificado y comprende aproximadamente 2 a aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2 a aproximadamente 12 átomos de carbono en la cadena; y de mayor preferencia aproximadamente 2 a aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior, tales como metilo, etilo o propilo, están unidos a

una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 a aproximadamente 6 átomos de carbono en la cadena que puede ser lineal o ramificada. Los ejemplos no limitantes de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. "Alquinilo" puede estar no sustituido o sustituido opcionalmente con uno o más sustituyentes que pueden ser iguales o diferentos, siendo cada sustituyente independientemente seleccionado del grupo que consta de alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema anular aromático multicíclico o monocíclico que comprende aproximadamente 6 a aproximadamente 14 átomos de carbono, de preferencia aproximadamente 6 a aproximadamente 10 átomos de carbono. El grupo arilo puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes y son como se definió aquí. Los ejemplos no limitantes de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema anular aromático multicíclico o monocíclico comprende aproximadamente 5 a aproximadamente 14 átomos anulares, de preferencia aproximadamente 5 a aproximadamente 10 átomos anulares, en los que uno o más de los átomos anulares es un elemente diferente del carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos anulares. El "heteroarilo" puede estar sustituido opcionalmente con uno o más "sustituyentes del sistema anular" que pueden ser iguales o diferentes y son como se definió aquí. El prefijo aza, oxa o tia previo al nombre de la raíz heteroarilo root significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presenta como un átomo anular, Un átomo nitrógeno de un heteroarilo puede estar opcionalmente oxidado en el correspondiente N-óxido. "Heteroarilo" puede incluir asimismo un heteroarilo com se definió antos, fusionado a un arilo como se definió antes. Los ejemplos no limitantes de

heteroarilos adecuados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridone (incluyendo piridonas N-sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere asimismo restos heteroarilo parcialmente saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo- en el que arilo y alquilo son como se describieron previamente. Los aralquilos de preferencia comprenden un grupo alquilo inferior. Los ejemplos no limitantes de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo. La unión con el resto precursor es a través de alquilo.

"Alquilarilo" significa un grupo alquil-arilo-, en el que el alquilo y arilo son como se describieron previamente. Los alquilarilos de preferencia comprenden un grupo alquilo inferior. Un ejemplo no limitante de un grupo alquilarilo adecuado es tolilo. La unión con el resto precursor es a través de arilo.

"Cicloalquilo" significa un sistema anular no aromático mono o multicíclico que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, de preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 a aproximadamente 7 átomos anulares. El cicloalquilo puede estar sustituido opcionalmente con uno o más "sustituyentes de sistema anular" que pueden ser iguales o diferentes y son como se definió antes. Los ejemplos no limitantes de cicloalquilos monocíclicos adecuados incluyen ciclopropilo, ciclopentilo,

ciclohexilo, cicloheptilo y similares. Los ejemplos no limitantes de cicloalquilos multicíclicos adecuados incluyen 1-decalinilo, norbornilo, adamantilo y similares.

"Cicloalquilalquilo" significa un resto cicloalquilo como se definió antes enlazad a través de un resto alquilo (como se definió antes) a un núcleo precursor. Los ejemplos no limitantes de cicloalquilalquilos adecuados incluyen ciclohexilmetilo, adamantilmetilo y similares.

"Cicloalquenilo" significa un sistema anular no aromático mono o multicícliclo que comprende aproximadamente 3 a aproximadamente 10 átomos de carbono, de preferencia aproximadamente 5 a aproximadamente 10 átomos de carbono que comprenden al menos un doble enlace carbono-carbono. Los anillos cicloalquenilo preferidos contienen aproximadamente 5 a aproximadamente 7 átomos anulares. El cicloalquenilo puede estar sustituido opcionalmente con uno o más "sustituyentes de sistema anular" que pueden ser iguales o diferentes y son como se definió antes. Los ejemplos no limitantes de cicloalquenilos monocíclicos adecuados incluyen ciclopentenilo, ciclohexenilo, ciclohepta-1,3-dienilo, y similares. Un ejemplo no limitante de un cicloalquenilo multicíclico adecuado es norbornilenilo.

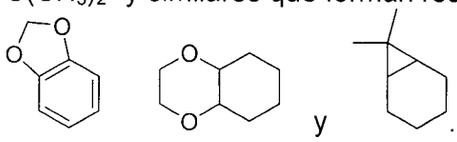
"Cicloalquenilalquilo" significa un resto cicloalquenilo como se definió antes enlazada a través de un resto alquilo (como se definió antes) a un núcleo precursor. Los ejemplos no limitantes de cicloalquenilalquilos adecuados incluyen ciclopentenilmetilo, ciclohexenilmetilo y similares.

"Halógeno" significa flúor, cloro, bromo, o yodo. Son de preferencia flúor, cloro y bromo.

El término "haloalquilo" como se utilizó aquí se refiere a un grupo alquilo, como se definió antos, donde uno o más de los átomos de hidrógeno del grupo alquilo están reemplazados de manera independiente con un halógeno. En una realización, un grupo haloalquilo es un "grupo fluoroalquilo."

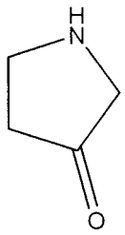
El término "grupo fluoroalquilo" como se utilizó aquí, se refiere a un grupo alquilo, donde uno o más de los átomos de hidrógeno del grupo alquilo están reemplazados con un átomo –F. En diferentes realizaciones, un grupo fluorooalquilo incluye un átomo F, dos átomos F o tres átomos F. Los Ejemplos ilustrativos de grupos fluoroalquilo incluyen, pero sin constituir limitación alguna, -CH_2F, -$CH(F)_2$, CH_2CH_2F, -CF_3 y -$(CH_2)_3CF_3$.

"Sustituyente de sistema anular" significa un sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Los sustituyentes de sistema anular pueden ser iguales o diferentos, siendo cada uno independientemente seleccionado del grupo que consta de alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alquilo), Y_1Y_2N-, Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- y -$SO_2NY_1Y_2$, donde Y_1 y Y_2 pueden ser iguales o diferentes y son independientemente seleccionados del grupo que consta de hidrógeno, alquilo, arilo, cicloalquilo y aralquilo. "Sustituyente de sistema anular" también puede significar un resto individual que simultáneamente reemplaza dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema anular. Los ejemplos de tal resto son metileno dioxi, etilenodioxi, -$C(CH_3)_2$- y similares que forman residuos tales como, por ejemplo:



"Heteroarilalquilo" significa un residuo heteroarilo como se definió antes enlazada a través de un resto alquilo (como se definió antes) a un núcleo precursor. Los ejemplos no limitantes de heteroarilos adecuados incluyen 2-piridinilmetilo, quinolinilmetilo y similares.

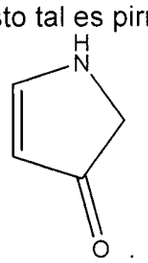
"Heterociclilo" significa un sistema anular multicíclico o monocíclico saturado no aromático que comprende aproximadamente 3 a aproximadamente 10 átomos anulares, de preferencia aproximadamente 5 a aproximadamente 10 átomos anulares, en los que uno o más de los átomos del sistema anular es un elemento diferente de carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o combinado. No existen átomos de oxígeno y/o azufre en el sistema anular. Los heterociclilos preferidos contienen aproximadamente 5 a aproximadamente 6 átomos anulares. El prefijo aza, oxa o tia previo al nombre de la raíz heterociclilo significa que el menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo anular. Cualquier –NH en un anillo heterociclilo pueden existir protegidos, tales como, por ejemplo, como un grupo -N(Boc), -N(CBz), -N(Tos) y similares; tales protecciones también se consideran parte de esta invención. El heterociclilo puede estar sustituido de manera opcional con uno o más "sustituyentes de sistema anular" que pueden ser iguales o diferentes y son como se definió aquí. El átomo de nitrógeno o azufre del heterociclilo puede estar opcionalmente oxidado en el correspondiente N-óxido, S-óxido o S,S-dióxido. Los ejemplos no limitantes de anillos heterociclilo monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona y similares. "Heterociclilo" también puede significar un resto individual (p. ej., carbonilo) que simultáneamente reemplaza dos hidrógenos disponibles en el mismo átomo de carbono en un sistema anular. Un ejemplo de tal resto es pirrolidona:



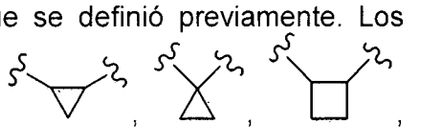
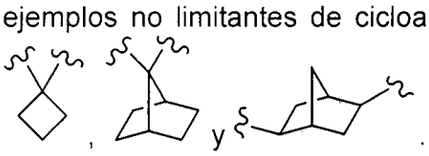
"Heterociclilalquilo" significa un resto heterociclilo como se definió antes enlazado a través de un resto alquilo (como se definió antes) a un núcleo precursor. Los ejemplos no limitantes de heterociclilalquilos adecuados incluyen piperidinilmetilo, piperazinilmetilo y similares.

"Heterociclenilo" significa un sistema anular multicíclico o monocíclico saturado no aromático que comprende aproximadamente 3 a aproximadamente 10 átomos anulares, de preferencia aproximadamente 5 a aproximadamente 10 átomos anulares, en el que uno o más de los átomos en el sistema anular es un elemento diferente de carbono, por ejemplo un átomo de nitrógeno, oxígeno o azufre, solo o combinado y que contiene al menos un doble enlace carbono-carbono o un doble enlace carbono-nitrógeno. No existen átomos de oxígeno y/o azufre adyacentes en el sistema anular. Los anillos heterociclenilo preferidos contienen aproximadamente 5 a aproximadamente 6 átomos anulares. El prefijo aza, oxa o tia previo al nombre de la raíz heterociclilo significa que el menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo anular. El heterociclenilo puede estar sustituido de manera opcional con uno o más sustituyentes de sistema anular, donde "sustituyente de sistema anular" es como se definió antes. El átomo de nitrógeno o azufre del heterociclenilo puede estar opcionalmente oxidado en el correspondiente N-óxido, S-óxido o S,S-dióxido. Los ejemplos no limitantes de grupos heterociclenilo adecuados 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,

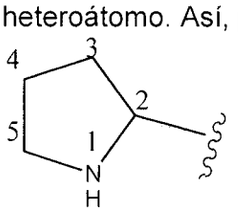
dihidrooxazolilo, dihidrooxadiazolilo, dihidrotiazolilo, 3,4-dihidro-2H-piranilo, dihidrofuranilo, fluorodihidrofuranilo, 7-oxabiciclo[2,2,1]heptenilo, dihidrotiofenilo, dihidrotiopiranilo, y similares. "Heterociclenilo" también puede significar un resto individual (p. ej., carbonilo) que simultáneamente reemplaza dos hidrógenos disponibles en el mismo átomo de carbono en un sistema anular. Un ejemplo de un resto tal es pirrolidinona:



"Heterociclenilalquilo" significa un resto heterociclenilo como se definió antes enlazada a través de un resto alquilo (como se definió antes) a un núcleo precursor.

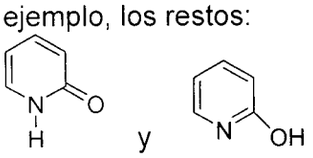
"Cicloalquileno" significa un grupo disfuncional obtednio por remoción de un átomo de hidrógeno de un grupo cicloalquilo que se definió previamente. Los ejemplos no limitantes de cicloalquileno incluyen  ,  y .

Ha de notarse que en sistemas anulares de esta invención que contienen hetero-átomos, no existen grupos hidroxilo en átomos de carbono adyacentes a N, O o S, así como tampoco existen grupos N o S en carbonos adyacentes a otro heteroátomo. Así, por ejemplo, en el anillo:



no hay un -OH unido directamente a carbonos marcados con 2 y 5.

También ha de notarse que las formas tautoméricas tales como, por ejemplo, los restos:



se consideran equivalente en determinadas realizaciones de esta invención.

"Alquinilalquilo" significa un grupo alquinil-alquilo- en el que el alquinilo y alquilo son como se describieron previamente. Alquinilalquilos pueden incluir un grupo alquinilo inferior y un grupo alquilo inferior. La unión con el resto precursor es a través de alquilo. Los ejemplos no limitantes de grupos alquinilalquilo adecuados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquilo- en el que el heteroarilo y alquilo son como se describieron previamente. Los heteroaralquilos contienen un grupo alquilo inferior. Los ejemplos no limitantes de grupos aralquilo adecuados incluyen piridilmetilo y quinolin-3-ilmetilo. La unión con el resto precursor es a través de alquilo.

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

"Acilo" significa un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, en el que los diferentes grupos son como se describieron previamente. La unión con el resto precursor es a través de carbonilo. Los acilos preferidos contienen un alquilo inferior. Los ejemplos no limitantes de grupos acilo adecuados incluyen formilo, acetilo y propanoilo.

"Aroilo" significa un grupo aril-C(O)-, en el que el grupo arilo es como se describió previamente. La unión con el resto precursor es a través de carbonilo. Los ejemplos no limitantes de grupos adecuados incluyen benzoilo y 1-naftoilo.

"Alcoxi" significa un grupo alquil-O-, en el que el grupo alquilo es como se describió previamente. Los ejemplos no limitantes de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. La unión con el resto precursor es a través de éter oxígeno.

"Ariloxi" significa un grupo aril-O-, en el que el grupo arilo es como se describió previamente. Los ejemplos no limitantes de grupos ariloxi adecuados incluyen fenoxi y naftoxi. La unión con el resto precursor es a través de éter oxígeno.

"Aralquiloxi" significa un grupo aralquil-O-, en el que el grupo aralquilo es como se describió previamente. Los ejemplos no limitantes de grupos aralquiloxi adecuados incluyen benciloxi y 1- o 2-naftalenometoxi. La unión con el resto precursor es a través de éter oxígeno.

"Alquiltio" significa un grupo alquil-S- en el que el grupo alquilo es como se describió previamente. Los ejemplos no limitantes de grupos alquiltio adecuados incluyen metiltio y etiltio. La unión con el resto precursor es a través de azufre.

"Ariltio" significa un grupo aril-S- en el que el grupo arilo es como se describió previamente. Los ejemplos no limitantes de grupos ariltio adecuados incluyen feniltio y naftiltio. La unión con el resto precursor es a través de azufre.

"Aralquiltio" significa un grupo aralquil-S- en el que el grupo aralquilo es como se describió previamente. Un ejemplo no limitante de un grupo aralquiltio es benciltio. La unión con el resto precursor es a través de azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Los ejemplos no limitantes de grupos alcoxicarbonilo adecuados incluyen metoxicarbonilo y etoxicarbonilo. La unión con el resto precursor es a través de carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Los ejemplos no limitantes de grupos ariloxicarbonilo adecuados incluyen fenoxicarbonilo y naftoxicarbonilo. La unión con el resto precursor es a través de carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitante de un grupo aralcoxicarbonilo adecuado es benciloxicarbonilo. La unión con el resto precursor es a través de carbonilo.

"Alquilsulfonilo" significa un grupo alquil-$S(O_2)$-. Los grupos preferidos son aquellos, en los que el grupo alquilo es alquilo inferior. La unión con el resto precursor es a través de sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. La unión con el resto precursor es a través de sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado es reemplazado con una selección del grupo indicado, siempre que no sea excedida la valencia normal designada del átomo en las circunstancias existentes, y que la sustitución resulte en un compuesto estable. Las combinaciones de sustituyentes y/o variables se permiten sólo, si tales combinaciones resultan en compuestos estables. Se entiende por "compuesto estable" o "estructura estable" cuando un compuesto es suficiente fuerte para soportar la aislación hasta un grado útil de pureza de una mezcla de reacción y formulación para obtener un agente terapéutico eficiente.

El término "opcionalmente sustituido" significa una sustitución opcional con los grupos, radicales o restos especificados.

El término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto después de ser aislado de un proceso de síntesis (es decir, de una mezcla de reacción), o fuente natural o combinación de los mismos. Así, el término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto después de haber sido obtenido de un proceso o procesos de purificación que se describieron aquí o son bien conocidos por el especialista en el arte (p. ej., cromatografía, recristalización

y similares), con la suficiente pureza para poder caracterizarse mediante técnicas analíticas estándar que se describieron aquí o son bien conocidos por el especialista en el arte.

Ha de notarse asimismo que se asume que cualquier carbono, así como heteroátomo, con valencias no satisfechas en el texto, esquemas, ejemplos y tablas, cuenta con la suficiente cantidad 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 presenta en forma modificada a fin de prevenir reacciones colaterales no deseadas en el sitio protegido, cuando el compuesto se somete a una reacción. Los grupos protectores adecuados serán evidentes por los especialistas en el arte, así como se mencionan a título de referencia en libros de texto estándar, tales como, por ejemplo, T. W. Greene *et al*, *Protective Grupos en o ganic Synthesis* (1991), Wiley, Nueva York.

Cuando existe cualquier variable (p. ej., arilo, heterociclo, R^2, etc.) más de una vez en cualquier constituyente o en la fórmula I, se definición en cada es independiente de la definición en otros casos.

Como se utilizó aquí, se pretende que el término "composición" incluye un producto que incluye los ingredientes especificados en las cantidades especificadas, así como también cualquier producto que resulta directa o indirectamente, de la combinación de los ingredientes especificados en las cantidades especificadas.

Asimismo se contemplan aquí los profármacos y solvatos de los compuestos de la invención. Se brinda una explicación de los profármacos en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de las A.C.S. Symposium Series y en *Bioreversible Carriers en Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association y Pergamon Press. El término

"profármaco" significa un compuesto (p. ej. un precurso del medicamento) que es transformado *in vivo* para proporcionar un compuesto de fórmula (I) o una sal aceptable para uso farmacéutico, un hidrato o un solvato del compuesto. La transformación puede ocurrir por diversos mecanismos (p. ej., por procesos metabólicos o químicos), tales como, por ejemplo, a través de la hidrólisis en sangre. Una explicación del uso de profármacos es proporcionada por T. Higuchi y W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 de las A.C.S. Symposium Series y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association y Pergamon Press, 1987.

Por ejemplo, si un compuesto de fórmula (I) o una sal aceptable para uso farmacéutico, un hidrato o un solvato del compuesto contiene un grupo funcional ácido carboxílico, un profármaco puede comprender un éster formado por el reemplazo del átomo de hidrógeno por el grupo ácido con un grupo tal como, por ejemplo, alquilo (C_1–C_8), alcanoiloximetilo (C_2-C_{12}), 1-(alcanoiloxi)etilo que presenta de 4 a 9 átomos de carbono, 1-metil-1-(alcanoiloxi)-etilo que presenta de 5 a 10 átomos de carbono, alcoxicarboniloximetilo que presenta de 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi)etilo que presenta de 4 a 7 átomos de carbono, 1-metil-1-(alcoxicarboniloxi)etilo que presenta de 5 a 8 átomos de carbono, N-(alcoxicarbonil)aminometilo que presenta de 3 a 9 átomos de carbono, 1-(N-(alcoxicarbonil)amino)etilo que presenta de 4 a 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gama-butrolacton-4-ilo, di-N,N-alquilamino (C_1-C_2)-alquilo (C_2-C_3) (tal como β-dimetilaminoetilo), carbamoil-alquilo (C_1-C_2), N,N-di-alquilcarbamoil-(C_1-C_2)-alquilo (C_1-C_2) y piperidin-, pirrolidin- o morfolin-alquilo (C_2-C_3) y similares.

De modo similar, si un compuesto de fórmula (I) contiene un grupo funcional alcohol, puede formarse un profármaco por la sustitución del átomo de hidrógeno del grupo alcohol con un grupo tal como, por ejemplo, alcanoiloximetilo

(C_1-C_6), 1-(alcanoiloxi (C_1-C_6))etilo, 1-metil-1-(alcanoiloxi (C_1-C_6))etilo, (C_1-C_6), N-alcoxicarboniloximetilo (C_1-C_6), succinoilo, alcanoilo (C_1-C_6), α-amino-alcanoilo(C_1-C_4), arilacilo y α-aminoacilo, o α-aminoacil-α-aminoacilo, donde cada grupo α-aminoacilo es seleccionado de manera independiente de los L-aminoácidos naturales, $P(O)(OH)_2$, -P(O)(O-alquil-(C_1-C_6)$_2$ glicosilo (el radical resultante de la remoción del grupo hidroxilo de la forma hemiacetalo de un hidrato de carbono) y similares.

Si un compuesto de fórmula (I) incorpora un grupo funcional amina, puede formarse un profármaco por la sustitución del 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 independientemente alquilo (C_1-C_{10}), cicloalquilo (C_3-C_7), bencilo, o R-carbonilo es un α-aminoacilo natural o β-aminoacilo natural, —C(OH)C(O)OY^1 donde Y^1 es H, alquilo (C_1-C_6) o bencilo, —C(OY^2)Y^3 donde Y^2 es alquilo (C_1-C_4) e 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 donde 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 formas no solvatadas, así como en formas solvatadas con solventes aceptables para uso farmacéutico, tales como agua, etanol y similares y se pretende que esta invención incluye ambas formas, la solvatada y la no solvatada. "Solvato" significa una asociación física de un compuesto de esta invención con uno o más moléculas solventes. Esta asociación física incluye diferentes grados de uniones iónicas y covalentes, incluyendo la unión con hidrógeno. En determinadas circunstancias, el solvato tendrá la capacidad de aislarse, por ejemplo cuando una o más moléculas solventes son incorporadas en la esctructura cristalina del del sólido en forma de cristal. "Solvato" incluye a ambos, la fase de solución y los

solvatos aislables. Los ejemplos no limitantes de solvatos adecuados incluyen etanolatos, metanolatos y similares. "Un hidrato" es un solvato donde la molécula solvente es H_2O.

Uno o más compuestos de la invención pueden opcionalmente convertirse en un solvato. La preparación de solvatos es de conocimiento general. Así, por ejemplo, M. Caira *et al*, *J. Pharmaceutical Sci.*, 93(3), 601-611 (2004) describe la preparación de los solvatos del fluconazol antifúngico en acetato etílico así como en agua. Se describieron preparaciones similares de solvatos, hemisolvatos, hidratos y similares 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 limitante incluye disolver el compuesto de la invención en cantidades deseadas del solvente deseado (orgánico o agua o mezclas de los mismos) a una temperatura mayor que la temperatura ambiente y enfriar la solución a una velocidad suficiente para formar cristales, que luego son aislados por métodos estándar. Las técnicas analíticas, tales como, por ejemplo, espectroscopia IR, muestran la presencia del solvente (o agua) en los cristales como un solvato (o un hidrato).

Se pretende que una "cantidad efectiva" o "cantidad terapéuticamente efectiva" describa una cantidad de un compuesto o una composición de la presente invención efectiva para inhibir las enfermedades antes indicadas, produciendo así el deseado efecto terapéutico, mejorador, inhibitorio o preventivo.

Los compuestos de fórmula I pueden formar sales que se encuentran asimismo dentro del alcance de esta invención. Se entiende que una referencia a un compuesto de fórmula I incluye la referencia a sales del mismo, salvo indicación en contrario. El término "sal(es)", como empleado aquí, incluye sales ácidas formadas con ácidos inorgánicos y/o orgánicos, así como, sales básicas formadas con bases orgánicas y/o inorgánicas. Además, cuando un compuesto

de fórmula I contiene a ambos, un resto básico, tal como piridina o imidazol, pero sin limitarse a lo mismos, y un resto ácido, tal como, ácido carboxílico sin ser limitante, pueden formarse zwitteriones ("sales internas") y se incluyen en el término "sal(es)" como se utilizó aquí. Son de preferencia las sales aceptables para uso farmacéutico (es decir, se prefieren sales no-tóxicas, fisiológicamente aceptables) aunque otras sales también son útiles. Las sales de los compuestos de fórmula I pueden formarse, por ejemplo, al hacer reaccionar un compuesto de fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno, en el que precipita la sal o en un medio acuoso seguido de liofilización.

Las sales de adición de ácidos citadas a modo de ejemplo 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. Además, los ácidos que por lo general son considerados adecuados para la formación de sales aceptables para uso farmacéutico a partir de compuestos farmacéuticos básicos son indicadas, por ejemplo, por P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Sales. Properties, Selection y Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, Nueva York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio Web). Estas revelaciones también se incluyen aquí a título de referencia.

Las sales básicas citadas a modo de ejemplo incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalinotérreos, tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas y sales con aminoácidos tales como arginina, lisina y similares. Los grupos básicos que contienen nitrógeno pueden ser cuaternizados con agentes tales como haluros de alquilo inferior (p.ej., cloruros, bromuros y yoduros de metilo, etilo y butilo), sulfatos de dialquilo (p.ej., sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (p.ej., cloruros, bromuros y yoduros de decilo, laurilo y estearilo), haluros de aralquilo (p.ej., bromuros de bencilo y fenetilo) y otros.

Se pretende que todas las sales ácidas y básicas sean sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales ácidas y básicas se consideran equivalente a las formas libres de los correspondientes compuestos a los fines de la invención.

Los ésteres aceptables para uso farmacéutico de los presentes compuestos incluyen los siguientes grupos: (1) ésteres de ácidos carboxílicos obtenidos por esterificación de los grupos hidroxi, en los que el resto no carbonilo de la porción del ácido carboxílico del agrupamiento éster se seleccionó de alquilo de cadena lineal o ramificada (por ejemplo, acetilo, n-propilo, t-butilo, o n-butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo, fenoximetilo), arilo (por ejemplo, fenilo opcionalmente sustituido con, por ejemplo, halógeno, alquilo C_{1-4} o alcoxi C_{1-4} o amino); (2) ésteres de sulfonato, tales como alquil- o aralquilsulfonilo (por ejemplo, metansulfonilo); (3) ésteres de aminoácidos (por ejemplo, L-valilo o L-isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono-, di- o trifosfato. Los ésteres de

fosfato pueden estar además esterificados con, por ejemplo, un alcohol C_{1-20} o un derivado reactivo del mismo o con un 2,3-di acil-(C_{6-24}) glicerol.

Los compuestos de fórmula I y las sales, solvatos, ésteres y profármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como un amida o imino éter). Todas aquellas formas tautoméricas se contemplan aquí como parte de la presente invención.

Los compuestos de fórmula (I) pueden contener centros asimétricos o quirales y por lo tanto, existen en diferentes formas estereoisoméricas. Se pretende que todas las formas estereoisoméricas de los compuestos de fórmula (I) así como las mezclas de los mismos, incluyendo mezclas racémicas, forman parte de la presente invención. Además, la presente invención incluye todos los isómeros geométricos y posicionales. Por ejemplo, si un compuesto de fórmula (I) incorpora un doble enlace o un anillo fusionado, ambas formas cis y trans, así como sus mezclas, se incluyen en el alcance de la invención.

Las mezclas diaestereoméricas pueden separarse en sus diastereómeros individuales sobre la base de sus diferencias físico-químicas mediante métodos bien conocidos por aquellos especialistas en el arte, tales como, por ejemplo, cromatografía y/o cristalización fraccional. Los enantiómeros pueden separarse al convertir la mezcla enantiomérica en una mezcla diaestereomérica mediante la reacción con un compuesto apropiado ópticamente activo (p. ej., auxiliares quirales, tales como un alcohol quiral o cloruro de ácido Mosher), separando los diastereómeros y convertir (p. ej., hidrolización) los diastereómeros individuales en los correspondientes enantiómeros puros. Asimismo, algunos de los compuestos de fórmula (I) pueden ser atropisómeros (p. ej., biarilos sustituidos) y se consideran como parte de esta invención. Los enantiómeros pueden asimismo separarse mediante HPLC de columna quiral.

También es posible que los compuestos de fórmula (I) puedan existir en diferentes formas tautoméricas y todas aquellas formas están incluidas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas ceto-enol y imina-enamina de los compuestos se incluyen en esta invención.

Todos los estereoisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos, ésteres y profármacos de los compuestos, así como las sales, solvatos y ésteres de los profármacos), tales como aquellos que pueden existir debido a carbonos asimétricos en diferentes sustituyentos, incluyendo las formas enantioméricas (que pueden existir incluso en ausencia de carbonos asimétricos), formas rotaméricas, atropisómeros y formas diastereoméricas, se incluyen dentro del alcance de esta invención como isómeros posicionales (tal como, por ejemplo, 4-piridilo y 3-piridilo). (Por ejemplo, si un compuesto de fórmula (I) incorpora un doble enlace o un anillo fusionado, se incluyen formas cis y trans, así como las mezclas, están incluidas en el alcance de la invención. Asimismo, por ejemplo, todas las formas ceto-enol y imina-enamina de los compuestos están incluidas en la invención.

Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, ser sustancialmente libres de otros isómeros, o pueden ser mezclados, por ejemplo, como racematos o con todos los demás estereoisómeros o con otros seleccionados. Los centros quirlaes de la presente invención pueden presentar la configuración S o R, como se definió por las recomendaciones *IUPAC* 1974. Se pretende que el uso de los términos "sal", "solvato", "éster", "profármaco" y similares, sea aplicable del mismo modo a la sal, el solvato, el éster y el profármaco de enantiómeros, stereoisómeros, rotámeros, tautómeros, isómeros posiciones, racematos o profármacos de los compuestos de la invención.

La presente invención asimismo incluye compuestos de la presente invención etiquetados isotópicamente que son idénticos a aquellos aquí indicados, pero debido al hecho que uno o más atomos son reemplazados por un átomo que presenta una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza. Los ejemplos de isótopos que pueden ser incorporados 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.

Determinados compuestos de fórmula (I) etiquetados isotópicamente (p. ej., aquellos etiquetados con ^{3}H y ^{14}C) son útiles en los ensayos del compuesto y/o distribución en el sustrato tisular. Los isótopos titulados (es decir, ^{3}H) y de carbono-14 (es decir, ^{14}C) son de preferencia particular, debido a su fácil preparación y detectabilidad. Además, la sustitución con isótopos más pesados, tales como deuterio (es decir, ^{2}H) puede brindar determinadas ventajas terapéuticas resultante de una mayor estabilidad metabólica (p. ej., mayor permanencia in vivo o menores dosificaciones requeridas) y debido a ello puede ser de preferencia en ciertas circunstancias. Los compuestos isotópicamente etiquetados de fórmula (I) pueden por lo general ser preparados mediante los siguientes procedimientos análogos a aquellos revelados en los Esquemas y/o en los ejemplos a continuación, mediante la sustitución de un reactivo apropiado etiquetado isotópicamente por un reactivo etiquetado no isotópicamente.

Se pretende que las formas polimórficas de los compuestos de fórmula I y de las sales, solvatos, ésteres y profármacos de los compuestos de fórmula I, estén incluidos en la presente invención.

Se pretende que el término "composición farmacéutica" asimismo incluya a ambos, la composición a granel y unidades de dosificación individuales que

comprende más de un (p. ej., dos) agentes de actividad farmacéutica tales como, por ejemplo, un compuesto de la presente invención y un agente adicional seleccionado de las listas de los agentes adicionales que se describen aquí, junto con cualquier excipiente que no presente actividad farmacéutico. La composición a granel y cualquier unidad de dosificación puede incluir una cantidad determinada del antes mencionado "más de un agente de actividad farmacéutica". La composición a granel constituye material, con el cual aún no se conformaron unidades de dosificación individual. Una unidad de dosificación ilustrativa es una unidad de dosificación oral, tal como comprimidos, píldoras y similares. De modo similar, el método que se describe aquí para tratar un paciente mediante la administración de una composición farmacéutica de la presente invención asimismo pretende incluir la administración de la composición a granel antes mencionada y unidades de dosificación individual.

Los compuestos de fórmula (I), o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo de acuerdo con la invención presentan propiedades farmacológicas; en particular, los compuestos de fórmula (I) puede ser agonistas del receptor del ácido nicotínico.

Los compuestos de fórmula (I) de la presente invención, o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo son útiles para el tratamiento de enfermedades o afecciones incluyendo dislipidemia y síndrome metabólico.

Los compuestos de fórmula (I), o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo, pueden administrarse en cualquier forma adecuada, p. ej., solos o en combinación con un vehículo aceptable para uso farmacéutico, excipiente o diluyente en una composición farmacéutica, conforme la práctica farmacéutica estándar. Los compuestos de fórmula (I), o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo, pueden administrarse por vía oral o parenteral, incluyendo vías de administración endovenosa, intramuscular,

interperitoneal, subcutánea, rectal o tópica, o en caso de determinarse, mediante una combinación de uno o más de los métodos que se mostraron antes.

Las composiciones farmacéuticas comprenden al menos un compuesto de fórmula (I), o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo que puede presentarse en una forma adecuada para administración oral, p. ej., como comprimidos, comprimidos para disolución oral, cápsulas, pastillas, suspensiones acuosas u oleosas, polvos o gránulos dispersibles, emulsiones, jarabes o elixires. Las composiciones orales pueden prepararse por cualquier método farmacéutico convencional y pueden asimismo contener agentes endulcorantes, saborizantos, colorantes y conservantes.

La cantidad del compuesto de fórmula (I), o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo, administrada a un paciente puede ser determinada por un médico sobre la base de la edad, el peso y la respuesta del paciente, así como de acuerdo con la gravedad de la afección tratada. Por ejemplo, la cantidad de compuesto de fórmula I, o una sal aceptable para uso farmacéutico, un solvato, éster o tautómero del mismo, administrada al paciente puede ubicarse en un rango de aproximadamente 0,1 mg/kg peso corporal por día a aproximadamente 60 mg/kg/d. En una realización, la cantidad es de aproximadamente 0,5 mg/kg/d a aproximadamente 40 mg/kg/d. En otra realización, la cantidad es de aproximadamente 0,5 mg/kg/d a aproximadamente 10 mg/kg/d. En otra realización, la cantidad es de aproximadamente 1 mg/kg/d a aproximadamente 5 mg/kg/d. En aún otra realización, la cantidad es de aproximadamente 1 mg/kg/d a aproximadamente 3 mg/kg/d. En una realización importante, la cantidad es aproximadamente 1 mg/kg/d. En otra realización específica, la cantidad es aproximadamente 3 mg/kg/d. En otra realización específica, la cantidad es aproximadamente 5 mg/kg/d. En otra realización

específica, la cantidad es aproximadamente 7 mg/kg/d. En aún otra realización específica, la cantidad es aproximadamente 10 mg/kg/d.

Los compuestos de fórmula (I), o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo, también pueden administrarse en combinación con otros agentes terapéuticos. Por ejemplo uno o más compuestos de fórmula (I) o sales aceptables para uso farmacéutico, solvatos o ésteres del mismo, pueden administrarse con uno o más principios activos adicionales seleccionados del grupo que consta de agentes anti-rubor, compuestos de azetidinona hidroxi-sustituidos, comnpuestos β-lactama-sustituidos, compuestos inhibidores de HMG CoA reductasa, inhibidores de HMG CoA sintetasa, inhibidores de la síntesis de escualeno, inhibidores de la escualeno epoxidasa, inhibidores de la biosíntesis de ésteroles, derivados del ácido nicotínico, secuestrantes de ácidos biliares, secuestrantes inorgánicos de colesterol, inhibidores de AcilCoA:colesterol O-aciltransferasa, inhibidores de la proteína de transferencia de ésteres de colesterilo, aceites de pescado que contienen ácidos grasos Omega 3, fibras naturales solubles en agua, estanoles de plantas y/o ésteres de ácidos grasos de estanoles de plantas, anti-oxidantos, agonistas de PPAR-α, agonistas de PPAR-γ, moduladores del receptor FXR, agonistas del receptor FXR, inhibidores de la síntesis de lipoproteína, inhibidores de la renin angiotensina, inhibidores de la proteína de transporte de triglicéridos microsomales, inhibidores de la recaptación de ácidos biliares, agonistas de PPAR-δ, inhibidores de la síntesis de triglicéridos, inhibidores de la escualeno epoxidasa, inductores del receptor de lipoproteína de baja densidad o activadores, inhibidores de la agregación plaquetaria, inhibidores 5-LO o FLAP, agonistas parciales de PPAR-δ, agonistas de niacina o del receptor de niacina, inhibidores de transportadores 5HT, inhibidores de transportadores NE, CB_1 antagonistas/agonistas inversos, antagonistas de grelina, H_3 antagonistas/agonistas inversos, antagonistas de MCH1R, agonistas/

antagonistas de MCH2R/, antagonistas de NPY1, antagonistas de NPY5, agonistas de NPY2, agonistas de NPY4, antagonistas de mGluR5, leptinas, agonistas/moduladores de leptina, derivados de leptina, antagonistas de opioides, antagonistas del receptor de orexina, agonistas de BRS3, agonistas de CCK-A, CNTF, derivados de CNTF, agonistas/moduladores de CNTF, agonistas de 5HT2c, agonistas de Mc4r, inhibidores de la recaptación de monoamina, inhibidores de la recaptación de serotonina, GLP-1, agonistas GLP-1, GLP-1 mimetics, fentermina, topiramato, fitofarm compuesto 57, anticuerpos de grelina, agonistas de Mc3r, Inhibidores de ACC, agonistas β3, inhibidores de DGAT1, inhibidores de DGAT2, inhibidores de FAS, inhibidores de PDE, agonistas de la hormona ß tiroidea, activadores de UCP-1, activadores de UCP-2, activadores de UCP-3, acil-estrógenos, agonistas/antagonistas de glucocorticoides, inhibidores 11β HSD-1, inhibidores de SCD-1, inhibidores de lipasa, inhibidores de transportadores de ácido graso, inhibidores de transportadores de dicarboxilato, inhibidores de transportadores de glucosa, inhibidores de transportadores de fosfato, agentes anti-diabéticos, agentes antihipertensivos, agentes antidislipidémicos, antagonistas del receptor DP, inhibidores de la secreción de apoliproteína/proteína de transferencia microsomal de triglicéridos (apo-B/MTP), agonistas simpatomiméticos, agonistas de dopamina, análogos del receptor de la hormona estimuladora de melanocitos, antagonistas de la hormona concentradora de melanina, leptonas, antagonistas del receptor de galanina, agonistas de bombesina, antagonistas de neuropéptidos Y, agentes tiromiméticos, dehidroepiandrosterona, análogos de dehidroepiandrosterona, antagonistas de la proteína de unión de urocortina, agonistas del receptor de péptidos-1 tipo glucágonos, proteínas humanas relacionadas con agouti (AGRP), agonistas del receptor de neuromedina U, agentes anoréxicos noradrenérgicos, supresores de apetito, antagonistas de lipasas sensibles a hormonas, análogos del receptor de

MSH, inhibidores de la α-glucosidasa, inhibidores del transporte inverso del colesterol apo A1 milano, inhibidores de la proteína de unión a ácidos grasos (FABP) y inhibidores de la proteínas transportadoras de ácidos graso (FATP).

Los ejemplos no limitantes de compuestos de azetidinona hidroxi-sustituidos y compuestos β-lactama sustituidos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son aquellos revelados en las Patentes Estadounidenses Nos. 5.767.115, 5.624.920, 5.668.990, 5.656.624 y 5.688.787, 5.756.470, Solicitud de Patentes Estadounidenses Nos. 2002/0137690 y 2002/0137689 y Solicitud de Patente PCT Nº WO 2002/066464, incorporándose cada una aquí en su totalidad a título de referencia. Un compuesto azetidinona preferido es ezetimibe (por ejemplo, ZETIA® que está disponible de Schering-Plough Corporation).

En una realización, el agente adicional es un agente anti-rubor.

Los ejemplos no limitantes de compuestos inhibidores de HMG CoA reductasa útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son lovastatina (por ejemplo MEVACOR® que está disponible de Merck & Co.), simvastatina (por ejemplo ZOCOR® que está disponible de Merck & Co.), pravastatina (por ejemplo PRAVACHOL® que está disponible de Bristol Meyers Squibb), atorvastatina, fluvastatina, cerivastatina, CI-981, rivastatina (sodium 7-(4-fluorofenil)-2,6-diisopropil-5-metoximetilpiridin-3-il)-3,5-dihidroxi-6-heptanoato), rosuvastatina cálcica (CRESTOR® de AstraZeneca Pharmaceuticals), pitavastatina (tal como NK-104 de Negma Kowa de Japón).

Un ejemplo no limitante de un inhibidor de sintetasa HMG CoA útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es, por ejemplo, L-659,699 (ácido (E,E)-11-[3'R-(hidroxi-metil)-4'-oxo-2'R-oxetanil]-3,5,7R-trimetil-2,4-undecadienoico).

Un ejemplo no limitante de un inhibidor de la síntesis de escualeno útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es, por ejemplo, escualestatina 1.

Un ejemplo no limitante de un inhibidor de la escualeno epoxidasa útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es, por ejemplo, NB-598 (clorhidrato de (E)-N-etil-N-(6,6-dimetil-2-hepten-4-inill)-3-[(3,3'-bitiofen-5-il)metoxi]benceno-metanamina).

Un ejemplo no limitante de un inhibidor de la biosíntesis de ésteroles útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es, por ejemplo, DMP-565.

Los ejemplos no limitantes de derivados del ácido nicotínico (p. ej., compuestos que comprenden una estructura piridina-3-carboxilato o una estructura pirazina-2-carboxilato, incluyendo formas ácidas, sales, ésteres, zwitteriones y tautómeros) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son niceritrol, nicofuranosa y acipimox (4-óxido del ácido 5-metilo pirazin-2-carboxílico).

Los ejemplos no limitantes de secuestrantes de ácidos biliares útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son colestiramina (un copolímero estireno-divinilbenceno que contiene gruos catiónicos de amonio cuaternario con capacidad de unir ácidos biliares, tales como QUESTRAN® o QUESTRAN LIGHT® colestiramina que puede obtenerse de Bristol-Myers Squibb), colestipol (un copolímero de dietilenotriamina y 1-cloroo-2,3-epoxipropano, tal como comprimidos COLESTID® que puede obtenerse de Pharmacia), clorhidrato de colesevelam (tal como comprimidos WelChol® (poli(clorhidrato de alilamina) de enlace cruzado con epiclorohidrina y alquilado on 1-bromodecano y bromuro de (6-bromohexil)-trimetilamonio) que puede obtenerse de Sankyo), derivados solubles en agua tales como 3,3-yoeno,

N-(cicloalquil) alquilaminas y poliglusam, poliestirenos cuaternizados no solubles, saponinas y mezclas de los mismos.

Los ejemplos no limitantes de secuestrantes inorgánicos de colesterol útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son salicilato de bismuto más arcilla de montmorilonita, hidróxido de aluminio y antiácidos de carbonato de calcio.

Los ejemplos no limitantes de inhibidores de AcilCoA:colesterol *O*-aciltransferasa ("ACAT") útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son avasimibe (ácido [[2,4,6-tris(1-metiletil)fenil]acetil]sulfámico, 2,6-bis(1-metiletil)fenil éster, conocido anteriormente como CI-1011), HL-004, lecimibide (DuP-128) y CL-277082 (*N*-(2,4-difluorofenil)-*N*-[[4-(2,2-dimetilpropil)fenil]metil]-*N*-heptilurea) y los compuestos que se describieron en P. Chang et al., "Current, New y Future Treatments en Dyslipidaemia y Atherosclerosis", Drugs 2000 Jul; 60(1); 55-93, que se incorpora aquí a título de referencia.

Los ejemplos no limitantes de inhibidores de proteína de transferencia de ésteres de colesterilo ("CETP") útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son aquellos revelados en Solicitud de Patente PCT Nº WO 00/38721, Patentes Estadounidenses Nos. 6.147.090, 6.958.346, 6.924.313 6.906.082, 6.861.561, 6.803.388, 6.794.396, 6.787.570, 6.753.346, 6.723.752, 6.723.753, 6.710.089, 6.699.898, 6.696.472, 6.696.435, 6.683.113, 5.519.001, 5.512.548, 6.410.022, 6.426.365, 6.448.295, 6.387.929, 6.683.099, 6.677.382, 6.677.380, 6.677.379, 6.677.375, 6.677.353, 6.677.341, 6.605.624, 6.586.433, 6.451.830, 6.451.823, 6.462.092, 6.458.849, 6.458.803, 6.455.519, 6.583.183, 6.562.976, 6.555.113, 6.544.974, 6.521.607, 6.489.366, 6.482.862, 6.479.552, 6.476.075, 6.476.057 y 6.897.317, que se incorpora cada una aquí a título de referencia; compuestos que fueron descritos

por Yan Xia et al., "Sustituido 1,3,5-Triazines As Cholésteral Éster Transfer Protein Inhibitors", Bioorganic & Medicinal Chemistry Letters, vol. 6, Nº 7, 1996, pp. 919-922, incorporados aquí a título de referencia; productos naturales que fueron descritos por S. Coval et al., "Wiedendiol-A y -B, Cholésterilo Éster Transfer Protein Inhibitors de The Marine Sponge Xestosponga Wiedenmayeri", Bioorganic & Medicinal Chemistry Letter, vol. 5, Nº 6, pp. 605-610, 1995, incorporados aquí a título de referencia; los compuestos que fueron descritos por Barrett et al. *J. Am. Chem. Soc.,* 188, 7863-63 (1996), incorporados aquí a título de referencia; los compuestos que fueron descritos por Kuo et al. *J. Am. Chem. Soc.,* 117, 10629-34 (1995), incorporados aquí a título de referencia; los compuestos que fueron descritos por Pietzonka et al. *Bioorg. Med. Chem. Lett.,* 6, 1951-54 (1996), incorporados aquí a título de referencia; los compuestos que fueron descritos por Lee et al., *J. Antibiotics,* 49, 693-96 (1996), incorporados aquí a título de referencia; los compuestos que fueron descritos por Busch et al. *Lipids,* 25, 216-220, (1990), incorporados aquí a título de referencia; los compuestos que fueron descritos por Morton y Zilversmit *J. Lipid Res.,* 35, 836-47 (1982), incorporados aquí a título de referencia; los compuestos que fueron descritos por Connolly et al. *Biochem. Biophys. Res. Comm.,* 223, 42-47 (1996), incorporados aquí a título de referencia; los compuestos que fueron descritos por Bisgaier et al. Lipids, 29, 811-8 (1994), incorporados aquí a título de referencia; los compuestos que fueron descritos en la EP 818448, incorporados aquí a título de referencia; los compuestos que fueron descritos en la JP 10287662, incorporados aquí a título de referencia; los compuestos que fueron descritos en las solicitudes PCT WO 98/35937, WO 9914174, WO 9839299 y WO 9914215, incorporándose aquí cada una a título de referencia; los compuestos de solicitudes europeas EP 796846, EP 801060, 818448 y 818197, incorporándose aquí cada una a título de referencia; probucol o derivados del mismo, tales como AGI-1067 y otros derivados revelados

en las Patentes Estadounidenses Nos. 6,121,319 y 6,147,250, incorporados aquí a título de referencia; activadores del receptor de lipoproteína de baja densidad (LDL) tales como HOE-402, un derivado de imidazolidinil-pirimidina que estimula directamente la actividad del receptor de LDL, que se describieron en M. Huettinger et al., "Hypolipidemic activity of HOE-402 is Mediated por Stimulation of the LDL Receptor Pathway", Arterioscler. Thromb. 1993; 13:1005-12, incorporados aquí a título de referencia; 1,2,3,4-tetrahidroquinolinas 4-carboxiamino-2-sustituido, p. ej., torcetrapib, que se describieron en WO 00/017164, WO 00/017166, WO 00/140190, WO 00/213797 y WO 2005/033082 (incorporándose aquí cada una a título de referencia). Torcetrapib puede combinarse con inhibidores de la HMG-CoA reductasa, tales como atorvastatina (WO 00/213797, WO 2004/056358, WO 2004/056359 y WO2005/011634).

Un ejemplo no limitante un aceite de pescado que contienes ácidos grasos Omega 3 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es 3-PUFA.

Los ejemplos no limitantes de miméticos de GLP-1 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen exendin-3, exendin-4, Byetta-Exanatida, Liraglutinida, CJC-1131 (ConjuChem), Exanatide-LAR (Amilin), BIM-51077 (Ipsen/LaRoche), ZP-10 (Zealy Pharmaceuticals) y compuestos revelados en la Publicación Internacional Nº WO 00/07617.

Los ejemplos no limitantes de fibras naturales solubles en agua útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención son psillium, guar, avena y pectina.

Un ejemplo no limitante de un estanol de planta y/o un éster del ácido graso de estanoles de plantas útiles en combinación con los agonistas del

receptor del ácido nicotínico de la presente invención es el éster de sitostanol usado en margarina BENECOL®.

Un ejemplo no limitante de un anti-oxidante útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluye probucol.

Los ejemplos no limitantes de agonistas de PPAR-α útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen beclofibrato, benzafibrato, ciprofibrato, clofibrato, etofibrato, fenofibrato y gemfibrocilo.

Los ejemplos no limitantes de inhibidores de la síntesis de lipoproteína útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen niacina o ácido nicotínico.

Los ejemplos no limitantes de inhibidores del transportes de 5HT (serotonina) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen paroxetina, fluoxetina, fenfluramina, fluvoxamina, sertralina, e imipramina.

Los ejemplos no limitantes de inhibidores del transporte de NE (norepinefrina) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen GW 320659, despiramina, talsupram y nomifensina.

Los ejemplos no limitantes de antagonistas/agonistas inversos de CB_1 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen rimonabant, SR-147778 (Sanofi Aventis) y los compuestos que se describieron en US 5.532.237, US 4.973.587, US 5.013.837, US 5.081.122, US 5.112.820, US 5.292.736, US 5.624.941, US 6.028.084, WO 96/33159, WO 98/33765, WO 98/43636, WO 98/43635, WO 01/09120, WO 98/31227, WO 98/41519, WO 98/37061, WO 00/10967, WO 00/10968, WO

97/29079, WO 99/02499, WO 01/58869, WO 02/076949 y EP-658546 (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de antagonistas de grelina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en WO 01/87335 y WO 02/08250 (incorporándose aquí a título de referencia cada una de las referencias precedentes). Los antagonistas de grelina se conocen asimismo como antagonistas de GHS (receptor de secretagogos de la hormona de crecimiento). Las combinaciones farmacéuticas y métodos de la presente invención por lo tanto incluye el uso de los antagonistas de GHS en lugar de los antagonistas de grelina (en combinación con los agonistas del receptor del ácido nicotínico de la presente invención).

Los ejemplos no limitantes de antagonistas/agonistas inversos de H_3 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen tioperamida, 3-(1H-imidazol-4-il)propilo N-(4-pentenil)carbamato, clobenpropit, yodofenpropit, imoproxifan y GT2394 (Gliatech), aquellas que se describen en WO 02/15905 (incorporados aquí a título de referencia); O-[3-(1H-imidazol-4-il)propanol]carbamatos que se describieron en Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000) (incorporados aquí a título de referencia), antagonistas del receptor H_3 de histamina que contiene piperidina que se describieron en Lazewska, D. et al., Pharmazie, 56:927-32 (2001) (incorporados aquí a título de referencia), derivados de benzofenona y compuestos relacionados que se describieron en Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)(incorporados aquí a título de referencia), N-fenilcarbamatos sustituidos que se describieron en Reidemeister, S. et al., Pharmazie, 55:83-6 (2000) (incorporados aquí a título de referencia) y derivados

de proxifan que se describieron en Sasse, A. et al., J. Med. Chem. 43:3335-43 (2000) (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de antagonistas/agonistas de MCH1R (receptor de la hormona 1 concentradora de melanina) y MCH2R (receptor de la hormona 2 concentradora de melanina) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en WO 01/82925, WO 01/87834, WO 02/06245, WO 02/04433, WO 02/51809 y JP 13226269 (incorporándose aquí a título de referencia cada una de las referencias precedentes) y T-226296 (Takeda).

Los ejemplos no limitantes de antagonistas de NPY1 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en US 6.001.836, WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173 y WO 01/89528 (incorporándose aquí a título de referencia cada una de las referencias precedentes); y BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906 y GI-264879A.

Los ejemplos no limitantes de antagonistas de NPY5 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en US 6.140.354, US 6.191.160, US 6.258.837, US 6.313.298, US 6.337.332, US 6.329.395, US 6.340.683, US 6.326.375, US 6.335.345, EP-01010691, EP-01044970, WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/27063, WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, WO 02/49648, WO 01/14376, WO 04/110375, WO

05/000217 y Norman et al., J. Med. Chem. 43:4288-4312 (2000) (incorporándose aquí a título de referencia cada una de las referencias precedentes); y 152,804, GW-569180A, GW-594884A, GW-58708_1, GW-54811_8; FR226928, FR 240662, FR252384; 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A y JCF-104.

Los ejemplos no limitantes de agonistas de NPY2 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen PYY3-36 tal como se describieron en Batterham, et al., Nature. 418:650-654 (2003), NPY3-36 y otros agonistas Y2, tales como N acetilo [Leu(28,31)] NPY 24-36 (White-Smith y Potter, Neuropeptides 33:526-33 (1999)), TASP-V (Malis et al., Br. J. Pharmacol. 126:989-96 (1999)), ciclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY (Cabrele y Beck-Sickinger J-Pept-Sci. 6:97-122 (2000)) (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de agonistas de NPY4 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen péptido pancreático (PP) tal como se describió en Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003) y otros agonistas Y4 tales como 1229U91 (Raposinho et al., Neuroendocrinology. 71:2-7(2000) (ambas referencias se incorporan aquí a título de referencia).

Los ejemplos no limitantes de antagonistas de mGluR5 (receptor del glutamato subtipo 5 metabotrófico) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen 2-metil-6-(fenilethinill)-piridina (MPEP) y (3-[(2-metil-1,3-tiazol-4-il)ethinill]piridina) (MTEP) y aquellos compuestos que se describieron en Anderson J. et al., J, Eur J Pharmacol. Jul. 18, 2003;473(1):35-40; Cosford N. et al., Bioorg Med Chem Lett. Feb. 10, 2003;13(3):351-4; y Anderson J. et al., J Pharmacol Exp Ther. December

2002:303(3):1044-51 (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de leptinas, derivados de leptina y agonistas/moduladores de leptina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen leptima humana recombinante (PEG-OB, Hoffman La Roche) y leptina humana recombinante de metionilo (Amgen). Los derivados de leptina (p. ej., formas truncadas de leptina) útiles en la presente invención incluyen aquellos que se describieron en US 5.552.524, US 5.552.523, US 5.552.522, US 5.521.283, WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519 y WO 96/23520 (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de antagonistas de opioides útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen nalmefeno (Revex™), 3-metoxinaltrexona, naloxona y naltrexona, así como también antagonistas de opioides que se describieron en WO 00/21509 (incorporadas aquí a título de referencia).

Los ejemplos no limitantes de antagonistas del receptor de orexina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen SB-334867-A, así como aquellas que se describen en WO 01/96302, WO 01/68609, WO 02/51232 y WO 02/51838 (incorporándose aquí a título de referencia cada una de las referencias precedentes).

Los ejemplos no limitantes de CNTF (factores neurotróficos ciliares específicos) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen GI-181771 (Glaxo-SmithKline); SR146131 (Sanofi Aventis); butabindido; PD170,292, PD 149164 (Pfizer).

Los ejemplos no limitantes de derivados de CNTF y agonistas/moduladores de CNTF útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen axoquina (Regeneron) y aquellas que se describen en WO 94/09134, WO 98/22128 y WO 99/43813 (incorporándose aquí cada una a título de referencia).

Los ejemplos no limitantes de agonistas de 5HT2c útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen BVT933, DPCA37215, WAY161503 y R-1065, así como aquellas que se describen en US 3.914.250, WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456 y WO 02/40457 (incorporándose aquí cada una a título de referencia).

Los ejemplos no limitantes de agonistas de Mc4r útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen CHIR86036 (Chiron); ME-10142 y ME-10145 (Melacure), así como aquellas que se describen en WO 01/991752, WO 01/74844, WO 02/12166, WO 02/11715 y WO 02/12178 (incorporándose aquí cada una a título de referencia).

Los ejemplos no limitantes de inhibidores de la recaptación de monoamina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen sibutramina (Meridia™/Reductil™), así como aquellas que se describen en WO 01/27068, WO 01/62341, US 4.746.680, US 4.806.570, US 5.436.272 y US 2002/0006964 (incorporándose aquí cada una a título de referencia).

Los ejemplos no limitantes de inhibidores de la recaptación de serotonina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen dexfenfluramina, fluoxetina y aquellas que se describen en US 6.365.633, WO 01/27060 y WO 01/162341 (incorporándose aquí cada una a título de referencia).

Un ejemplo no limitante de un acil-estrógeno útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluye oleoil-estrona.

Los ejemplos no limitantes de inhibidores 11β HSD-1 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en WO 03/065983 y WO 03/104207 (incorporándose aquí ambas a título de referencia).

Un ejemplo no limitante de un inhibidor de lipasa útil en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen orlitato.

Agentes anti-diabéticos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen sulfonilureas, meglitinidas, inhibidores de α-amilasa, inhibidores de α-glucósido hidrolasa, agonistas PPAR-γ, agonistas PPARα/γ, biguanidas, inhibidores de PTP-1B, inhibidores de DP-IV, inhibidores de DPP-IV, secretagogos de insulina, inhibidores de la oxidación de ácido graso, antagonistas de A2, inhibidores de quinasa c-jun amino-terminal, insulina, miméticos de insulina, inhibidores de glicógeno fosforilasa, agnistas del receptor de VPAC2, activadores de glucoquinasa y ligandos PPAR no-tiazolidinediona. Los ejemplos no limitantes de sulfonilureas útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen acetohexamida, cloropropamida, diabinese, glibenclamida, glipizida, gliburida, glimepirida, gliclazida, glipentida, gliquidona, glisolamida, tolazamida y tolbutamida.

Los ejemplos no limitantes de meglitinidas útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen repaglinida, mitiglinida y nateglinida.

Los ejemplos no limitantes de inhibidores de α-amilasa útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen tendamistato, trestatina y Al-3688.

Los ejemplos no limitantes de inhidbidores de α-glucósido hidrolasa útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen acarbosa, adiposa, camiglibosa, emiglitato, miglitol, voglibosa, pradimicin-Q, salbostatina, CDK-711, MDL-25,637, MDL-73,945 y MOR 14.

Los ejemplos no limitantes de agonistas PPAR-γ útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen balaglitazona, ciglitazona, darglitazona, englitazona, isaglitazona (MCC-555), pioglitazona, rosiglitazona, troglitazona, tesaglitazar, netoglitazona, GW-409544, GW-501516, CLX-0921, 5-BTZD, GW-0207, LG-100641, LY-300512, LY-519818, R483 (Roche) y T131 (Tularik).

Los ejemplos no limitantes de agonistas PPARα/γ útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen CLX-0940, GW-1536, GW-1929, GW-2433, KRP-297, L-796449, LR-90, MK-0767 y SB 219994.

Los ejemplos no limitantes de biguanidas útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen buformina, metformina y fenformina.

Los ejemplos no limitantes de inhibidores de PTP-1B (inhibidores de la proteína tirosina fosfatasa-1B) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen A-401,674, KR 61639, OC-060062, OC-83839, OC-297962, MC52445 y MC52453.

Los ejemplos no limitantes de inhibidores de DPP-IV (inhibidores de la dipeptidil peptidasa IVi) útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen sitagliptina, saxagliptina,

denagliptina, vildagliptina, alogliptina, benzoato de alogliptina, Galvus (Novartis), ABT-279 y ABT-341 (Abbott), ALS-2-0426 (Alantos), ARI-2243 (Arisaph), BI-A y BI-B (Boehringer Ingelheim), SYR-322 (Takeda), MP-513 (Mitsubishi), DP-893 (Pfizer) y RO-0730699 (Roche), isoleucina tiazolidida, NVP-DPP728, P32/98, LAF 237, TSL 225, valina pirrolidida, TMC-2A/2B/2C, inhibidores de CD-26 y SDZ 274-444.

Los ejemplos no limitantes de secretagogos de insulina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen linoglirida y A-4166.

Los ejemplos no limitantes de inhibidores de oxidación de ácidos grasos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen clomoxir y etomoxir.

Los ejemplos no limitantes de antagonistas de A2 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen midaglizol, isaglidol, deriglidol, idazoxano, earoxano y fluparoxano.

Los ejemplos no limitantes de miméticos de insulina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen biota, LP-100, novarapida, insulina detemir, insulina lispro, insulina glargina, insulina suspensión de zinc (lente y ultralente), insulina Lys-Pro, GLP-1 (73-7) (insulintropina) y GLP-1 (7-36)-NH_2).

Los ejemplos no limitantes de inhibidores de glicogen fosforilasa útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen CP-368.296, CP-316.819 y BAYR3401.

Los ejemplos no limitantes de ligandos de PPAR no-tiazolidinediona útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen JT-501 y farglitazar (GW-2570/GI-262579).

Los agentes antihipertensivos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen diuréticos, bloqueadores β-adrenérgicos, bloqueadores α-adrenérgicos, inhibidores de aldosterona, bloqueadores alfa 1, bloqueadores del canal de calcio, inhibidores de enzimas convertidores de angiotensina, inhibidores neutrales de endopeptidasa, antagonistas de receptores de angiotensina II, antagonistas de endotelina, vasodilatadores, agonistas alfa 2a y bloqueadores α/β-adrenérgicos.

Los ejemplos no limitantes de diuréticos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen clorotalidona, clorotiazida, diclorofenamida, hidroflumetiazida, indapamida, hidroclorotiazida, bumetanida, ácido etacrinílico, furosemida, torsemida, amilorida, triamtereno, espironolactona y epirenona.

Los ejemplos no limitantes de bloqueadores β-adrenérgicos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen acebutolol, atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, carteolol, carvedilol, celiprolol, esmolol, indenolol, metaprolol, nadolol, nebivolol, penbutolol, pindolol, propanolol, sotalol, tertatolol, tilisolol y timolol.

Los ejemplos no limitantes de bloqueadores alfa 1 útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen terazosina, urapidilo, prazosina, bunazosina, trimazosina, doxazosina, naftopidilo, indoramina, WHIP 164 y XEN010.

Los ejemplos no limitantes de bloqueadores del canal de calcio útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen amlodipina, aranidipina, azelnidipina, barnidipina, benidipina, bepridilo, cinaldipina, clevidipina, diltiazem, efonidipina, felodipina, gallopamilo, isradipina, lacidipina, lemildipina, lercanidipina, nicardipina, nifedipina, nilvadipina, nimodepina, nisoldipina, nitrendipina, manidipina, pranidipina y verapamilo.

Los ejemplos no limitantes de inhibidores de enzimas convertidores de angiotensina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen alacepril, benazepril, ceronapril, captopril, cilazapril, delapril, enalapril, fosinopril, imidapril, losinopril, moveltopril, moexipril, quinapril, quinaprilat, ramipril, perindopril, peridropril, quanipril, spirapril, temocapril, trandolapril y zofenopril.

Los ejemplos no limitantes de inhibidores de endopeptidasa neutral útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen omapatrilato, cadoxatril, ecadotril, fosidotril, sampatrilat, AVE7688 y ER4030.

Los ejemplos no limitantes de antagonistas del receptor de angiotensina II útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen candesartán, eprosartán, irbesartán, losartán, pratosartán, tasosartán, telisartán, valsartán, EXP-3137, FI6828K, RNH6270, losartán monopotásico y losartan hidroclorootiazida potasio.

Los ejemplos no limitantes de antagonistas de endotelina útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen tezosentan, A308165 y YM62899.

Los ejemplos no limitantes de vasodilatores útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen hidralazina (apresolina), clonidina (catapres), minoxidilo (loniten) y alcohol nicotinílico (roniacol).

Los ejemplos no limitantes de agonistas alfa 2a útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen lofexidina, tiamenidina, moxonidina, rilmenidina y guanobenzo.

Los ejemplos no limitantes de bloqueadores α/β adrenérgicos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen nipradilol, arotinolol y amosulalol.

Los antagonistas del receptor DP útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aquellos que se describieron en US 2004/0229844 (incorporadas aquí a título de referencia).

Los ejemplos no limitantes de agentes adicionales que pueden combinarse con los agonistas del receptor del ácido nicotínico de la presente invención incluyen aspirina, Niaspan, Norvsac® (amlodipina), NSAIDS agents (p. ej., Celecoxib (Celebrex®), Diclofenac (Cataflam®, Voltaren®, Arthrotec®,) Diflunisal (Dolobid®), Etodolac (Lodine®), Fenoprofeno (Nalfon®), Flurbirofeno (Ansaid®), Ibuprofen (Motrin®, ADVIL®, NUPRIN®, Tab-Profen®, Vicoprofen®, Combunox®), Indornetacina (Indocin®, Indo-Lemmon®, Indornethagan®), cetoprofeno (Oruvail®), Ketorolac (Toradol®), ácido mefenámico (Ponstel®, disponible en el mercado de First Horizon Pharmaceutical), ácido flufenámico (ácido [N-(3-trifluorometilfenil)antranílico]), Meloxicam (Mobic®), Naburnetona (Relafen®), Naproxeno (Naprosyn®, ALEVE®, Anaprox®, Naprelan®, Naprapac®), Oxaprozina (Daypro®), Piroxicam (Feldene®), Sulindac (Clinoril®) y Tolmetina (Tolectin®)), agentes antihpertensivos (Prazosin®, Propranolol, nadolol, timolol, metoprolol, pindolol, labetalol, guanetidina, reserpina, clonidina, metildopa, guanabenzo, captopril, enalapril, lisinopril, losartán, verapamil, diltiazem, nifedipina, hidroclorotiazida, clorotalidona, furosemida, triamtereno, hidralazina, minoxidilo), antagonistas del receptor de PGE2 (p. ej., EP2 y EP4).

Los ejemplos no limitantes de agentes adicionales que pueden combinarse con los agonistas del receptor del ácido nicotínico de la presente invención incluyen homocisteinasa, modular orfan GPCR, terapia génica basada en HRE, terapia génica, agonistas PPARα/γ duales, FGF-1 recombinante, VRI-1, CRx-150,

terapia basada en VEGF-114, CT-500, regadenosan, CK-1827452, inhibidores de tirosina quinasa JAK2, células regenerativas derivadas de adiposidad, agentes de contraste RMI STARBURST basado en dendrimero, TBC-11299, HEMOxigenación, heparina, GO-EPO, IDN-6734, ISIS-301012, terapia génica HIF-alfa, antagonistas de adrenorecpetores α2b, KI-0002, moduladores de adenosina, Ki-23095, PR-5 (Melacure), L-364373, inhibidores de histona deacetilasa, inhibidores de adenilato ciclasa (p. ej., HI-30435 de Millennium), MITO-0139 (de MitoKor), NV-04 (de Novogen), M-118 (Momenta), elemento de respuesta a la hipoxia, PI-99 (de Progen), NEXVAS (de Resverlogix), CS-207 (de Shenzhen Chipscreen Biosciences), terapia génica regulada con estrógenos, SLV-327 (de SolvaY), TNX-832 (de Sunol Molecular Corp), SLx-2101 (de Surface Logix), anexina recombinante humana (de SurroMed), inhibidores de Chymasa (p. ej. de Toa Eiyo), VM-202 (de ViroMed), modulares del receptor x hepático (p. ej., de Exelixis/Bristol Myers Squibb), Heberquinasa (de Y. M. Biosciences), combinació de atorvastatina-amlodipina, AGN-195795 (Allergan), agonistas de angiotensina (1-7) (p. ej., de Arena), Toprol XL/hidroclorotiazida (de AstraZeneca), Teczem (Aventis), estimuladores de sGC, bloqueadores del canal de calcio, CYT-006-AngQb (CytosBiotechnology), inhibidores de renina (p. ej., de Roche/ Speedel), Coxagen (de geneRx+ Inc), MC-4262 (de Medicure), VNP-489 (de Novartis), felodipina (de Pierre Fabre SA), 2-metoxiestradiol (de PR Pharmaceuticals), antagonistas de adrenoreceptores α1 (p. ej., de Recordati SpA), combinación de lercanidipina-enalapril (de Recordati SpA), donantes de NO (p. ej., de Renopharm), CR-3834 (de Rottapharm Gr), iloprost (de Schering AG), SPP-1100 (de The Speedel Group), angiotensinógeno, MC-4232 (de Medicure), inhibidor de ACE (de Servier), LCP-Feno/Stat. (de LifeCycle Pharma), combinación de APA-01/estatina (de Phosphagenics Ltd), KH-01502 (de Kos), KS-01019 (de Kos), combinación de niacina-lovastatina (de Kos/Merck KGaA),

combinación de MK-0524/niacina/simvastatina de liberación lenta (de Merck), combinación de liberación prolongada MK-0524/ (de Merck), Pro-NAD (de Niadyne Inc), beraprost, perindopril erbumina, barnidipina, irbesartán, valsartán, combinación de valsartán-HCTZ, meclinertant, TAK-536, SR-121463, combinación de irbesatrán + HCTZ, darusentan, PMD-2850, CR-2991, SLV-306, combinación de bisoprolol fumarato+ HCTZ, NV-04, FG-3019, TRC-4149, AVE-7688, PV-903, diltiazem, QC-BT16, cardioterapia (de Cytopia), treprostinil sódico, combinación de enalapril+diltiazem, combinación de mesilato de eprosartán +HCTZ, inhibidor de renina (de Vitae), inhibidores de LG-105 (de Lexicon), inhibidores de LG-844 (de Lexicon), inhibidores de PDE de intensificación de NO, hialuronidasa, clorhidrato de propranolol, BIO-236, RWJ-351647, metoprolol, YM-222546, bLN-5, combinación de olmesartán+azelnidipina (de Sanyo), combinación de moxonidina + HCTZ, NS-304, BIO-123, antagonistas de aldosterona, clonidina, BIO-003 y CR-3834.

Además, los agonistas del receptor del ácido nicotínico de la presente invención también pueden usarse en combinación con dos o más agentes terapéuticos. Un ejemplo no limitante de dos o más agentes terapéuticos útiles en combinación con los agonistas del receptor del ácido nicotínico de la presente invención es la combinación de un compuesto de la presente invención con VYTORIN® (una combinación de simvastatina y ezetimibe).

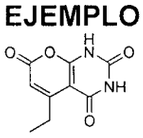
La invención que se revela aquí es ejemplificada por las siguientes preparaciones y ejemplos que no deben considerarse como limitantes del alcance de la revelación. Los especialistas en el arte obviamente conocerán vías mecánicas y estructuras análogas.

EJEMPLOS

En los ejemplos y tablas a continuación, los compuestos de la invención citados a modo de ejemplo presentan un número de referencia. En algunos casos,

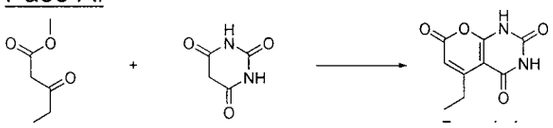
se los denomina como "Ejemplo X," donde "X" es el número representativo del ejemplo particular. En otras instancias, los compuestos de la invención se denominan como "compuesto X," donde "X" es el número representativo del compuesto particular. En otros casos, un compuesto de la invención puede simplemente denominarse con su número. Se sobreentiende que estos términos se utilizan de manera intercambiable. Por ejemplo, el compuesto denominado "Ejemplo 1" también puede ser indicado como "compuesto 1" y viceversa.

EJEMPLO DE PREPARACIÓN 1



Ejemplo 1

Paso A:



Ejemplo 1

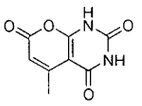
Se mezclaron juntos propionilacetato de metilo (12,5 g, 96,1 mmol, 1,23 eq.) y ácido barbitúrico (10 g, 78,1 mmol, 1 eq.) y sin solvente, la mezcla se calentó a 195°C al aire durante 2 hr., después de lo cual se habían evaporado todos los líquidos. El sólido se lavó dos veces con agua destilada hirviendo. El sólido residual se recristalizó con 2-metoxietanol/agua para dar 4 g del Ejemplo 1 como un sólido color amarillo (20% rendimiento).

^{1}H RMN (CD_3OD): δ 1,20 (t, 3 H, J = 7,3 Hz), 3,00 (q, 2 H, J = 7,3 Hz), 5,80 (s, 1 H)

^{13}C RMN (CD_3OD): δ 12,6, 27,4, 92,0, 104,2, 149,5, 158,4, 161,8, 162,1, 164,1

Masa para $C_9H_9N_2O_4$ $(MH)^+$: 209. Experimental: 209.

EJEMPLO DE PREPARACIÓN 2



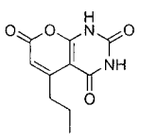
Ejemplo 2

Ejemplo 2 se preparó por un método análogo al método utilizado para preparar el **Ejemplo 1**, excepto que se utilizó acetonilacetato de metilo en lugar de propionilacetato de metilo.

^{1}H RMN (CD_3OD): δ 2,41 (s, 3 H) 5,75 (s, 1 H)

Masa para $C_8H_7N_2O_4$ $(MH)^+$: 195. Experimental: 195.

EJEMPLO DE PREPARACIÓN 3



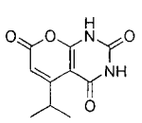
Ejemplo 3

Ejemplo 3 se preparó por un método análogo al método utilizado para preparar el E**jemplo 1**, excepto que se utilizó butanoilacetato de metilo en lugar de propionilacetato de metilo.

^{1}H RMN (CD_3OD): δ 0,96 (t, 3 H, J = 7,6 Hz), 1,57 (m, 2 H), 2,86 (m, 2 H), 5,75 (s, 1 H)

Masa para $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Experimental: 223.

EJEMPLO DE PREPARACIÓN 4



Ejemplo 4

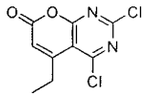
Ejemplo 4 se preparó por un método análogo al método utilizado para preparar el **Ejemplo 1**, excepto que se utilizó isobutilacetato de etilo en lugar de

propionilacetato de metilo, y el **Ejemplo 4** se purificó por HPLC (5% acetonitrilo en agua a 95% acetonitrilo en 10 min).

^{1}H RMN (CD_3OD): δ 1,14 (d, 6 H, J = 6,8 Hz), 4,03 (m, 1 H), 5,86 (s, 1 H)

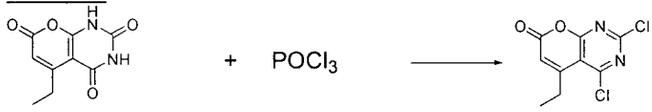
Masa para $C_{10}H_{11}N_2O_4$ $(MH)^+$: 223. Experimental: 223.

EJEMPLO DE PREPARACIÓN 5



Ejemplo 5

Paso A:



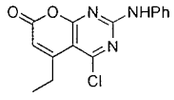
Ejemplo 1 Ejemplo 5

Ejemplo 1 (5 g, 24,04 mmol, 1 eq), $POCl_3$ (36,86 g, 240 mmol, 10 eq.) y piridina (0,95 g, 12 mmol, 0,5 eq) se mezclaron y se calentaron a 115°C durante 8 horas. Luego de enfriar a temperatura ambiente, se eliminó el solvente y el residuo amarronado se purificó usando cromatografía flash con 20% EtOAc/hexano como el solvente eluyente. El producto deseado (4 g) se obtuvo con un rendimiento del 68%.

^{1}H RMN (CD_3OD): δ 1,29 (t, 3 H, J = 7,2 Hz), 3,12 (m, 2 H), 6,39 (s, 1 H)

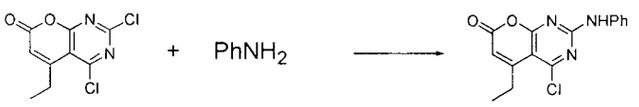
Masa para $C_9H_7Cl_2N_2O_2$ $(MH)^+$: 245. Experimental: 245.

EJEMPLO DE PREPARACIÓN 6



Ejemplo 6

Paso A:



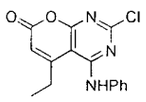
Ejemplo 5 Ejemplo 6

Compuesto 1 (0,15 g, 0,61 mmol, 1 eq.) y anilina (0,06 g, 0,64 mmol, 1,05 eq) se mezclaron en 3 ml de THF anhidro y se agitó durante 12 horas. Se eliminó el solvente y el residuo se purificó mediante TLC prep con 25% EtOAc/hexano como el solvente eluyente para dar el producto deseado como primera fracción (7 mg, 4% rendimiento).

^{1}H RMN (CD_3OD): δ 1,27 (t, 3 H, J = 7,2 Hz), 3,05 (m, 2 H), 6,11 (s, 1 H), 7,11 (t, 1 H, J = 7,6 Hz), 7,34 (m, 2 H), 7,48 (br s, 1 H), 7,60 (d, 2 H, J = 8,0 Hz)

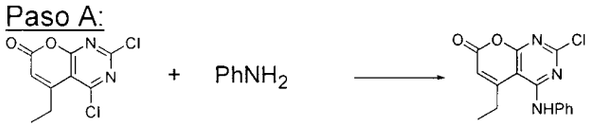
Masa para $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Experimental: 302.

EJEMPLO DE PREPARACIÓN 7



Ejemplo 7

Paso A:



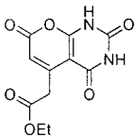
Ejemplo 5 Ejemplo 7

El **Ejemplo 7** se preparó utilizando el método utilizado para preparar el **Ejemplo 6**, excepto que el **Ejemplo 7** se obtuvo como la segunda fracción mediante TLC prep (8 mg, 4% rendimiento).

^{1}H RMN (CD_3OD): δ 1,43 (t, 3 H, J = 7,2 Hz), 2,96 (m, 2 H), 6,22 (s, 1 H), 7,37 – 7,48 (m, 5H)

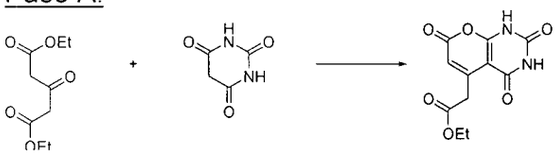
Masa para $C_{15}H_{13}ClN_3O_2$ $(MH)^+$: 302. Experimental: 302.

EJEMPLO DE PREPARACIÓN 8



Ejemplo 8

Paso A:



Ejemplo 8

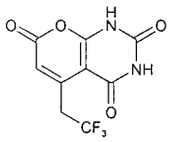
El **Ejemplo 8** se preparó usando un método análogo al método utilizado para preparar el **Ejemplo 1**, excepto que se utilizó 1,3-acetondicarboxilato de dietilo en lugar de propionilacetato de metilo.

^{1}H RMN (CD_3OD): δ 1,20 (t, 3 H, J = 7,3 Hz), 3,88 (s, 2 H), 4,10 (q, 2 H, J = 7,3 Hz), 5,81 (s, 1 H)

^{13}C RMN (CD_3OD): δ 13,4, 39,6, 61,2, 92,2, 108,1, 149,7, 153,1, 157,8, 161,7, 162,0, 170,3

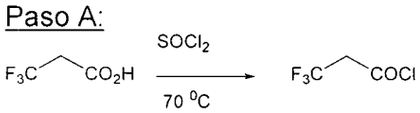
Masa para HRMS para $C_{11}H_{11}N_2O_6$ $(MH)^+$: calculado 267,0617, experimental 267,0623.

EJEMPLO DE PREPARACIÓN 9



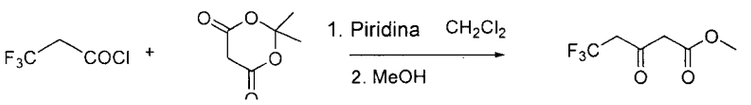
Ejemplo 9

Paso A:



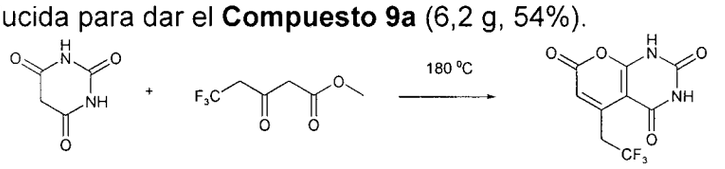
Una mezcla de ácido 3,3,3,-trifluoropropiónico (16 g, 125 mmol), cloruro de tionilo (29,75 g, 250 mmol), y DMF (0,5 ml) se calentó a 70°C durante 4 horas. La mezcla de reacción se destiló bajo presión reducida para dar 3,3,3,-cloruro de trifluoropropionilo (11,5 g, 72%).

Paso B:



Compuesto 9a

A una solución de ácido de Meldrum (2,2-dimetil-4,6-dioxo-1,3-dioxano; 9 g, 62 mmol) y piridina (9,8 g, 68 mmol) en CH_2Cl_2 anhidro (10 ml), que se enfrió a 0°C, se agregó cloruro de 3,3,3,-trifluoropropionilo (10 g, 68 mmol). La mezcla de reacción resultante se agitó bajo N_2 a 0°C durante 1 hora luego a temperatura ambiente durante 2 horas. La mezcla de reacción luego se concentró bajo presión reducida. La pasta resultante se mezcló con MeOH (20 ml), y se calentaron a 80°C durante 5 horas. Se eliminó el solvente y la mezcla resultante se destiló bajo presión reducida para dar el **Compuesto 9a** (6,2 g, 54%).

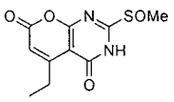


Compuesto 9 a

Ejemplo 9

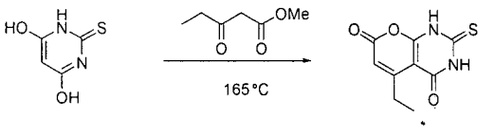
Una mezcla del **Compuesto 9a** (2,2 g, 12 mmol) y ácido barbitúrico se calentó a 180°C durante 1 hora para proporcionar el un sólido negro. Luego de enfriar a temperatura ambiente, el sólido color negro se disolvió en agua caliente (70 ml). La mezcla resultante se extrajo con acetato etílico (4 x 50 ml). La solución orgánica se secó (Na_2SO_4) y se concentró bajo presión reducida. El producto en bruto se purificó por HPLC de fase reversa eluyendo con ácido fórmico (0,1%)/acetonitrilo para dar el **Ejemplo 9** (0,17 g, 5 %). Electroaspersión MS $[M+1]^+$ 263.

EJEMPLO DE PREPARACIÓN 10



Ejemplo 10

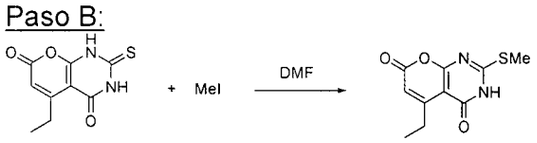
Paso A:



Compuesto 10 a

Una mezcla de 4,6-dihidroxi-2-mercapto-pirimidina (20,0 g, 138,7 mmol) y propionilacetato de metilo (21,8 ml, 173,4 mmol) se calentó a 165°C hasta que había reaccionado por completo el éster. La mezcla de reacción se enfrió y se vertió en agua (75 ml) y luego se filtró a través de un embudo sinterizado. El residuo sólido se lavó con agua (2 x 20 ml) y se secó bajo vacío para proporcionar el **Compuesto 10a** (11,6 g, 37%).

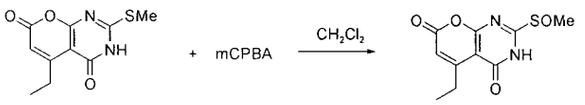
Paso B:



Compuesto 10 a Compuesto 10 b

Se agregó MeI (2,23 ml, 35,72 mmol) a una suspensión del Com**puesto 10a** (4,0 g, 17,86 mmol) en DMF (40 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción luego se vertió en agua (250 ml) y se filtró a través de un embudo sinterizado. El residuo sólido se lavó con agua (2 x 50 ml) y se secó bajo vacío para dar el C**ompuesto 10b** (4,1 g, 96%).

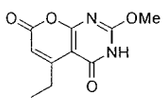
Paso C:



Compuesto 10 b Ejemplo 10

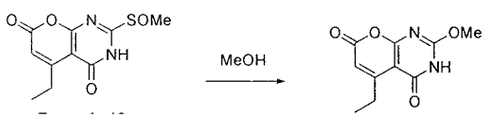
Se agregó *m*-CPBA (3,1 g, 70%, 12,6 mmol) a una suspensión del **Compuesto 10b** (2,0 g, 8,4 mmol) en CH_2Cl_2 (150 ml) a temperatura ambiente. Se eliminó el solvente de la suspensión después de 3 horas y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice, eluyendo primero con hexano/EtOAc (v/v = 1/1) luego CH_2Cl_2/MeOH (v/v = 2/1) para dar el **Ejemplo 10** (2,0 g, 94%). Electroaspersión MS $[M+1]^+$ 255,1.

EJEMPLO DE PREPARACIÓN 11



Ejemplo 11

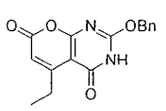
Paso A:



Ejemplo 10 Ejemplo 11

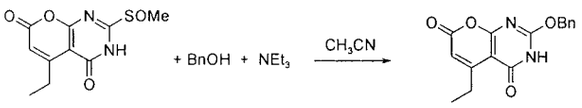
Ejemplo 10 (0,35 g, 1,37 mmol) en MeOH (40 ml) se calentó a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el solvente bajo presión reducida y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con CH_2Cl_2/MeOH (v/v = 50/1) para dar el **Ejemplo 11** (0,23 g, 76%). Electroaspersión MS $[M+1]^+$ 223,1.

EJEMPLO DE PREPARACIÓN 12



Ejemplo 12

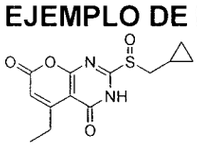
Paso A:



Ejemplo 10 Ejemplo 12

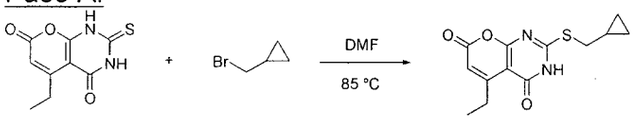
BnOH (2,46 ml, 23,76 mmol) se agregó a una solución del Ej**emplo 10** (0,404 g, 1,58 mmol) y NEt_3 (0,22 ml, 1,58 mmol) en CH_3CN (12,0 ml) a temperatura ambiente. La mezcla de reacción se calentó a 85°C hasta el día siguiente. Luego de enfriar a temperatura ambiente, se agregó HOAc (0,09 ml, 1,58 mmol) y se eliminó el solvente bajo presión reducida. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con CH_2Cl_2/MeOH (v/v = 50/1) para dar el E**jemplo 12** (0,20 g, 42%). Electroaspersión MS $[M+1]^+$ 299,1.

EJEMPLO DE PREPARACIÓN 13



Ejemplo 13

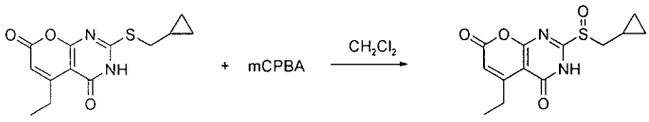
Paso A:



Compuesto 10 a Compuesto 13 a

Se agregó metilbromuro de ciclopropilo (1,30 ml, 13,4 mmol) a una suspensión del Com**puesto 10a** (0,5 g, 2,24 mmol) en DMF (5,0 ml) a temperatura ambiente. La mezcla de reacción se agitó a 85°C durante dos días. La mezcla de reacción se enfrió y se vertió en agua (75 ml) y luego se filtró a través de un embudo sinterizado. El residuo sólido se lavó con agua (2 x 20 ml) y se secó bajo vacío para dar el C**ompuesto 13a** (0,55 g, 88%).

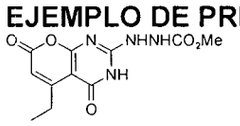
Paso B:



Compuesto 13 a Ejemplo 13

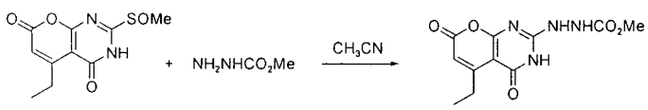
Se agregó *m*-CPBA (0,33 g, 70%, 1,35 mmol) a una suspensión del Com**puesto 13a** (0,25 g, 0,9 mmol) en CH_2Cl_2 (30 ml) a temperatura ambiente. Se eliminó el solvente después de 3 horas, y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con EtOAc/CH_2Cl_2/MeOH (v/v = 4/1/2) para dar el E**jemplo 13** (0,15 g, 57%). Electroaspersión MS $[M+1]^+$ 295,1.

EJEMPLO DE PREPARACIÓN 14



Ejemplo 14

Paso A:



Ejemplo 10 Ejemplo 14

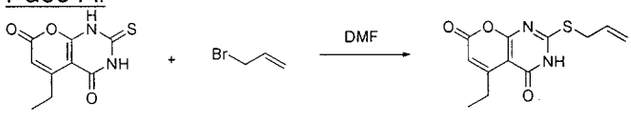
Una mezcla del Ej**emplo 10** (0,205 g, 0,804 mmol) y NH_2NHCO_2Me (0,145 g, 1,608 mmol) en MeCN (4,0 ml) se calentó a reflujo durante 3 horas. Luego de enfriar a temperatura ambiente, se eliminó el solvente bajo presión reducida y el producto en bruto se lavó con agua (3 x 25 ml) con filtración. El sólido se secó bajo vacío para dar el E**jemplo 14** (0,2 g, 89%). Electroaspersión MS $[M+1]^+$ 281,1.

EJEMPLO DE PREPARACIÓN 15



Ejemplo 15

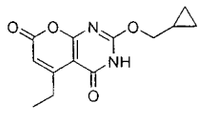
Paso A:



Compuesto 10 a Ejemplo 15

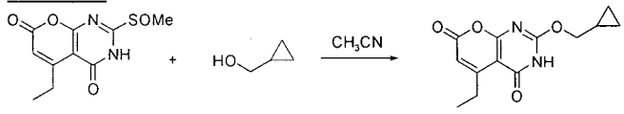
Se agregó bromuro de alilo (1,74 ml, 20,1 mmol) a una suspensión del **Compuesto 10a** (1,5 g, 6,7 mmol) en DMF (15,0 ml) a temperatura ambiente. La mezcla de reacción se agitó a 45°C hasta el día siguiente. La mezcla de reacción se enfrió y se vertió en agua (200 ml) y luego se filtró a través de un embudo sinterizado. El residuo sólido se lavó con agua (2 x 40 ml) y se secó bajo vacío para dar el E**jemplo 15** (1,55 g, 92%). Electroaspersión MS $[M+1]^+$ 265,1.

EJEMPLO DE PREPARACIÓN 16



Ejemplo 16

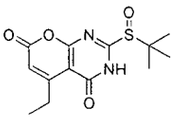
Paso A:



Ejemplo 10 Ejemplo 16

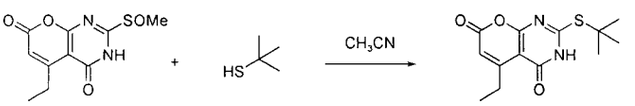
Se agregó ciclopropil carbinol (0,79 ml, 9,8 mmol) a una solución del **Ejemplo 10** (0,050 g, 0,196 mmol) en CH_3CN (0,8 ml) a temperatura ambiente. La mezcla de reacción se calentó a 85°C hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el solvente bajo presión reducida. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con hexano/EtOAc (v/v = 1/1) para dar el E**jemplo 16** (0,027 g, 52%). Electroaspersión MS $[M+1]^+$ 263,1.

EJEMPLO DE PREPARACIÓN 17



Ejemplo 17

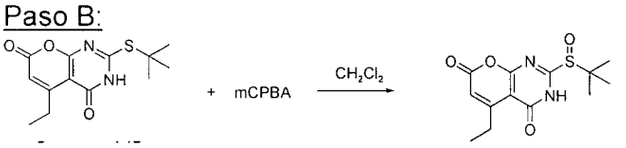
Paso A:



Ejemplo 10 Compuesto 17 a

Una mezcla del Ejemplo **10** (0,10 g, 0,392 mmol) y *t*-BuSH (0,66 ml, 5,88 mmol) en 1,4-dioxano (2,0 ml) se calentó a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el solvente bajo presión reducida. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con hexano/EtOAc (v/v = 1/1) para dar el **Compuesto 17a** (0,045 g, 41%).

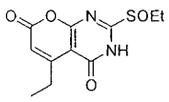
Paso B:



Compuesto 17 a Ejemplo 17

Se agregó *m*-CPBA (0,049 g, 70%, 0,20 mmol) a una suspensión del **Compuesto 17a** (0,040 g, 0,143 mmol) en CH_2Cl_2 (2,5 ml) a temperatura ambiente. Se eliminó el solvente después de 3 horas y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo primero con hexano/EtOAc (v/v = 1/1) luego con CH_2Cl_2/MeOH (v/v = 5/1) para dar el **Ejemplo 17** (0,030 g, 71%). Electroaspersión MS $[M+1]^+$ 297,1.

EJEMPLO DE PREPARACIÓN 18



Ejemplo 18

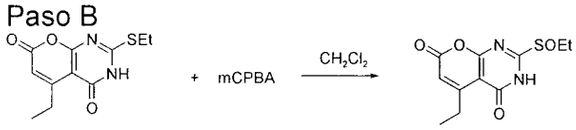
Paso A:



Compuesto 10 a Compuesto 18

Se agregó EtI (2,1 g, 13,4 mmol) a una suspensión del Com**puesto 10a** (1,5 g, 6,7 mmol) en DMF (20 ml). Después de agitar a temperatura ambiente hasta el día siguiente, la mezcla de reacción se vertió en agua (50 ml) y se filtró a través de un embudo Buchner. El residuo sólido se lavó con agua (2 x 50 ml) y se secó bajo vacío para dar el C**ompuesto 18a** (1,3 g, 76%).

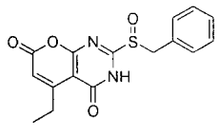
Paso B



Compuesto 18 a Ejemplo 18

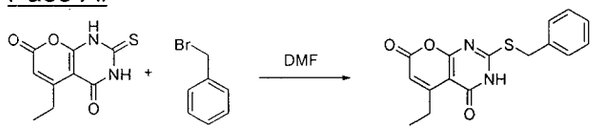
Se agregó *m*-CPBA (74 mg, 70%, 3 mmol) a una suspensión del **Compuesto 18a** (0,5 g, 2 mmol) en CH_2Cl_2 (50 ml) a temperatura ambiente. Después de agitar a temperatura ambiente 3 horas, se eliminó el solvente, y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con AcOH/MeOH/CH_2Cl_2 (v/v/v = 0,1/4,9/95) para dar el E**jemplo 18** (0,4 g, 74%). Electroaspersión MS $[M+1]^+$ 269.

EJEMPLO DE PREPARACIÓN 19



Ejemplo 19

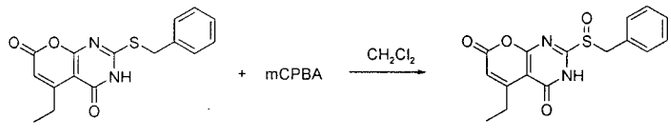
Paso A:



Compuesto 10 a Compuesto 19 a

Se agregó bromuro de bencilo (1,54 g, 9 mmol) a una suspensión del **Compuesto 10a** (1 g, 4,5 mmol) en DMF (20 ml). Después de agitar a temperatura ambiente hasta el día siguiente, la mezcla de reacción se vertió en agua (50 ml) y se filtró a través de un embudo Buchner. El residuo sólido se lavó con agua (2 x 50 ml) y se secó bajo vacío para dar el **Compuesto 19a** (1,3 g, 92%).

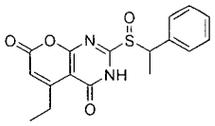
Paso B:



Compuesto 19 a Ejemplo 19

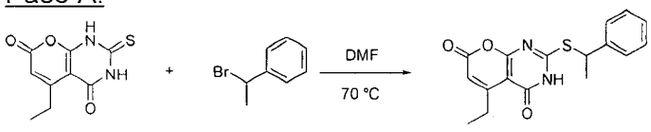
Se agregó *m*-CPBA (72 mg, 70%, 3 mmol) a una suspensión del **Compuesto 19a** (0,5 g, 2 mmol) en CH_2Cl_2 (50 ml) a temperatura ambiente. Después de agitar a temperatura ambiente 3 horas, se eliminó el solvente, y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con AcOH/MeOH/CH_2Cl_2 (v/v/v = 0,1/2,9/97) para dar el **Ejemplo 19** (0,5 g, 76%). Electroaspersión MS $[M+1]^+$ 331.

EJEMPLO DE PREPARACIÓN 20



Ejemplo 20

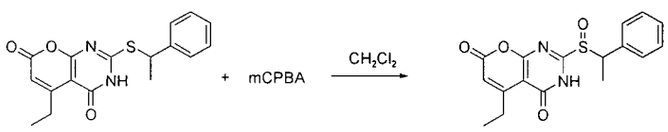
Paso A:



Compuesto 10 a Compuesto 20 a

Se agregó (1-bromoetil)benceno (3,4 g, 18 mmol) a una suspensión del **Compuesto 10a** (1 g, 4,5 mmol) en DMF (20,0 ml) a temperatura ambiente. La mezcla de reacción se agitó a 70°C durante un día. La mezcla de reacción se enfrió y se vertió en agua (50 ml) y luego se filtró a través de un embudo Buchner. El residuo sólido se lavó con agua (2 x 20 ml) y se secó bajo vacío para obtener el **Compuesto 20a** (1,3 g, 87%). Electroaspersión MS $[M+1]^+$ 329.

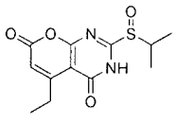
Paso B:



Compuesto 20 a Ejemplo 20

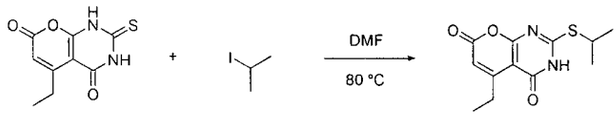
Se agregó *m*-CPBA (0,3 g, 70%, 1,2 mmol) a una suspensión del **Compuesto 20a** (0,33 g, 1 mmol) en CH_2Cl_2 (30 ml) a temperatura ambiente. Se eliminó el solvente después de 3 horas y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con 5% de EtOH en EtOAc/hexanos (v/v = 1:1) para dar el **Ejemplo 20** (0,1 g, 50%). Electroaspersión MS $[M+1]^+$ 345.

EJEMPLO DE PREPARACIÓN 21



Ejemplo 21

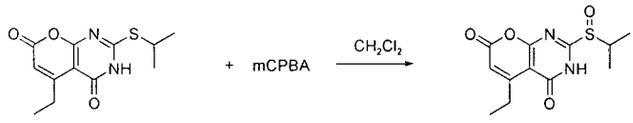
Paso A:



Compuesto 10 a Compuesto 21 a

Se agregó 2-yodopropano (1,53 g, 9 mmol) a una suspensión del **Compuesto 10a** (1 g, 4,5 mmol) en DMF (20 ml). La mezcla de reacción se agitó a 80°C durante un día. La mezcla de reacción se enfrió y se vertió en agua (50 ml) y luego se filtró a través de un embudo Buchner. El residuo sólido se lavó con agua (2 x 20 ml) y se secó bajo vacío para dar el C**ompuesto 21a** (1,05 g, 88%).

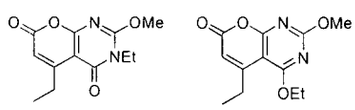
Paso B



Compuesto 21 a Ejemplo 21

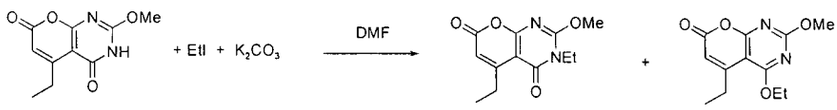
Se agregó *m*-CPBA (0,74 g, 70%, 3 mmol) a una suspensión del **Compuesto 21a** (0,53 g, 2 mmol) en CH_2Cl_2 (30 ml) a temperatura ambiente. Se eliminó el solvente después de 3 horas, el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con 0,1% AcOH en MeOH/CH_2Cl_2 (v/v = 2:98) para dar el E**jemplo 21** (0,45 g, 80%). Electroaspersión MS $[M+1]^+$ 283.

EJEMPLOS DE PREPARACIONES 22 y 23



Ejemplo 22 Ejemplo 23

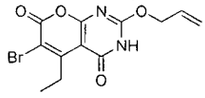
Paso A:



Ejemplo 11 Ejemplo 22 Ejemplo 23

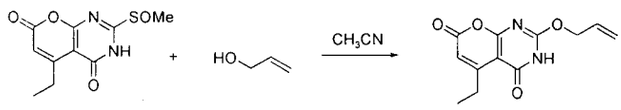
Se agregó K_2CO_3 (36,7 mg, 0,266 mmol) a una mezcla del Ejemplo **11** (29,6 mg, 0,133 mmol) y EtI (0,064 ml, 0,8 mmol) en DMF (1,0 ml) a temperatura ambiente. La reacción se agitó hasta el día siguiente antes de que se diluyó mediante la adición de EtOAc (50 ml) y agua (10 ml). La fase orgánica se lavó con agua (3x15 ml), salmuera (15 ml), y se secó sobre $MgSO_4$. Después de la filtración y concentración, el producto en bruto se purificó utilizando TLC prep con hexano/CH_2Cl_2/EtOAc (v/v/v = 7/3/1) como eluyente para dar el **Ejemplo 22** (7,0 mg, 21%) y **Ejemplo 23** (20 mg, 60%). Electroaspersión MS $[M+1]^+$ 251,1.

EJEMPLO DE PREPARACIÓN 24



Ejemplo 24

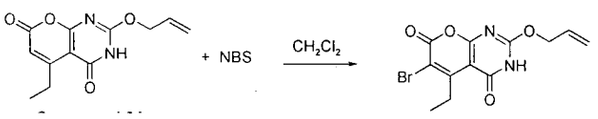
Paso A:



Ejemplo 10 Compuesto 24 a

Se calentó el **Ejemplo 10** (0,216 g, 0,847 mmol) en alcohol alílico (3,0 ml) a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el solvente bajo presión reducida y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con EtOAc/MeOH (v/v = 5/1) para dar el **Compuesto 24a** (0,1 g, 48%).

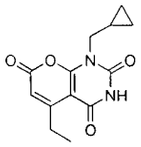
Paso B:



Compuesto 24 a Ejemplo 24

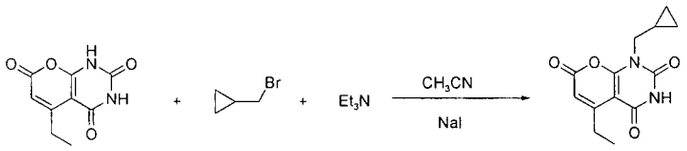
Se agregó NBS (36 mg, 0,202 mmol) a una solución del **Compuesto 24a** (0,040 g, 0,161 mmol) en CH_2Cl_2 (2,0 ml) a temperatura ambiente. Se eliminó el solvente durante 1 hora y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con hexano/EA (v/v = 1/1) para dar el E**jemplo 24** (0,025 g, 48%). Electroaspersión MS $[M+1]^+$ 327,1.

EJEMPLO DE PREPARACIÓN 25



Ejemplo 25

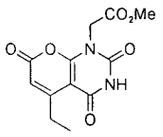
Paso A:



Ejemplo 1 Ejemplo 25

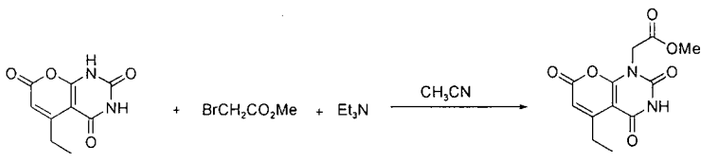
El **Ejemplo 1** (0,5 g, 2,4 mmol) a CH_3CN (10 ml). Se agregó trietilamina (0,33 ml, 2,4 mmol) a la suspensión seguido de metilbromuro de ciclopropilo (0,26 ml, 2,64 mmol) y NaI (0,36 g, 2,4 mmol). La mezcla de reacción se calentó a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, el solvente se evaporó al vacío. El producto en bruto se purificó por cristalización de EtOAc/hexanos para dar el E**jemplo 25** (0,25 g, 40%).

EJEMPLO DE PREPARACIÓN 26



Ejemplo 26

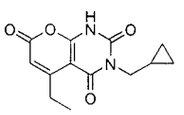
Paso A:



Ejemplo 1 Ejemplo 26

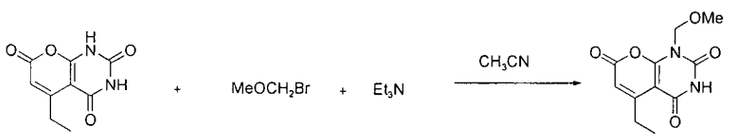
Ejemplo 1 (0,1 g, 0,48 mmol) a CH_3CN (3,0 ml). Se agregó trietilamina (0,067 ml, 0,48 mmol) a la suspensión seguido de bromoacetato de metilo (0,046 ml, 0,48 mmol). La mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. Se eliminó el solvente bajo presión reducida y la mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Ejemplo 26** (0,06 g, 45%).

EJEMPLO DE PREPARACIÓN 27



Ejemplo 27

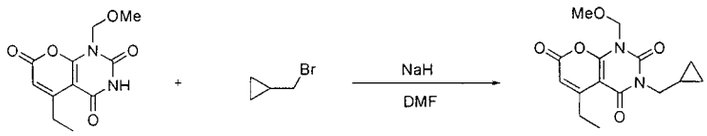
Paso A:



Ejemplo 1 Compuesto 27 a

Ejemplo 1 (1,0 g, 4,8 mmol) a CH_3CN (20 ml). Se agregó trietilamina (0,67 ml, 4,8 mmol) a la suspensión seguido de metiléter de bromometilo (0,44 ml, 4,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 10 min después de lo cual se concentró. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 27a** (0,6 g, 50%).

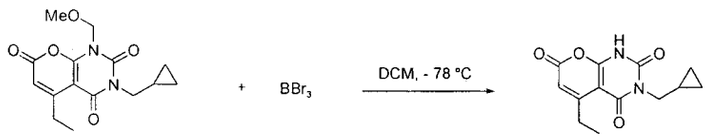
Paso B:



Compuesto 27 a Compuesto 27 b

Se agregó hidruro de sodio (0,058 g, 1,46 mmol) a una mezcla del **Compuesto 27a** (0,335 g, 1,33 mmol) en 8 ml de DMF a 0°C seguido de metilbromuro de ciclopropilo (0,142 ml, 1,46 mmol). La suspensión se agitó a temperatura ambiente hasta el día siguiente antes de ser diluído con EtOAc (10 ml) y desactivado mediante el agregado de agua (5 ml). La fase acuosa se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 27b** (0,175 g, 43%).

Paso C:

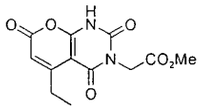


Compuesto 27 b Ejemplo 27

Se agregó tribromuro borónico (2,85 ml, 2,85 mmol, solución 1,0 M en DCM) a una solución del **Compuesto 27b** (0,175 g, 0,57 mmol) en CH_2Cl_2 (8,0

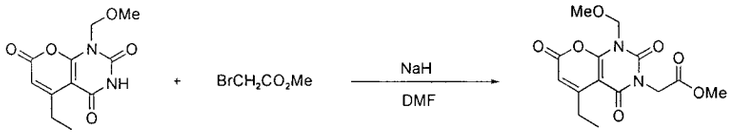
ml) a -78°C. La reacción se agitó durante 2 h antes de ser desactivada con agua (5,0 ml). La mezcla de reacción se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Ejemplo 27** (0,1 g, 67%).

EJEMPLO DE PREPARACIÓN 28



Ejemplo 28

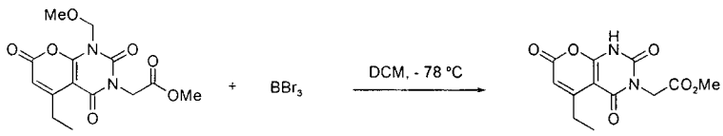
Paso A:



Compuesto 27 a Compuesto 28a

Se agregó hidruro de sodio (0,016 g, 0,396 mmol) a una mezcla del **Compuesto 27a** (0,100 g, 0,396 mmol) en 2 ml de DMF a 0°C seguido de bromoacetato de metilo (0,041 ml, 0,44 mmol). La suspensión se agitó a temperatura ambiente hasta el día siguiente antes de ser diluído con EtOAc (5 ml) y desactivado mediante el agregado de agua (5 ml). La fase acuosa se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 28a** (0,07 g, 54%).

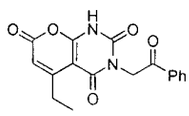
Paso B:



Compuesto 28 a Ejemplo 28

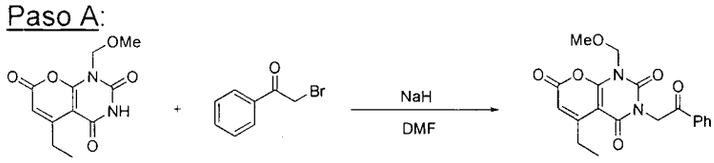
Se agregó tribromuro borónico (1,1 ml, 1,1 mmol, solución 1,0 M en DCM) a una solución del **Compuesto 28a** (0,07 g, 0,22 mmol) en CH_2Cl_2 (3,0 ml) a -78°C. La reacción se agitó durante 2 h antes de ser desactivada con agua (5,0 ml). La mezcla de reacción se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Ejemplo 28** (0,02 g, 33%).

EJEMPLO DE PREPARACIÓN 29



Ejemplo 29

Paso A:

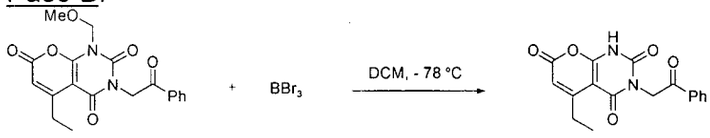


Compuesto 27 a Compuesto 29 a

Se agregó hidruro de sodio (0,080 g, 1,98 mmol) a una mezcla del **Compuesto 27a** (0,500 g, 1,98 mmol) en 8 ml de DMF a 0°C seguido de 2-bromoacetofenona (0,434 g, 1,98 mmol). La suspensión se agitó a temperatura ambiente hasta el día siguiente antes de ser diluída con EtOAc (5 ml) y desactivada mediante el agregado de agua (5 ml). La fase acuosa se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por

cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 29a** (0,37 g, 50%).

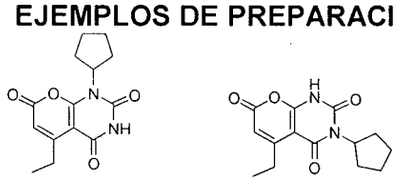
Paso B:



Compuesto 29 a Ejemplo 29

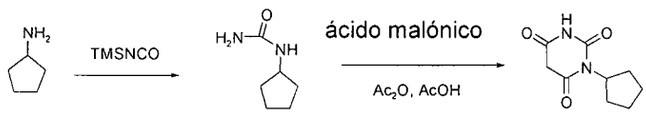
Se agregó tribromuro borónico (4,7 ml, 4,7 mmol, solución 1,0 M en DCM) a una solución del **Compuesto 29a** (0,350 g, 0,95 mmol) en CH_2Cl_2 (10,0 ml) a -78°C. La reacción se agitó durante 2 h antes de ser desactivada con agua (5,0 ml). La mezcla de reacción se extrajo con EtOAc (2 x 15 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Ejemplo 29** (0,175 g, 56%).

EJEMPLOS DE PREPARACIÓN 30 y 31



Ejemplo 30 Ejemplo 31

Paso A:

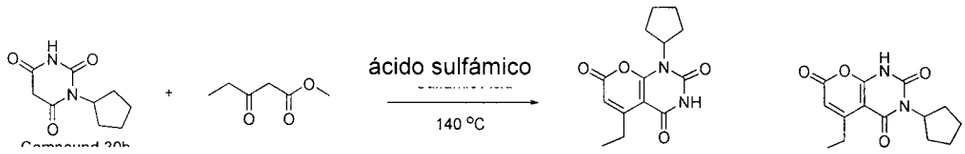


Compuesto 30 a Compuesto 30 b

Se agregó a una solución CH_2Cl_2 de ciclopentilamina, isocianato de trimetilsililo. La mezcla de reacción se agitó hasta el día siguiente. A ello se agregó 200 ml de CH_3OH, y la mezcla se agitó durante otras 2 hrs. La mezcla de reacción se concentró y se tituló utilizando dietiléter para dar un precipitado

blanquecino. El precipitado se filtró a través de un embudo Buchner para dar el **Compuesto 30a** ciclopentilo urea como un compuesto sólido cristalino color blanco (13,0 g, 86%). A este **Compuesto 30a** de urea (5,0 g, 38,7 mmol) en ácido acético (11 ml), se agregó ácido malónico (4,0 g, 38,7 mmol) seguido de anhídrido acético (18 ml) y la reacción se agitó a 70°C durante 12 hrs. La mezcla de reacción se concentró, se enfrió en un baño helado y se tituló utilizando 4/1 EtO_2/EtOAc. Se produjo la precipitación de un sólido cristalino color amarillo pálido. El precipitado se filtró y se lavó 2-3 veces utilizando dietiléter frío para obtener un sólido color amarillo pálido **Compuesto 30b** (2,5 g, 33%).

Paso B:

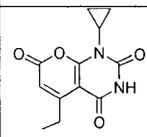
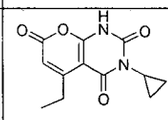
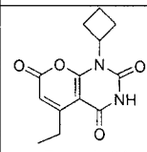
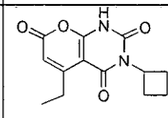
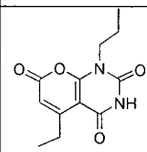
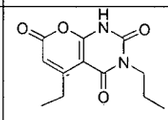
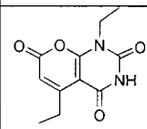
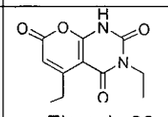
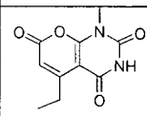
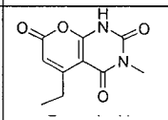
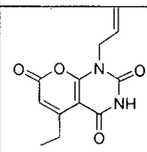
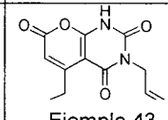


Compuesto 30 b Ejemplo 30 Ejemplo 31

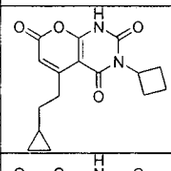
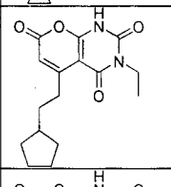
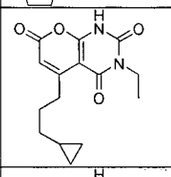
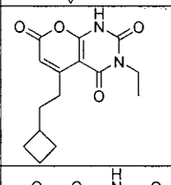
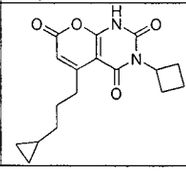
Compuesto 30b (0,75 g, 1,0 equiv., 3,82 mmol) se condensó con propional acetato de metilo (0,48mL, 3,82 mmol) en presencia de ácido sulfámico y se calentaron a 140°C durante 6 hrs, formando un sólido color marrón oscuro. La mezcla de reacción se diluyó con EtOAc, se lavó con H_2O, se secó utilizando Na_2SO_4 y se concentró para dar un mezcla en bruto. La purificación por TLC prep de la mezcla en bruto en 95/5 CH_2Cl_2/CH_3OH proporcionó ambos isómeros N_1 y N_3, **Ejemplo 30** LCMS: (M+1) 277,1 y **Ejemplo 31** LCMS: (M+1). 277,1

Se utilizó un procedimiento similar de dos pasos para sintetizar los **Ejemplos 32-43**.

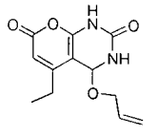
sustituyentes	Productos N-1	LCMS: (M+1) de productos N-1	Productos N-3	LCMS: (M+1) de productos N-3

sustituyentes	Productos N-1	LCMS: (M+1) de productos N-1	Productos N-3	LCMS: (M+1) de productos N-3
ciclopropilo	 Ejemplo 32	249,1	 Ejemplo 33	249,1
ciclobutilo	 Ejemplo 34	263,1	 Ejemplo 35	263,1
Pr	 Ejemplo 36	251,1	 Ejemplo 37	251,1
Et	 Ejemplo 38	237,1	 Ejemplo 39	237,1
Me	 Ejemplo 40		 Ejemplo 41	223,0
alil	 Ejemplo 42	249,1	 Ejemplo 43	249,1

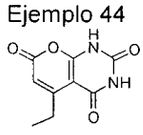
Utilizando el procedimiento indicado previamente para preparar el compuesto del Ejemplo 30, y sustituyendo los reactivos apropiados e intermediarios, se prepararon los compuestos **780-785**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS [M+1]+**
780		303,1
781		305,2
782		291,2
783		291,2
784		317,2

EJEMPLO DE PREPARACIÓN 44

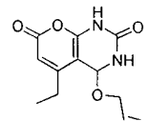


Ejemplo 44



Bromuro de alilo, LIOH

$CH_3OH:H_2O$ (1:1)

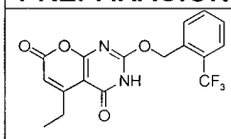
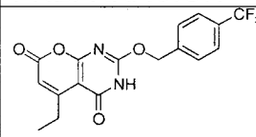
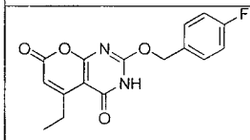
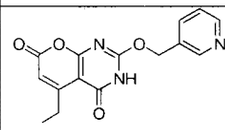
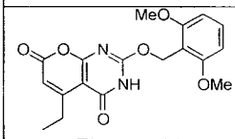
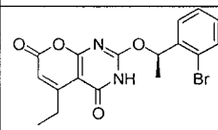
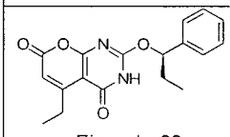
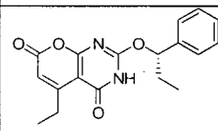


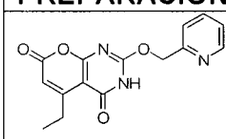
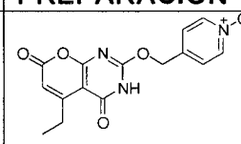
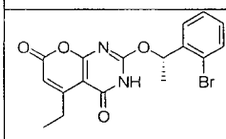
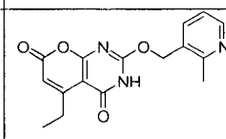
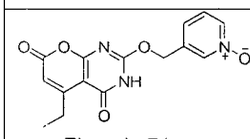
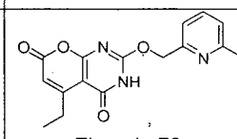
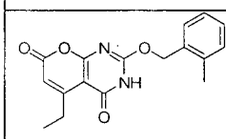
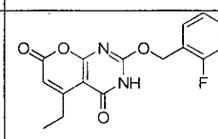
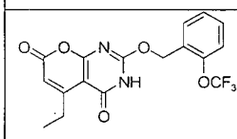
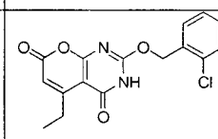
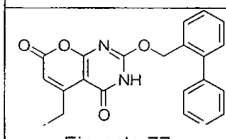
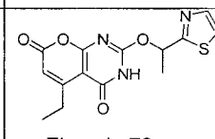
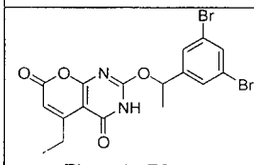
Ejemplo 1 Ejemplo 44

Al **Ejemplo 1** (0,456 g, 2,2 mmol) en MeOH:H_2O (1:1) se agregó bromuro de alilo seguido de LiOH, y la mezcla de reacción se calentó a 82°C durante 8

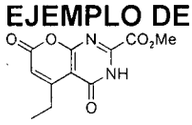
horas. Se monitoreó el progreso de la reacción mediante TLC, lo que indicó la presencia de algún material de partida. La mezcla de reacción luego se calentó durante otras 6 horas. Se produjo un precipitado color rojo anaranjado, que se filtró de la solución utilizando dietiléter. El filtrado se purificó utilizando TLC prep 95/5 CH_2Cl_2/CH_3OH para dar el **Ejemplo 44** LCMS: (M+1),249,0

Los siguientes **Ejemplos 45-47, 51, 61-64, 66-67, 69-79** se prepararon mediante un procedimiento similar a aquel utilizado para la preparación del **Ejemplo 12**, utilizando el **Ejemplo 10** y el correspondiente alcohol apropiado.

EJEMPLO DE PREPARACIÓN	Electroaspersión LCMS $[M+1]^+$	**EJEMPLO DE PREPARACIÓN**	Electroaspersión LCMS $[M+1]^+$
 Ejemplo 45	367,1	 Ejemplo 46	367,1
 Ejemplo 47	317,1	 Ejemplo 51	300,1
 Ejemplo 61	359,1	 Ejemplo 62	391,1
 Ejemplo 63	327,1	 Ejemplo 64	327,1

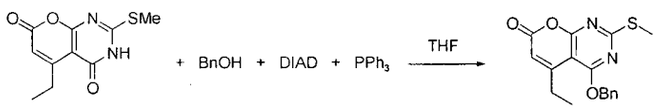
EJEMPLO DE PREPARACIÓN	Electroaspersión LCMS $[M+1]^+$	**EJEMPLO DE PREPARACIÓN**	Electroaspersión LCMS $[M+1]^+$
 Ejemplo 66	300,1	 Ejemplo 67	316,1
 Ejemplo 69	391,2	 Ejemplo 70	314,1
 Ejemplo 71	316,1	 Ejemplo 72	314,1
 Ejemplo 73	313,1	 Ejemplo 74	317,1
 Ejemplo 75	383,1	 Ejemplo 76	333,1
 Ejemplo 77	375,1	 Ejemplo 78	320,1
 Ejemplo 79	469,1		

EJEMPLO DE PREPARACIÓN 48



Ejemplo 48

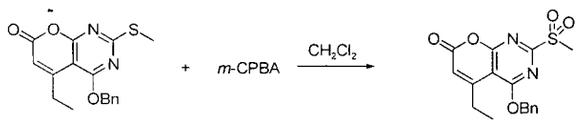
Paso A:



Compuesto 10 b compuesto 48 a

Se agregó DIAD (0,488 ml, 2,52 mmol) gota a gota a una solución del **Compuesto 10b** (0,5 g, 2,10 mmol), BnOH (0,261 ml, 2,52 mmol) y PPh_3 (0,661 g, 2,52 mmol) en THF (6,0 ml) a temperatura ambiente. La mezcla de reacción resultante se agitó durante 5 horas antes de su procesamiento mediante cromatografía flash en columna de gel de sílice utilizando un método de carga de muestra sólida, eluyendo con hexano/EtOAc (v/v = 5/1) para dar el **Compuesto 48a** (0,25 g, 36%).

Paso B:

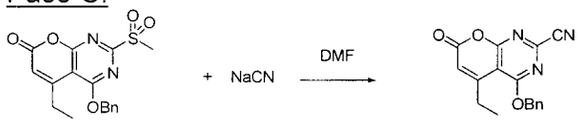


Compuesto 48 a Compuesto 48 b

Se agregó *m*-CPBA (0,384 g, 1,55 mmol, 60-70%) a temperatura ambiente a una solución del **Compuesto 48a** (0,17 g, 0,518 mmol) en CH_2Cl_2 (5 ml). La mezcla de reacción se agitó durante 5 horas antes de ser desactivada mediante el agregado de Me_2S (76 uL, 1,55 mmol). La mezcla luego se diluyó con EtOAc y se lavó con una solución de $NaHCO_3$. La fase orgánica se lavó con agua, salmuera, y se secó (Na_2SO_4). Se eliminó el solvente bajo presión reducida, y el producto en bruto se purificó mediante cromatografía flash en columna de gel de sílice

eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) para dar el C**ompuesto 48b** (0,15 g, 80%).

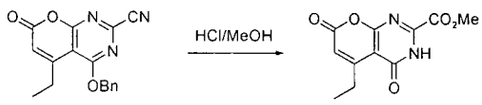
Paso C:



Compuesto 48 b Compuesto 48 c

Se agregó NaCN (14,0 mg, 0,286 mmol) a una solución del C**ompuesto 48b** (85,8 mg, 0,238 mmol) en DMF (1,5 ml) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante 2 horas antes de su procesamiento mediante la dilución con EtOAc y agua. La fase orgánica se lavó con agua (2x), salmuera, y se secó ($MgSO_4$). Se eliminó el solvente bajo presión reducida, y el producto en bruto se purificó mediante cromatografía flash en columna de gel de sílice, eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 5/1/1) para dar el C**ompuesto 48c** (37 mg, 50%).

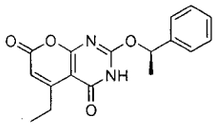
Paso D:



Compuesto 48 b Ejemplo 48

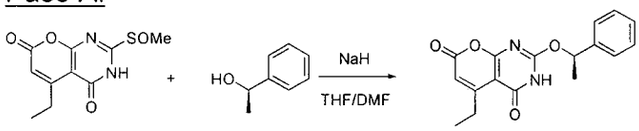
Una solución de **Compuesto 48c** (10 mg, 0,0326 mmol) en Hcl 4,0 M en dioxano (0,7 ml) y MeOH (0,7 ml) en un tubo sellado se calentó a 70°C durante 7 horas. La mezcla se enfrió a temperatura ambiente y se eliminó el solvente bajo presión reducida para dar el producto en bruto. El producto en bruto se purificó con cromatografía preparativa de capa fina con gel de sílice eluyendo con hexano/CH_2Cl_2/MeOH (v/v/v = 6/4/1) para dar el **Ejemplo 48** (5 mg, 61%). Electroaspersión MS $[M+1]^+$ 251,1.

EJEMPLO DE PREPARACIÓN 49



Ejemplo 49

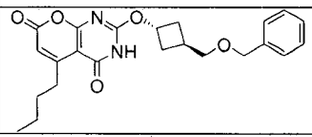
Paso A:

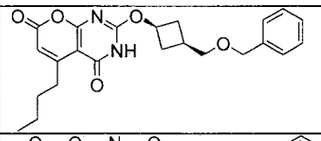
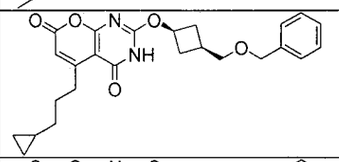
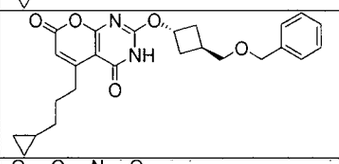
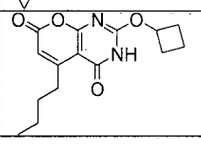


Ejemplo 10 Ejemplo 49

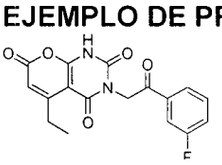
Se agregó (R)-fenetanol (0,24 ml, 2,0 mmol) gota a gota a una suspensión de NaH (87,4 mg, 2,0 mmol, 55% en aceite mineral) en THF (3,0 ml) a temperatura ambiente. La mezcla se agitó durante 2 horas hasta que la solución fuera clara. El alcóxido así formado luego se agregó gota a gota a una solución del **Compuesto 10** (0,27 g, 1,0 mmol) en DMF (3,0 ml) a temperatura ambiente. La mezcla de reacción se agitó durante 2 horas antes de ser desactivada mediante el agregado de HOAc (0,11 ml, 2,0 mmol). La mezcla de reacción a EtOAc/CH_2Cl_2 (8/2), se lavó con HCl diluido (0,1 M), agua y salmuera, luego se secó ($MgSO_4$). Se eliminó el solvente bajo presión reducida. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) para dar el **Compuesto 49** (0,25 g, 80%). Electroaspersión MS $[M+1]^+$ 313,1.

Utilizando el método indicado previamente y sustituyendo los reactivos e intermediarios apropiados, se prepararon los compuestos **791**-**795**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS [M+1]+**
791		411,2

792		411,2
793		437,2
794		437,2
795		291,2

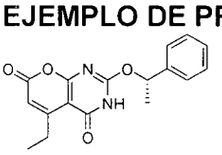
EJEMPLO DE PREPARACIÓN 50



Ejemplo 50

El **Ejemplo 50** se preparó mediante un procedimiento similar a aquel utilizado para preparar el **Ejemplo 29**, utilizando el **Compuesto 27a** y el correspondiente bromuro adecuado. Electroaspersión MS $[M+1]^+$ 345,1.

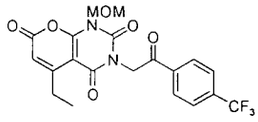
EJEMPLO DE PREPARACIÓN 52



Ejemplo 52

El **Ejemplo 52** se preparó mediante un procedimiento similar a aquel utilizado para preparar el E**jemplo 49**, utilizando el E**jemplo 10** y (S)-fenetanol. Electroaspersión MS $[M+1]^+$ 313,1.

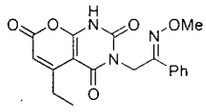
EJEMPLO DE PREPARACIÓN 53



Ejemplo 53

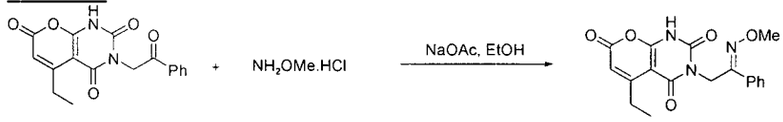
El **Ejemplo 53** preparado mediante un procedimiento similar a aquel utilizado en el Paso A de la preparación del **Ejemplo 29**, empleando el **Compuesto 27a** y el correspondiente bromuro adecuado. Electroaspersión MS $[M+1]^+$ 439,1.

EJEMPLO DE PREPARACIÓN 54



Ejemplo 54

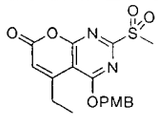
Paso A:



Ejemplo 29 Ejemplo 54

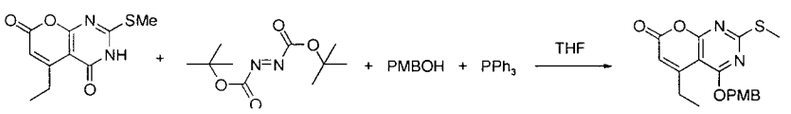
Se agregó el **Ejemplo 29** (0,05 g, 0,153 mmol) a etanol (3,0 ml). Se agregó clorhidrato de metoxilamina (0,051 g, 0,61 mmol) a la mezcla seguido de acetato de sodio (0,038 g, 0,46 mmol). La mezcla de reacción se agitó a 60°C hasta el día siguiente. Después de haberse enfriado a temperatura ambiente, se eliminó el solvente bajo presión reducida, se diluyó con CH_2Cl_2 (5 ml) y agua (5 ml). El producto se extrajo de CH_2Cl_2 (2 x 5 ml), se secó sobre $MgSO_4$, se concentró. El producto en bruto se disolvió en un mínimo de CH_2Cl_2, se diluyó con hexanos y se filtró para dar el **Ejemplo 54**. Electroaspersión MS $[M+1]^+$ 356,1.

EJEMPLO DE PREPARACIÓN 55



Ejemplo 55

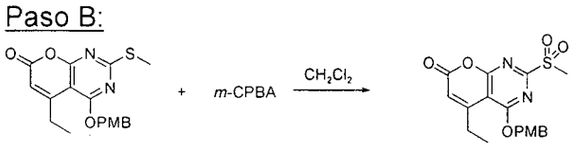
Paso A:



Compuesto 10 a Compuesto 55 a

Se agregó diazodicarboxilato de di-t-butilo (2,32 g, 10,08 mmol) a una solución del **Compuesto 10b** (2,0 g, 8,4 mmol), 4-metoxialcohol bencílico (1,39 g, 10,08 mmol) y PPh_3 (2,64 g, 10,08 mmol) en THF (20,0 ml) a temperatura ambiente. La mezcla de reacción resultante se agitó durante 4 horas antes de su procesamiento mediante cromatografía flash directa en columna de gel de sílice utilizando un método de carga de muestra sólida, eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 9/1/1) para dar el **Compuesto 55a** (1,6 g, 53%).

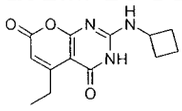
Paso B:



Compuesto 55 a Ejemplo 55

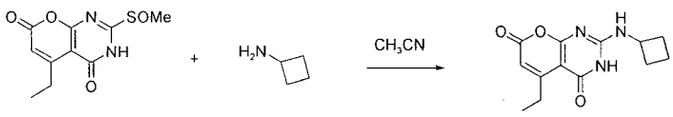
Se agregó *m*-CPBA (0,47 g, 1,92 mmol, 60-70%) a temperatura ambiente a una solución del **Compuesto 55a** (0,287 g, 0,80 mmol) en CH_2Cl_2 (8 ml). La mezcla de reacción se agitó durante 5 horas antes de ser desactivada mediante el agregado de Me_2S (124 µl, 1,92 mmol). La mezcla luego se diluyó con EtOAc y se lavó con una solución de $NaHCO_3$. La fase orgánica se lavó con agua, salmuera, y se secó (Na_2SO_4). Se eliminó el solvente bajo presión reducida, el producto en bruto se purificó con cromatografía flash en columna de gel de sílice eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 7/3/2) para dar el **Ejemplo 55** (0,15 g, 80%). Electroaspersión MS $[M+1]^+$ 391,1.

EJEMPLO DE PREPARACIÓN 56



Ejemplo 56

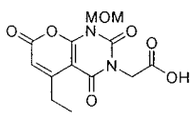
Paso A:



Ejemplo 10 Ejemplo 56

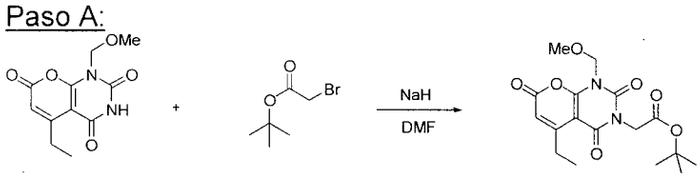
Se agregó ciclobutilamina (0,14 g, 2 mmol) a una suspensión del **Ejemplo 10** (0,25 g, 1 mmol) en CH_3CN (15 ml). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. Se eliminó el solvente y el producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con 10% NH_4OH en $MeOH/CH_2Cl_2$ (v/v = 3:97) para dar el **Ejemplo 56** (0,045 g, 17%). Electroaspersión MS $[M+1]^+$ 262,1

EJEMPLO DE PREPARACIÓN 57



Ejemplo 57

Paso A:

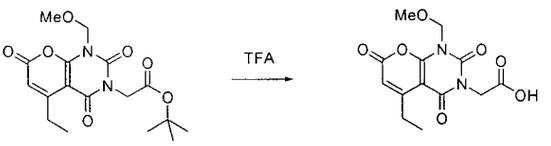


Compuesto 27 a Compuesto 57 a

Una mezcla del **Compuesto 27a** (2 g, 7,9 mmol) en DMF (100 ml), bromoacetato de t-butilo (1,7 g, 8,7 mmol), y diisopropil etilamina (1,1 g, 8,7 mmol) se agitó a 40°C durante 4 horas, luego a temperatura ambiente durante 16 horas. La mezcla de reacción se mezcló con agua (200 ml), y luego se extrajo con

acetato etílico (100 ml x 3). La solución orgánica se secó (Na_2SO_4) y se concentró. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con $MeOH/CH_2Cl_2$ (v/v = 2:98) para dar el **Compuesto 57a** (1,8 g, 62%). Electroaspersión MS $[M+1]^+$ 367,2.

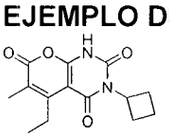
Paso B:



Compuesto 57 a Ejemplo 57

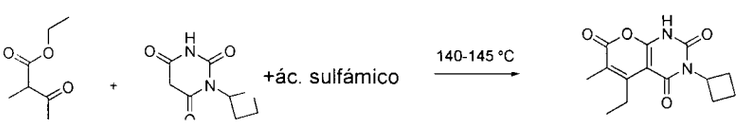
Una mezcla del **Compuesto 57a** (0,95 g, 2,6 mmol) en CH_2Cl_2 (5 ml) y ácido trifluoroacético (1,5 g, 13 mmol) se agitó a temperatura ambiente durante 4 horas. La eliminación del solvente y del ácido trifluoroacético excesivo brindó el **Ejemplo 57** (0,8 g, 100%). Electroaspersión MS $[M+1]^+$ 311,2

EJEMPLO DE PREPARACIÓN 58



Ejemplo 58

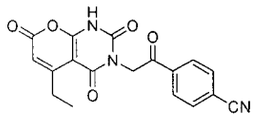
Paso A:



Ejemplo 58

A una mezcla de ácido mono-ciclobutilbarbitúrico (300 mg, 1,6 mmol) y etiléster del ácido 2-metil-3-oxo-pentanoico (1,041 g, 6,59 mmol) se agregó ácido sulfámico (77 mg, 0,8 mmol). La mezcla se calentó a 140-145°C durante 48h. El residuo se cargó sobre placas de gel de sílice preparativas y se eluyó con 5% $MeOH/CH_2Cl_2$ para proporcionar el **Ejemplo 58** (42 mg, 9%). LCMS: M+1: 277,1

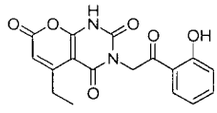
EJEMPLO DE PREPARACIÓN 59



Ejemplo 59

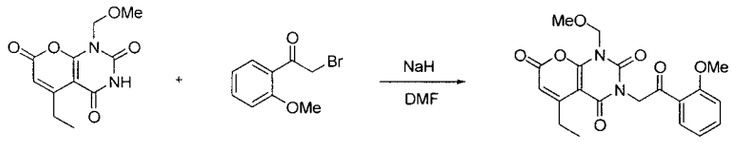
EJEMPLO 59 se preparó utilizando un procedimiento de dos pasos similar a aquel utilizado para la preparación del **Ejemplo 29**, utilizando el **Compuesto 27a** y el correspondiente bromuro adecuado. Electroaspersión MS $[M+1]^+$ 252,1.

EJEMPLO DE PREPARACIÓN 60



Compuesto 60

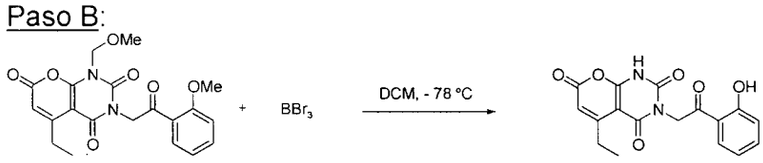
Paso A:



Compuesto 27 a Compuesto 60 a

Se agregó hidruro de sodio (0,035 g, 0,869 mmol) a una mezcla del **Compuesto 27a** (0,200 g, 0,79 mmol) en 3 ml de DMF a 0°C seguido de bromuro de 2-metoxifenacilo (0,2 g, 0,87 mmol). La suspensión se agitó a temperatura ambiente hasta el día siguiente antes de ser diluída con EtOAc (10 ml) y desactivada mediante el agregado de agua (5 ml). La fase acuosa se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 60a**.

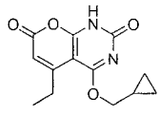
Paso B:



Compuesto 60 a Compuesto 60

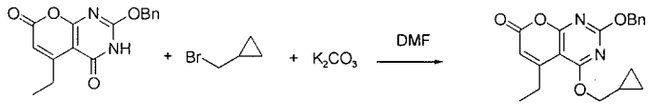
Se agregó tribromuro borónico (1,3 ml, 1,31 mmol, solución 1,0 M en DCM) se agregó a una solución del **Compuesto 60a** (0,105 g, 0,262 mmol) en CH_2Cl_2 (5,0 ml) a -78°C. La mezcla de reacción se agitó durante 2 h antes de ser desactivada con agua (5,0 ml). La mezcla de reacción se extrajo con EtOAc (2 x 5 ml). Se combinaron las capas orgánicas, se secó sobre $MgSO_4$, y se concentró para dar el producto en bruto. La mezcla en bruto se purificó por cromatografía en columna eluyendo con EtOAc/hexanos (2/3: v/v) para proporcionar el **Compuesto 60**. Electroaspersión MS $[M+1]^+$ 343,1.

EJEMPLO DE PREPARACIÓN 65



Ejemplo 65

Paso A:

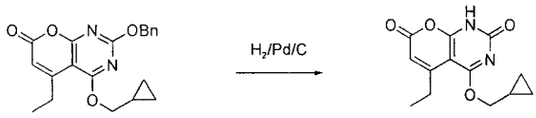


Compuesto 12 Compuesto 65 a

Se agregó K_2CO_3 (64,7 mg, 0,47 mmol) a una mezcla del **Ejemplo 12** (70 mg, 0,235 mmol) y metilbromuro de ciclopropilo (0,068 ml, 0,705 mmol) en DMF (2,0 ml) a temperatura ambiente. La mezcla de reacción se agitó hasta el día siguiente antes de que se diluyó mediante el agregado de EtOAc (50 ml) y agua (10 ml). La fase orgánica se lavó con agua (3x15 ml), salmuera (15 ml), y se secó

sobre $MgSO_4$. Después de la filtración y concentración, el producto en bruto se purificó utilizando TLC prep con hexano/CH_2Cl_2/EtOAc (v/v/v = 7/3/1) como eluyente para dar el **Compuesto 65a** (26 mg, 31%).

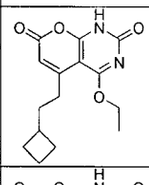
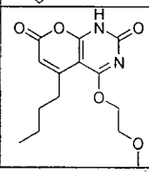
Paso B:

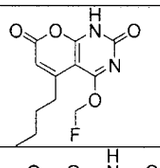
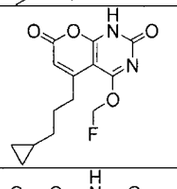
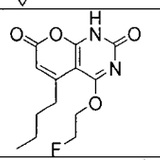


Compuesto 65 a Ejemplo 65

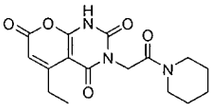
El **Compuesto 65a** (26 mg, 0,074 mmol) en EtOH (5,0 ml) se trató a temperatura ambiente con Pd/C (7,8 mg, 10 % en peso) y se hidrogenó con un globo de H_2 durante 30 minutos. La mezcla de reacción se filtró a través de un taco corto de Celite y el residuo se lavó con EtOH (15 ml). Se eliminó el solvente bajo presión reducida y el producto en bruto se purificó utilizando TLC prep con hexano/CH_2Cl_2/MeOH (v/v/v = 3/7/1) como eluyente para dar el **Ejemplo 65** (6 mg, 30%). Electroaspersión MS $[M+1]^+$ 263,1.

Utilizando el método indicado previamente y sustituyendo los reactivos e intermediarios apropiados, se prepararon los compuestos **786-790**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS [M+1]+**
786		291,2
787		295,2

788		269,1
789		295,2
790		283,2

EJEMPLO DE PREPARACIÓN 68



Ejemplo 68

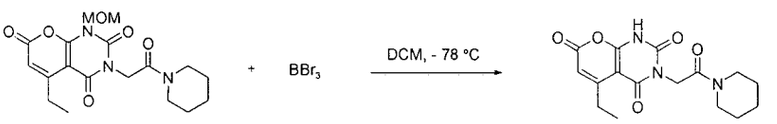
Paso A:



Ejemplo 57 Compuesto 68 a

La mezcla del **Ejemplo 57** (0,1 g, 0,32 mmol) en CH_2Cl_2 (5 ml), piperidina (0,027 g, 0,32 mmol), HATU (0,24 g, 0,64 mmol), y trietilamina (0,098 g, 0,96 mmol) se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se mezcló con agua (20 ml), y luego se extrajo con CH_2Cl_2 (10 ml x 2). La solución orgánica se secó (Na_2SO_4) y se concentró. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con EtOAc/hexanos (v/v = 1:1) para dar el **Compuesto 68a** (0,065 g, 54%). Electroaspersión MS $[M+1]^+$ 378,2.

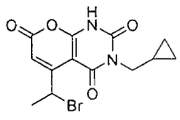
Paso B:



Compuesto 68 a Ejemplo 68

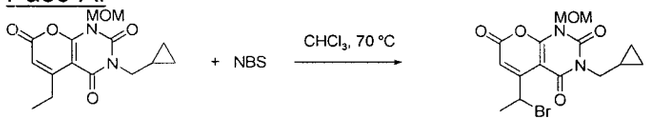
Se agregó una solución 1M de BBr_3 en CH_2Cl_2 (0,75 ml, 0,75 mmol) a una solución del C**ompuesto 68a** (0,056 g, 0,15 mmol) a -78°C. Después de que la mezcla de reacción se agitó a -78°C durante 2 horas, se agregó agua (5 ml). La solución orgánica se secó (Na_2SO_4) y se concentró. El producto en bruto se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con 10% NH_4OH en $MeOH/CH_2Cl_2$ (v/v = 3:97) para dar el E**jemplo 68** (0,01 g, 20%). Electroaspersión MS $[M+1]^+$ 334,2.

EJEMPLO DE PREPARACIÓN 80



Ejemplo 80

Paso A:

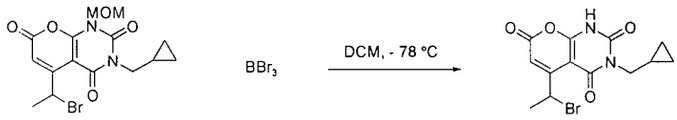


Compuesto 27 b Ejemplo 80 a

Se agregó el **Compuesto 27a** (0,1 g, 0,33 mmol) a CH_2Cl_2 a temperatura ambiente. Luego se agregó NBS y la reacción se agitó durante 4 horas. Después de que no se observó progreso en la reacción, se agregó una mezcla de NBS (0,061 g, 0,34 mmol) en cloroformo (4 ml). La mezcla de reacción se calentó durante 12 hrs a 70°C. Ambos análisis, la TLC (30/70 EtOAc/ Hexano) y el espectrograma de masa, indicaban que se había completado la reacción. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con CH_2Cl_2 y se lavó con H_2O. La fase orgánica se secó con Na_2SO_4 y se eliminó el solvente para dar el producto en bruto. De la purificación en cromatografía preparativa en gel de

sílice en EtOAc/Hexano (v/v = 30/70) se obtuvo el **Compuesto 80a** (0,075 g, 60 %).

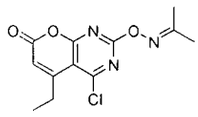
Paso B:



Compuesto 80 a Ejemplo 80

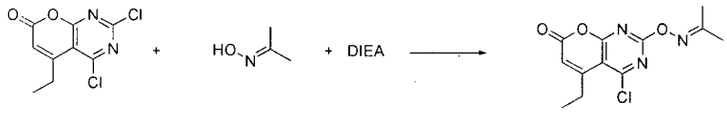
Compuesto 80a (0,070 g, 0,18 mmol) un CH_2Cl_2 y la mezcla se enfrió a -78°C. Se agregó BBr_3 1M (0,909 ml, 0,9 mmol). La mezcla de reacción se agitó durante 4 horas. Luego de completada la reacción, la mezcla se diluyó con CH_2Cl_2, se lavó con H_2O, se secó con Na_2SO_4, y luego se eliminó el solvente para dar el producto en bruto. El producto en bruto se purificó mediante cromatografía preparativa con gel de sílice utilizando 30/70 EtOAc/ Hexano, para dar el E**jemplo 80.** Electroaspersión MS $[M+1]^+$ 341,2.

EJEMPLO DE PREPARACIÓN 81



Ejemplo 81

Paso A:

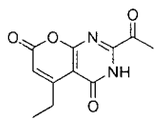


Ejemplo 5 Ejemplo 81

A una mezcla del **Ejemplo 5** (84 mg, 0,34 mmol) y oxima de acetona (27,5 mg, 0,37 mmol) se agregó DIEA (0,09 ml, 0,52 mmol) y la mezcla se agitó durante 3 días. La mezcla se concentró y se sometió a cromatografía en columna de gel de sílice para dar el E**jemplo 81** (30 mg, 31%). LCMS: M+1: 282,1

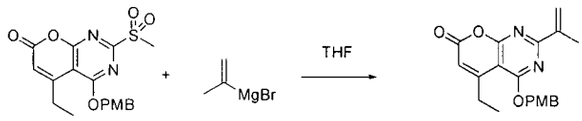
160

EJEMPLO DE PREPARACIÓN 92



Ejemplo 92

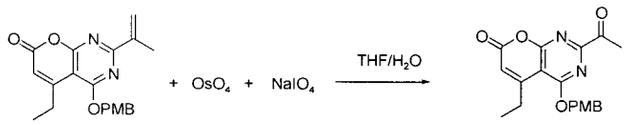
Paso A:



Ejemplo 55 Compuesto 92 a

Se agregó bromuro de isopropenilmagnesio (0,95 ml, 0,475 mmol, 0,5 M en THF) gota a gota a una solución del **Ejemplo 55** (0,133 g, 0,341 mmol) en THF (4,0 ml) a 0°C. La mezcla se agitó a 0°C durante 2 horas antes de ser desactivada con HCl (0,2 M). Se mezcló con EtOAc y se lavó con agua y salmuera. La fase orgánica se secó sobre $MgSO_4$. Se eliminó el solvente bajo presión reducida y el producto en bruto se purificó con cromatografía flash en columna de gel de sílice eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 4/1/1) para dar el C**ompuesto 92a** (59 mg, 49%).

Paso B:

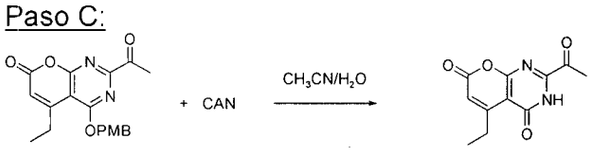


Compuesto 92 a Compuesto 92 b

Se agregó $NaIO_4$ (70,1 mg, 0,328 mmol) a una solución del **Compuesto 92a** (46,2 mg, 0,131 mmol) y OsO_4 (22,2 µl, 4% en peso en agua) en THF (5,0 ml) y agua (5,0 ml) a temperatura ambiente. La mezcla de reacción se agitó hasta

el día siguiente antes de ser desactivada mediante el agregado de Me_2S (20 µl, 0,328 mmol). La mezcla se diluyó con EtOAc y se lavó con HCl (0,5 M), agua y salmuera. La fase orgánica se secó sobre $MgSO_4$. Se eliminó el solvente bajo presión reducida y el producto en bruto se purificó mediante cromatografía flash en columna de gel de sílice eluyendo con hexano/CH_2Cl_2/EtOAc (v/v/v = 2/1/1) para dar el **Compuesto 92b** (39 mg, 84%).

Paso C:

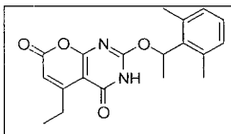
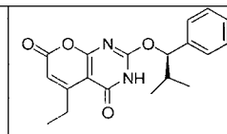
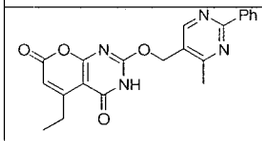
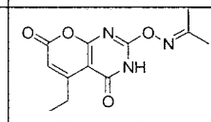
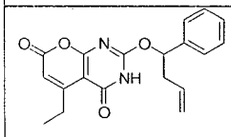
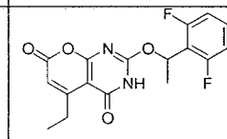
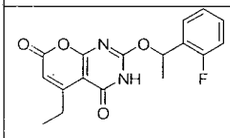
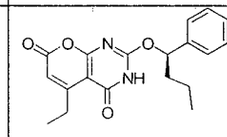


Compuesto 92 b Ejemplo 92

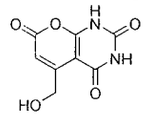
Se agregó nitrato de amonio cérico (70,9 mg, 0,129 mmol) a una solución del **Compuesto 92b** (20,8 mg, 0,059 mmol) en MeCN (3,0 ml) y agua (0,3 ml) a temperatura ambiente. La mezcla de reacción se agitó durante 2 horas antes de que se diluyó con EtOAc. La fase orgánica se lavó con HCl (0,5 M), agua, salmuera y se secó sobre $MgSO_4$. Se eliminó el solvente bajo presión reducida y el producto en bruto se purificó utilizando TLC prep con hexano/CH_2Cl_2/MeOH (v/v/v = 2/8/1) como eluyente para dar el **Ejemplo 92** (8 mg, 58%).Electroaspersión MS $[M+1]^+$ 235,1.

Los **Ejemplos 82-91** se prepararon mediante procedimientos similares a aquellos usados para la preparación del **Ejemplo 49**, utilizando el **Ejemplo 10** y los correspondientes alcoholes apropiados.

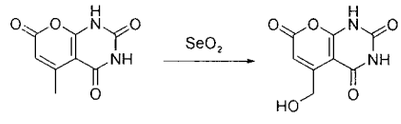
EJEMPLO DE PREPARACIÓN	Electroaspersión LCMS $[M+1]^+$	**EJEMPLO DE PREPARACIÓN**	Electroaspersión LCMS $[M+1]^+$
 Ejemplo 82	389,1	 Ejemplo 83	327,1

 Ejemplo 84	341,1	 Ejemplo 85	341,1
 Ejemplo 86	391,1	 Ejemplo 87	264,1
 Ejemplo 88	339,1	 Ejemplo 89	349,1
 Ejemplo 90	331,1	 Ejemplo 91	341,1

EJEMPLO DE PREPARACIÓN 92



Ejemplo 92



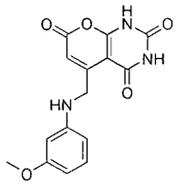
Ejemplo 2 Ejemplo 92

El **Ejemplo 2** (0,71 g, 3,66 mmol, 1 eq) y SeO_2 (0,46 g, 1,1 eq) se mezclaron juntos en 1,4-dioxano (10,5 ml) y THF (1,5 ml) y la mezcla se calentó a 90°C al aire durante 24 hr. 5% del producto en bruto resultante se purificó al cargarlo directamente en una columa de HPLC de fase reversa para obtener el producto deseado **Ejemplo 92** (7,4 mg) como un sólido color blanco.

^{1}H RMN (CD_3OD): δ 4,80 (s, 2 H) 6,20 (s, 1 H)

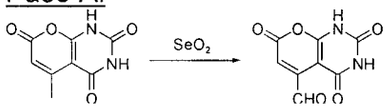
Masa de $C_8H_7N_2O_5$ $(MH)^+$: 211. Experimental: 211.

EJEMPLO DE PREPARACIÓN 93



Ejemplo 93

Paso A:

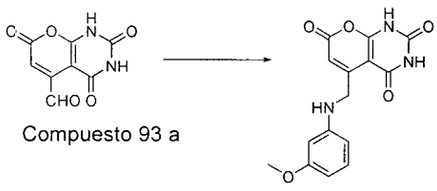


Ejemplo 2 Compuesto 93 a

Se preparó el **Compuesto 93a** mediante un procedimiento similar a aquel utilizado para preparar alcohol **Ejemplo 92**, excepto que se permitió la oxidación del alcohol antes del correspondiente aldehído. Después de purificar varias veces utilizando HPLC de fase reversa, se obtuvo el **Compuesto 93a** (90 mg).

Masa de $C_8H_5N_2O_5$ $(MH)^+$: 209. Experimental: 209.

Paso B:



Compuesto 93 a

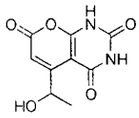
Ejemplo 93

Se mezcló el **Compuesto 93b** (90 mg, 0,43 mmol, 1 eq)) con 3-metoxianilina (109 mg, 2 equiv.) y triacetoxiborohidruro de sodio (185 mg, 2 equiv.) en 2 ml de THF. Después de agitar hasta el día siguiente, la mezcla de reacción se desactivó con metanol. La TLC preparativa brindó 15,3 mg del producto deseado **Ejemplo 93.**

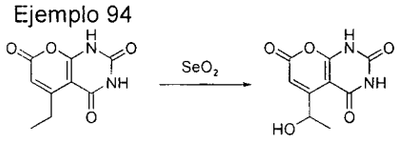
^{1}H RMN (CD_3OD): δ 3,60 (s, 3 H) 4,60 (s, 2 H) 5,75 (s, 1 H) 6,20 (m, 3 H) 6,95 (m, 1 H)

Masa de $C_{15}H_{14}N_3O_5$ $(MH)^+$: 316. Experimental: 316.

EJEMPLO DE PREPARACIÓN 94



Ejemplo 94



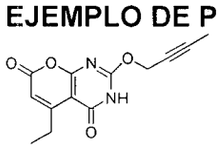
Ejemplo 1 Ejemplo 94

Se preparó el **Ejemplo 94** mediante un procedimiento similar a aquel utilizado para preparar el **Ejemplo 92**, excepto que **Ejemplo 1** fue oxidado en lugar del **Ejemplo 2**.

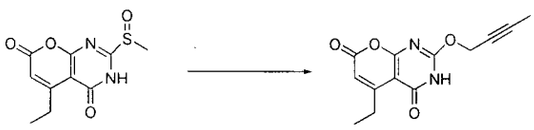
^{1}H RMN (CD_3OD): δ 1,38 (d, 2 H, J = 6,8 Hz) 5,50 (q, 1 H, J = 6,8 Hz) 6,20 (s, 1 H)

Masa de $C_9H_9N_2O_5$ $(MH)^+$: 225. Experimental: 225.

EJEMPLO DE PREPARACIÓN 95



Ejemplo 95



Ejemplo 10 Ejemplo 95

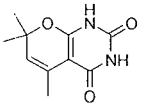
Se trató 2-butin-1-ol (140 mg, 2 mmol, 2 equiv.) en 4 ml de THF con n-BuLi 1,6 M (1,2 ml, 2 equiv.) a 0°C durante 5 min para proporcionar la solución del alcóxido. El **Ejemplo 10** (0,25 g, 1 mmol, 1 equiv.) luego se agregó a la solución

del alcóxido. Después de agitar 1,5 hr, se agregó 0,12 g de ácido acético (2 equiv.) a la solución. Se eliminó el solvente y la extracción con dietiléter y agua proporcionó un sólido color blanco. El sólido se lavó con dietiléter frío y se secó al vacío. Se obtuvieron 80 mg del producto deseado **Ejemplo 95**.

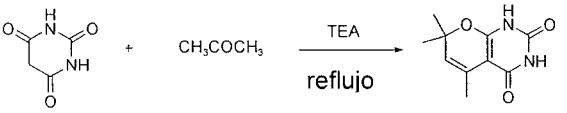
^{1}H RMN ($CDCl_3$): δ 1,20 (t, 2 H, J = 6,8 Hz) 1,83 (s; 3 H) 3,00 (q, 2 H, J = 6,98 Hz) 5,00 (s, 2 H) 6,00 (s, 1 H)

Masa de $C_{13}H_{13}N_2O_4$ $(MH)^+$: 261. Experimental: 261.

EJEMPLO DE PREPARACIÓN 96



Ejemplo 96

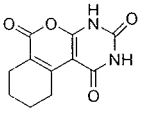


Ejemplo 96

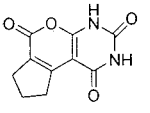
Se agregó ácido barbitúrico (1,0 g, 7,81 mmol) a acetona en exceso. Se agregó trietilamina (2 ml) y la mezcla de reacción se reflujó hasta el día siguiente después de lo que se enfrió y se filtró. El sólido en bruto se purificó mediante TLC prep (8:1:1/EtOAc:DCM:MeOH) para proporcionar el producto deseado, **Ejemplo 96**.

Electroaspersión MS $[M+1]^+$ por ejemplo **96** es 209,0

EJEMPLOS DE PREPARACIONES 97 y 98



Ejemplo 97



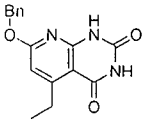
Ejemplo 98

Ejemplos 97 y 98 se prepararon mediante métodos análogos al método utilizado para preparar el **Ejemplo 1**, excepto que se utilizó metiléster del ácido 2-

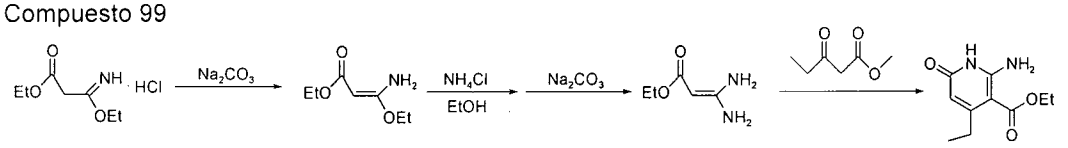
oxo-ciclohexancarboxílico y metiléster del ácido 2-oxo-ciclopentancarboxílico, respectivamente, en lugar de acetato de metilpropionilo.

Electroaspersión MS $[M+1]^+$ durante 9**6** y **97** son 235,1.

EJEMPLO DE PREPARACIÓN 99



Compuesto 99

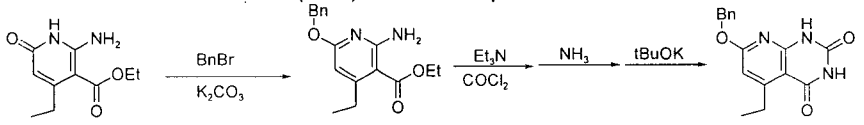


Compuesto 99 a Compuesto 99 b Compuesto 99 c Compuesto 99 c

Se agitó el **Compuesto 99a** (75 g, 383 mmol) (Aldrich) disponible en el mercado con Na_2CO_3 (15%, 450 ml) acuoso frío durante 2 h. De la extracción con EtOAc y el secado sobre Na_2CO_3 se obtuvo el **Compuesto 99b** en forma de aceite incoloro, que se trató inmediatamente con NH_4Cl (19,5 g, 364 mmol) en 200 ml de EtOH seco a 50°C durante 60 h. La mezcla del producto en bruto se enfrió y se eliminó el solvente. El sólido resultante color amarillo claro se trató con K_2CO_3 frío (30 %, 300 ml H_2O) durante 0,5 h. De la extracción con EtOAc se obtuvo el **Compuesto 99c** como un sólido color amarillo claro (37,92 g). Este sólido se hizo reaccionar con propionilacetato de metilo (38,0 g, 292 mmol), 2 ml piridina, en 400 ml de EtOH seco a 100°C durante 24 h. Después del enfriado y la filtración, el sólido se lavó con EtOH y se obtuvieron 18 g del **Compuesto 99d** como un sólido blanco (22% rendimiento del **Compuesto 99a**).

^1H RMN ($CDCl_3$): δ 1,20 (t, 3 H, J = 7,3 Hz) 1,40 (t, 3 H, J = 7,1 Hz) 2,90 (q, 2 H, J = 7,3 Hz) 4,30 (q, 2 H, J = 7,1 Hz) 5,75 (s, 1 H)

Masa de $C_{10}H_{15}N_2O_3$ $(MH)^+$: 211. Experimental: 211.



Compuesto 99d Compuesto 99e Ejemplo 99

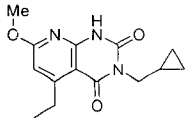
El **Compuesto 99d** (3,0 g, 14,28 mmol) se trató con BnBr (2,44 g, 1 eq) y K_2CO_3 (3,94 g, 2 eq) en 100 ml de acetona a 70°C durante 17 h. Se eliminó el solvente y la purificación cromatográfica (5% EtOAc en hexano) proporcionó 2,53 g del **Compuesto 99e** puro con 58% de rendimiento.

El **Compuesto 99e** (0,3 g, 1 mmol) se trató con Et_3N (0,22 g, 2,2 eq), $COCl_2$ (1,9 M en tolueno, 0,53 ml, 1 equiv) en 5 ml de DCM a -78°C durante 45 min. La mezcla de reacción se calentó a temperatura ambiente durante 1 h. Se agregó NH_3 (0,5 M en 1,4-dioxano, 2 ml, 1 eq) y la mezcla de reacción se agitó hasta el día siguiente. Luego se eliminó el solvente, se agregaron 3 ml de THF anhidro junto con t-BuOK (1 M en THF, 1 ml, 1 equiv), y la mezcla se agitó hasta el día siguiente. Se eliminó el solvente, se agregaron hexano y una pequeña cantidad de MeOH y se recolectó el sólido blanco resultante. El sólido se lavó luego con dietiléter anhidro para dar 3,8 mg del **Ejemplo 99** como un sólido blanco.

^{1}H RMN ($CDCl_3$): δ 1,20 (t, 3 H, J = 7,3 Hz) 3,10 (q, 2 H, J = 7,3 Hz) 5,40 (s, 2 H) 6,40 (s, 1 H) 7,20-7,40 (m, 4 H) 8,30 (m, 2 H)

Masa de $C_{16}H_{16}N_3O_3$ $(MH)^+$: 298. Experimental: 298.

EJEMPLO DE PREPARACIÓN 100



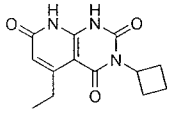
Ejemplo 100

El **Ejemplo 100** se preparó siguiendo procedimientos similares a aquellos utilizados para preparar el **Ejemplo 99**, excepto que se utilizó yoduro de metilo en lugar de BnBr, y ciclopropilmetilamina en lugar de amoníaco.

^{1}H RMN ($CDCl_3$): δ 0,40 (m, 4 H) 1,18-1,25 (m, 4 H) 3,10 (q, 2 H, J = 7,2 Hz) (3,82 (d, 2 H, J = 7,4 Hz) 3,90 (s, 3 H) 6,38 (s, 1 H) 8,10 (br s, 1 H)

Masa de $C_{14}H_{18}N_3O_3$ $(MH)^+$: 276. Experimental: 276.

EJEMPLO DE PREPARACIÓN 101



Ejemplo 101



Compuesto 101 a Ejemplo 101

Se preparó el **Compuesto 101a** intermediario siguiendo procedimientos similares a aquellos utilizados para preparar el Ejemplo 99, excepto que se utilizó ciclobutilamina en lugar de amoníaco.

^{1}H RMN ($CDCl_3$): δ 1,20 (t, 2 H, J = 7,3 Hz) 1,60-1,80 (m, 2 H) 2,10 (m, 2 H) 3,00 (m, 2 H) 3,10 (q, 2 H, J = 7,3 Hz) 5,30 (m, 1 H) 5,40 (s, 2 H) 6,40 (s, 1 H) 7,20-7,40 (m, 5 H) 8,20 (br s, 1 H)

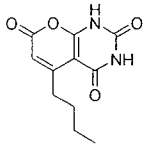
Masa de $C_{20}H_{22}N_3O_3$ $(MH)^+$: 352. Experimental: 352.

El **Compuesto 101a** (70 mg) se trató con 3% Pd/C (50 mg), 10 ml de MeOH bajo una atmósfera de hidrógeno (globo de hidrógeno) hasta el día siguiente. Después de la filtración, la purificación por HPLC prep proporcionó 1,2 mg del **Ejemplo 101**.

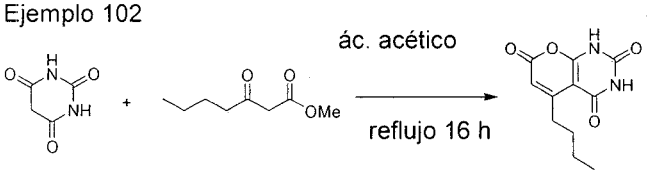
^{1}H RMN ($CDCl_3$): δ 1,20 (t, 2 H, J = 7,3 Hz) 1,60-1,80 (m, 2 H) 2,10 (m, 2 H) 2,95 (m, 2 H) 3,20 (q, 2 H, J = 7,3 Hz) 5,30 (m, 1 H) 6,40 (s, 1 H) 8,00 (br s, 1 H).

Masa de $C_{14}H_{17}N_3O_3$ $(MH)^+$: 276. Experimental: 276.

EJEMPLO DE PREPARACIÓN 102



Ejemplo 102



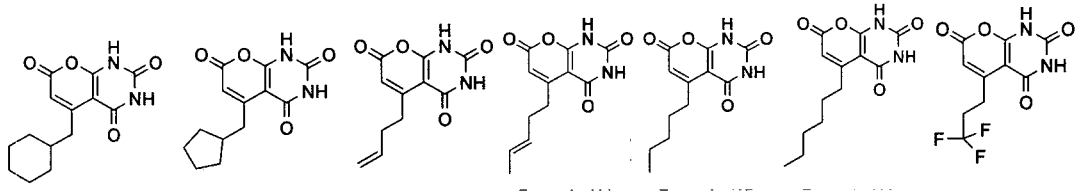
Ejemplo 102

En un balón de 25 ml equipado con una varilla magnética de agitación y un globo de nitrógeno se colocó 1,0 g de ácido barbitúrico (7,8 mmol) y 1,52 ml de metiléster del ácido 3-oxoheptanoico (9,6 mmol, 1,23 equiv.). Se agregaron 8 ml de ácido acético a la mezcla de reacción y se reflujó durante 16 h después de lo cual la reacción se enfrió a temperatura ambiente. El ácido acético en exceso se concentró y se secó al vacío para dar el producto en bruto **Ejemplo 102** junto con los materiales de partida sin reaccionar. El producto en bruto se agitó con 20 ml de agua hirviendo durante algunos minutos y se filtró. El precipitado se lavó con agua hirviendo (2 x 10 ml) y se secó para proporcionar el 0,65 g (35% rendimiento) del Ejemplo **102**.

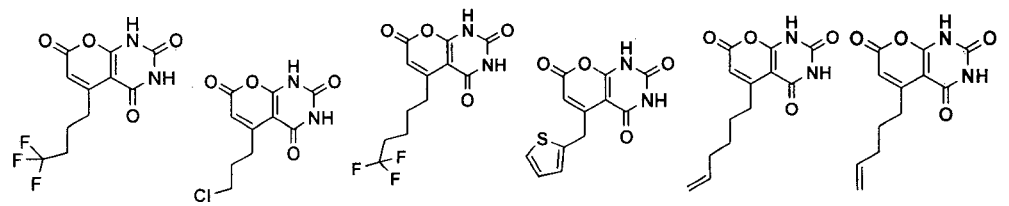
^{1}H RMN (DMSO): δ 0,9 (t, 3 H, J = 7,5 Hz) 1,32-1,40 (m, 2 H) 1,45-1,51 (m, 2 H) 2,84-2,87 (t, 2 H, J = 7,5 Hz) 5,82 (s, 1 H) 11,34 (s, 1 H) 12,72 (br s, 1 H)

Masa de $C_{11}H_{12}N_2O_4$ $(MH)^+$: 236,22. Experimental: 237,1.

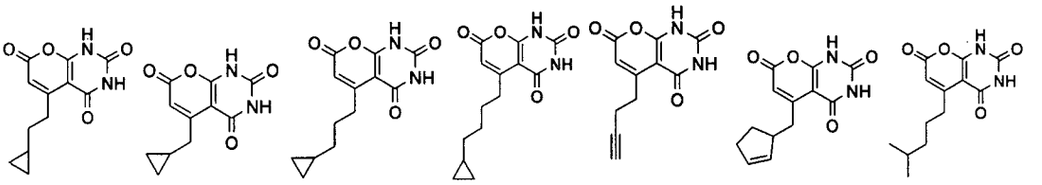
EJEMPLOS 103-135



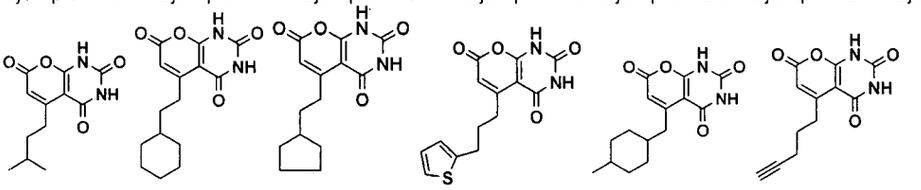
Ejemplo 103 Ejemplo 104 Ejemplo 105 Ejemplo 106 Ejemplo 107 Ejemplo 108 Ejemplo 109



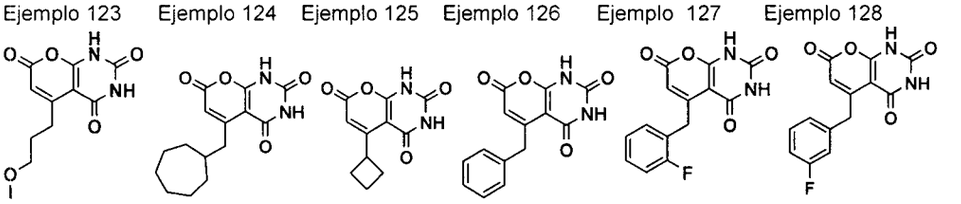
Ejemplo 110 Ejemplo 111 Ejemplo 112 Ejemplo 113 Ejemplo 114 Ejemplo 115



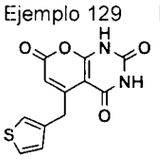
Ejemplo 116 Ejemplo 117 Ejemplo 118 Ejemplo 119 Ejemplo 120 Ejemplo 121 Ejemplo 122



Ejemplo 123 Ejemplo 124 Ejemplo 125 Ejemplo 126 Ejemplo 127 Ejemplo 128



Ejemplo 129 Ejemplo 130 Ejemplo 131 Ejemplo 132 Ejemplo 133 Ejemplo 134



Ejemplo 135

Se prepararon los **Ejemplos 103-135** utilizando procedimientos similares a aquellos utilizados para preparar el **Ejemplo 102**, excepto que se utilizó cetoéster apropiadamente sustituido en lugar de metiléster del ácido 3-oxoheptanoico.

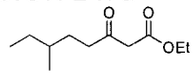
Los Ejemplos **200, 210, 241, 242, 245, 246, 252-260, 274-278, 280, 281, 282, 284, 285, 291** se prepararon mediante un procedimiento similar a aquel utilizado para la preparación del Ejemplo **30 y 31**.

Los Ejemplos **201, 202, 204-209, 211-218, 224-240, 243, 244, 247-251, 261-273, 279, 283, 286-290, 293, 294-297** se prepararon mediante un procedimiento similar a aquel utilizado para la preparación del Ejemplo **102**, utilizando ácido barbitúrico y el correspondiente ceto éster.

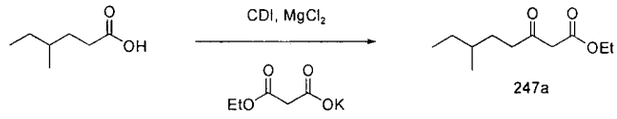
La preparación de material de partida cetoésteres en caso necesario se muestran a continuación.

La preparación de material de partida cetoésteres para el ejemplo **247** es como sigue:

EJEMPLO DE PREPARACIÓN 247a



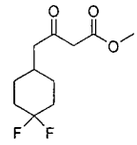
247a



247a

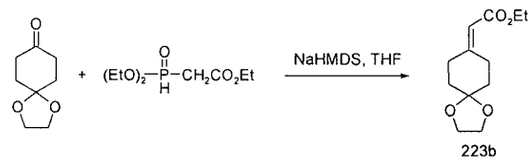
Se tomó ácido 4-metilhexanoico (3,0 g, 23,08 mmol) en 40 ml de THF. Se agregó 1,1'-carbonildiimidazol (4,49 g, 27,69 mmol) y la reacción se agitó a temperatura ambiente durante 1 h después de lo cual se agregó $MgCl_2$ (2,2 g, 23,08 mmol) y malonato de etil potasio (5,89 g, 34,62 mmol). Se permitió proceder a la reacción a temperatura ambiente hasta el día siguiente. La mezcla de reacción en bruto se filtró a través de un taco corto de gel de sílice y se eluyó con EtOAc/hexanos (1:3) para proporcionar el compuesto **247a**.

EJEMPLO DE PREPARACIÓN 223ª



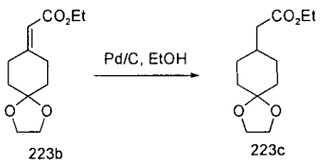
223a

El material de partida para la preparación del Ejemplo **223** es como sigue.



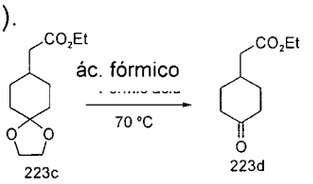
223b

Paso A: Una solución de fosfonato de trietilo (44,8 g, 200 mmol) en THF (30 ml) a 0°C se trató con una solución 1M (200 ml) de bis(trimetilsililamida) de sodio en THF. La mezcla resultante se agitó a temperatura ambiente durante 0,5 hora, y luego se enfrió a 0°C. Una solución de 1,4-ciclohexanodiona monetileno cetalo (15,6 g, 200 mmol) en THF (50 ml) se agregó gota a gota, y la solución resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción luego se enfrió a 0°C, se trató con ácido cítrico acuoso frío, y la mezcla se extrajo con EtOAc. El extracto se lavó con $NaHCO_3$ sat. ac., salmuera, se secó sobre Na_2SO_4, se filtró, y el filtrado se concentró. El residuo se cromatografió en gel de sílice, eluyendo con un gradiente de CH_2Cl_2/EtOAc para proporcionar **223b** (21 g, 91%).



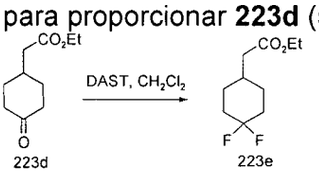
223b 223c

Paso B: El compuesto **223b** (20g) se disolvió en EtOH (150 ml) y se trató con 10% Pd/C bajo 1 atm. de hidrógeno durante 3 días. La mezcla se filtró y el filtrado se evaporó a **223c** (20,3 g, 100%).



223c 223d

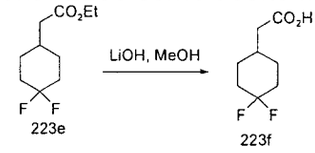
Paso C: El compuesto **223c** (7g) se disolvió en ácido fórmico (50 ml) y se calentó a 70ºC durante 1 h. La solución se concentró y el residuo a EtOAc y se lavó con $NaHCO_3$ sat. ac., salmuera, se secó sobre Na_2SO_4 y se concentró. El residuo se cromatografió en gel de sílice para proporcionar **223d** (5g).



223d 223e

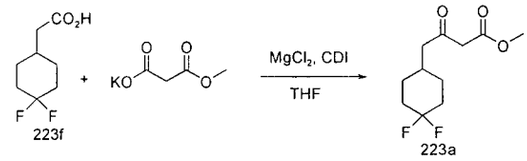
Paso D: El compuesto **223d** (4,6 g) se disolvió en CH_2Cl_2 (10 ml) y se trató con trifluoruro de dietilaminosulfuro (DAST, 5 ml) a temperatura ambiente durante 3

horas. La mezcla de reacción se vertió en hielo/agua (30 ml) y se extrajo con CH_2Cl_2. El extracto se lavó con $NaHCO_3$ sat. ac., salmuera, se secó sobre Na_2SO_4 y se concentró para proporcionar **223e** como aceite marrón (3,2 g, 62%).



223e 223f

Paso E: El compuesto **223e** (3,2 g, 15,5 mmol) se disolvió en MeOH (5 ml) y se trató con LiOH (559 mg, 23,3 mmol) hasta el día siguiente. La mezcla de reacción se acidificó con HCl 3 N a un valor de pH 4 y se extrajo con CH_2Cl_2. El extracto se secó sobre Na_2SO_4 y se concentró para proporcionar **223f** como aceite marrón (3 g, 100%).

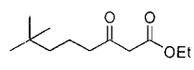


223f 223a

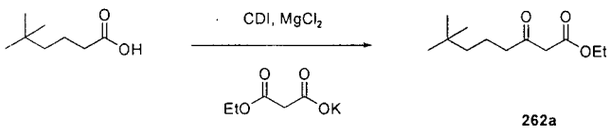
Paso F: El compuesto **223f** (900 mg, 5,0 mmol) se disolvió en THF (15 ml), se agregó CDI (972 mg, 6,0 mmol) y se agitó durante 45 min. Luego se agregaron malonato de metilo sal potásica (1,02 g, 6,0 mmol) y $MgCl_2$ (570 mg, 6,0 mmol) a la solución anterior. La mezcla resultante se agitó hasta el día siguiente y se filtró a través de un taco corto de gel de sílice y se lavó con EtOAc. El filtrado se concentró y cromatografió en gel de sílice para proporcionar **223a** como aceite incoloro (400 mg, 34%).

Los materiales de partida para las estructuras **262, 263** se prepararon en un modo similar a **218a**.

EJEMPLO DE PREPARACIÓN 262ª



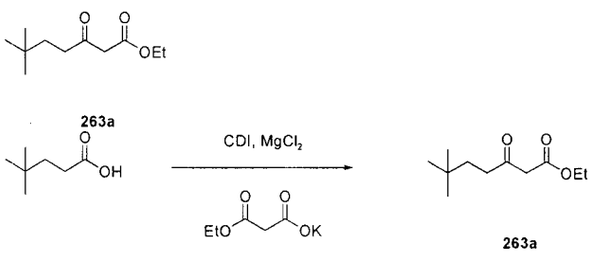
262a



262a

Se preparó de la misma manera que en el ejemplo **218a**.

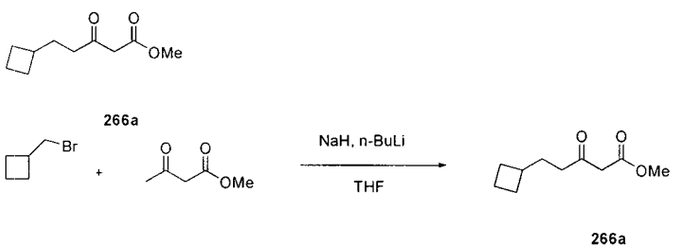
EJEMPLO DE PREPARACIÓN 263ª



263a

Se preparó de la misma manera que en el ejemplo **218a**.

EJEMPLO DE PREPARACIÓN 266ª

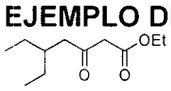


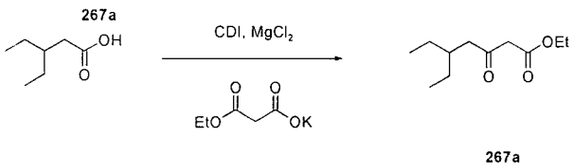
266a

Se tomó hidruro de sodio (1,42 g, 35,56 mmol) en THF (20 ml) en un balón equipado con una varilla agitadora y globo de nitrógeno. Se enfrió a 0°C y se disolvió acetoacetato de metilo (3,84 ml, 35,56 mmol) en 10 ml de THF, y se agregó gota a gota. La mezcla de reacción se agitó a 0°C durante 30 min después de lo cual se agregó *n*-BuLi (solución 2,5 M en hexanos, 14,2 ml, 35,56 mmol) gota a gota. La reacción se permitió continuar durante 30 min a 0°C y luego se enfrió a – 25°C. Se agregó bromometilciclobutano (4,82 g, 32,32 mmol) disuelto en 20 ml de THF se agregó gota a gota y la reacción se agitó a -25°C durante 4 h seguido de temperatura ambiente hasta el día siguiente. Se desactivó con el agregado de NH_4Cl sat., se extrajo con EtOAc (2 x 30 ml), se secó sobre $MgSO_4$,

se concentró al vacío. El producto en bruto se purificó por biotage (5% EtOAc/hexanos) para proporcionar el compuesto **266a**.

EJEMPLO DE PREPARACIÓN 267a

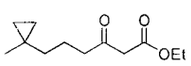


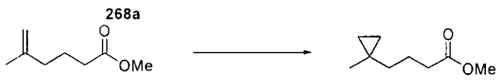


267a

Se preparó de la misma manera que en el ejemplo **218a**.

EJEMPLO DE PREPARACIÓN 268 a





268b

Ácido trifluoroacético (7,84 ml, 105,48 mmol) y diyodometano (8,5 ml, 105,48 mmol) en 50 ml de DCM se enfriaron a 0ºC. Se agregó dietilzinc (solución 1,0 M en hexanos, 105,5 ml, 105,48 mmol) gota a gota. La reacción se agitó a 0ºC durante 20 min después de lo cual se agregó metiléster del ácido 5-metil-5-hexenoico (5,0 g, 35,16 mmol) en 20 ml de DCM gota a gota. La reacción se agitó a temperatura ambiente hasta el día siguiente. La reacción se desactivó mediante el agregado de NH_4Cl sat., se extrajo con DCM (2 x 30 ml), se secó sobre $MgSO_4$, se concentró al vacío para proporcionar el compuesto **268b** que se transfirió al siguiente paso sin purificación ulterior.



268b 268c

Se tomó el ester **268b** (5,0 g, 32 mmol) en MeOH (50 ml) y se agregó NaOH (3,2 g, 80 mmol). La reacción se agitó a temperatura ambiente hasta el día

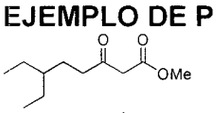
siguiente. La reacción se diluyó con agua (50 ml) y se acidificó con HCl conc. Se extrajo con Et_2O (2 x 30 ml), se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío. El producto en bruto **268c** se usó como tal sin purificación ulterior.



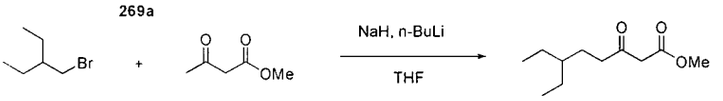
268c **268a**

Se preparó de la misma manera que en el ejemplo **262a**.

EJEMPLO DE PREPARACIÓN 269a



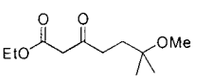
269a



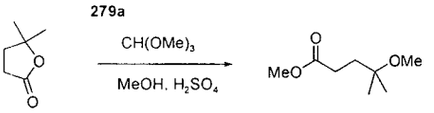
269a

Se preparó de la misma manera que en el ejemplo **266a**.

EJEMPLO DE PREPARACIÓN 279ª



279a



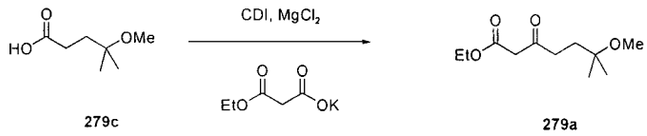
279b

Se tomaron 5,5-dimetil-dihidro-furan-2-ona (5,0 g, 43,8 mmol), ortoformato de trimetilo (11,5 ml, 105,12 mmol), y ácido sulfúrico (0,43 g, 4,38 mmol) en MeOH (50 ml). La mezcla de reacción se calentó a 50ºC hasta el día siguiente. Después del enfriado, se eliminó el solvente al vacío, se desactivó con $NaHCO_3$ sat. y se extrajo con EtOAc (2 x 30 ml). La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el compuesto **279b** que se usó sin purificación ulterior.



279b 279c

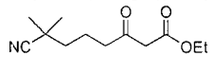
Se preparó de la misma manera que en el ejemplo **268c**.



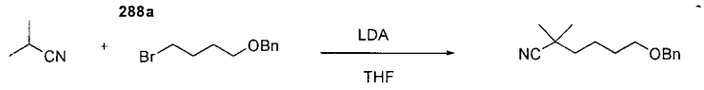
279c 279a

Se preparó de la misma manera que en el ejemplo **262a**.

EJEMPLO DE PREPARACIÓN 288a



288a



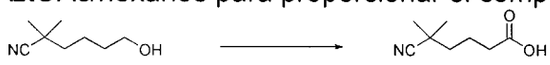
288b

Se tomó diisopropilamida de litio (solución 2,0 M en THF/heptano/etil benceno, 43,4 ml, 86,82 mmol) en THF (30 ml) y se enfrió a –78°C. Se agregó isobutironitrilo (6 g, 86,82 mmol) en THF (10 ml) gota a gota y la reacción se agitó a -78°C durante 1 h y a 0°C durante 2 h. Se agregó 4-bromobutiléter de bencilo (21,1 g, 86,82 mmol) en THF (10 ml) gota a gota y la mezcla de reacción se permitió calentar a temperatura ambiente hasta el día siguiente. La reacción se desactivó mediante el agregado de NH_4Cl sat. y se extrajo con Et_2O. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío. El compuesto en bruto obtenido se purificó mediante biotage (5% EtOAc/hexanos) para proporcionar el compuesto **288b**.



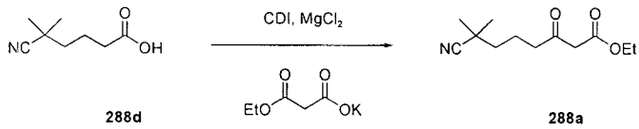
288b 288c

Se agregó el Compuesto **288b** a CH_2Cl_2 (25 ml) en un balón de 100 ml equipado con una varilla agitadora y globo de nitrógeno y se enfrió a –78°C. Se agregó tricloruro borónico (solución 1,0 M en hexanos, 43,2 ml, 43,2 mmol) gota a gota y la reacción se permitió calentar gradualmente a 0°C. Después de 1 h, la reacción se desactivó mediante el agregado de $NaHCO_3$ sat., se extrajo con CH_2Cl_2. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para proporcionar el compuesto en bruto que se purificó mediante filtración a través de un taco corto de gel de sílice eluyendo con 50% EtOAc/hexanos para proporcionar el compuesto **288c**.



288c **288d**

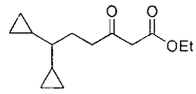
Se agregó el Compuesto **288c** (3,0 g, 21,2 mmol) a acetona (20 ml) y se enfrió a 0°C. Se agregó el reactivo de Jones gota a gota hasta que el color no cambió más a verde luego de agregar el reactivo. El reactivo excedente se desactivó mediante el agregado de *i*-PrOH, y se extrajo agua (20 ml) con Et_2O. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío para proporcionar el compuesto **288d** que se utilizó sin otra purificación.



288d **288a**

Se preparó de la misma manera que en el ejemplo **262a**.

EJEMPLO DE PREPARACIÓN 293a



293a



293b

Se agregó bis(trimetilsilil)amida de litio (solución 1,0 M en THF, 108,9 ml, 108,9 mmol) a 100 ml de THF en un balón de 500 ml equipado con una varilla agitadora y globo de nitrógeno. La solución se enfrió a 0°C y se agregó cloruro de (metoximetil)trifenilfosfonio (37,3 g, 108,9 mmol) en porciones y la solución de color rojo oscuro se agitó a 0°C durante 45 min. Se gregó diciclopropil cetona (10 g, 90,78 mmol) en THF (10 ml) gota a gota y la reacción se agitó a 0°C durante 3 h después de lo cual la mezcla de reacción se vertió en hexano. La mezcla se filtró a través de gel de sílice eluyendo con hexano. De la eliminación del solvente resultó el enol éter en bruto.

Se agregó el enol éter en bruto a THF (100 ml) y se agregó 10 % HCl (100 ml). La reacción se reflujó hasta el día siguiente. Luego del enfriado, se diluyó con agua y se extrajo con Et_2O (2 x 50 ml), se lavó con salmuera, se secó sobre $MgSO_4$, se concentró al vacío. La mezcla en bruto **293b** se usó como tal sin otra purificación.



293b **293c**

Se tomó hidruro de sodio (6,44 g, 161 mmol) en THF (30 ml) en un balón de 250 ml equipado con una varilla magnética de agitación y globo de nitrógeno. La mezcla se enfrió a 0°C. Se agregó trietilfosfonoacetato (36,1 g, 161 mmol) en 20 ml de THF gota a gota y la mezcla se agitó a temperatura ambiente durante 1 h después de lo cual se enfrió nuevamente a 0°C y el compuesto **293b** (10 g, 80,5 mmol) en 20 ml de THF se agregó gota a gota y la reacción se agitó a temperatura ambiente durante 2 h. La reacción se desactivó mediante el agregado de agua y se extrajo con Et_2O. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío. El producto en bruto se purificó por biotage (2% EtOAc/haxanes) para proporcionar el compuesto **293c**.



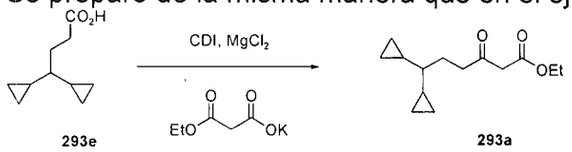
293c 293d

Se agregó el compuesto **293c** a 100 ml EtOH en un balón de 200 ml. A la solución se agregó Pd/C (10 % en peso, 7,0 g, 5,7 mmol) y la mezcla se hidrogenó utilizando un globo de hidrógeno a temperatura ambiente durante 12 h. La mezcla se filtró a través de celite y se eluyó con EtOH, de lo que después de eliminar el solvente, resultó el compuesto **293d** en bruto.



293d 293e

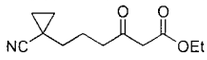
Se preparó de la misma manera que en el ejemplo **268c**.

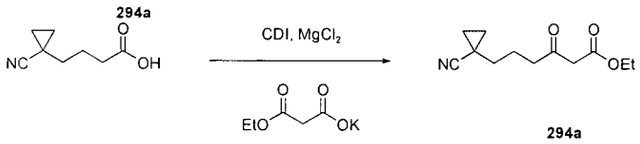


293e 293a

Se preparó de la misma manera que en el ejemplo **262a**.

EJEMPLO DE PREPARACIÓN 294a

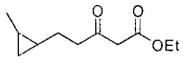




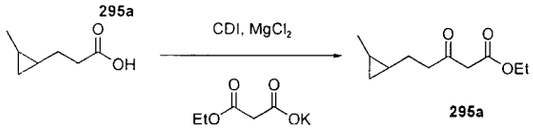
294a 294a

Se preparó de la misma manera que en el ejemplo **288a**.

EJEMPLO DE PREPARACIÓN 295a



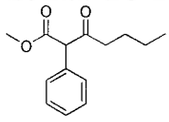
295a



295a

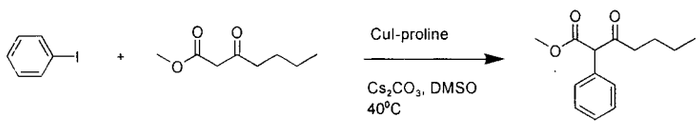
Se preparó de la misma manera que en el ejemplo **262a**.

EJEMPLO DE PREPARACIÓN 292a



292a

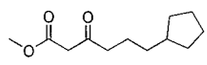
El material de partida para la preparación del Ejemplo **292** es como sigue.



292a

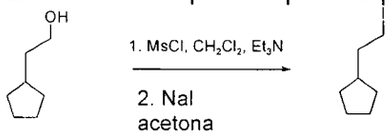
A la solución de yodobenceno (10,2 g, 50 mmol) en DMSO anhidro (150 ml) y metiléster del ácido 3-oxoenántico (15,8 g, 100 mmol) se agregó yoduro de cobre(I) (1,9 g, 10 mmol), L-prolina (2,3 g, 20 mmol), y carbonato de cesio (65,2 g, 200 mmol). Después de que se agitó bajo N_2 a 40°C durante 18 horas, la mezcla de reacción se disolvió en acetato etílico (250 ml), se lavó con agua (4 x 150 ml). La solución orgánica se secó con sulfato de sodio, y se concentró bajo presión reducida. El producto en bruto resultante se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con etilo acetato/hexanos (v/v = 5/95) para dar el Compuesto **292a** (4,5 g, 38%).

EJEMPLO DE PREPARACIÓN 297ª



297a

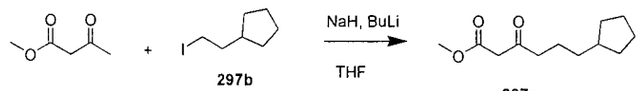
El material de partida para la preparación del Ejemplo **297** es como sigue.



297b

A una solución de 2-ciclopentilo etanol (11,4 g, 100 mmol), CH_2Cl_2 anhidro (80 ml), y trietil amina (12 g, 120 mmol), que se enfrió a 0°C, se agregó vía jeringa MsCl (13,7 g, 120 mmol). Después de agitar bajo N_2 a 0°C durante 1 hora, luego a

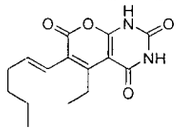
temperatura ambiente durante 18 horas, la mezcla de reacción se lavó con agua (2 x 100 ml), se secó con sulfato de sodio, y se concentró bajo presión reducida para dar un aceite claro (19 g, 100%). El aceite se disolvió en CH_2Cl_2 anhidro (250 ml) y se mezcló con NaI (20 g, 200 mmol). Después de agitar a temperatura ambiente durante 18 horas, la mezcla de reacción se filtró del sólido. El filtrado resultante se concentró bajo presión reducida para dar una pasta color marrón. La pasta se disolvió en dietiléter (300 ml), se lavó con agua (2 x 150 ml), se secó con sulfato de sodio, se concentró bajo presión reducida para dar el Compuesto **297b** (20 g, 89%).



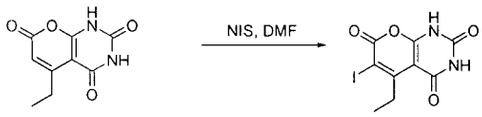
297b 297a

A una solución de acetoacetato de metilo (5,8 g, 50 mmol) y THF anhidro (100 ml), que se enfrió a 0°C, se agregó NaH (60%, 2,4 g, 60 mmol). Después de agitar bajo N_2 a 0°C durante 0,5 hora, se agregó n-BuLi (2,5 M en hexanos, 20 ml) se agregó mediante una jeringa. Después de agitar a 0°C durante 0,5 hora, la reacción mixtures se enfrió a -25°C, el compuesto **297b** se agregó mediante una jeringa. La mezcla de reacción se agitó a 0^0C durante 0,5 hora, luego a temperatura ambiente durante 18 horas. La mezcla de reacción se desactivó con cloruro de amonio saturado (200 ml) y se extrajo con acetato etílico (2 x 200 ml) se lavó con agua (2 x 100 ml). La solución orgánica se secó con sulfato de sodio, y se concentró bajo presión reducida para dar un aceite color marrón, que se purificó utilizando cromatografía flash en columna de gel de sílice eluyendo con etilo acetato/hexanos (v/v = 7/93) para dar el Compuesto **297a** (3,2 g, 32%).

EJEMPLO DE PREPARACIÓN 214

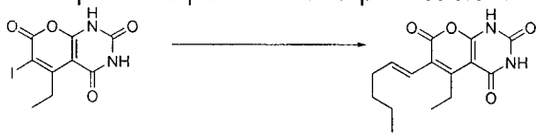


214



214a 214b

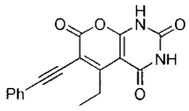
Se agregó el Compuesto **214a** (10 g, 48,04 mmol) a DMF (50 ml) en un balón equipado con una barra agitadora magnética. Se agregó *N*-yodosuccinimida (22 g, 97,79 mmol) en porciones y la mezcla de reacción se calentó a 50°C hasta el día siguiente. Después del enfriado a temperatura ambiente, se agregó H_2O (100 ml). El producto se filtró, se lavó con agua seguido de éter para dar una mezcla blanca polvorienta (> 95% rendimiento). El producto **214b** se usó como tal en el próximo paso sin otra purificación.



214b 214

Se agregó el Compuesto **214b** (0,1 g, 0,3 mmol) a C_6H_6 (1 ml) en un balón de 10 ml. Se agregó $Pd(OAc)_2$ (0,004 g, 0,018 mmol), PPh_3 (0,014 g, 0,054 mmol), y Na_2CO_3 (0,5 ml, solución 2M) y la mezcla de reacción se agitó a temperatura ambiente durante 30 min. Se agregó ácido *trans*-1-Hexen-1-ilborónico (0,042 g, 0,33 mmol) en EtOH (0,5 ml) y la mezcla de reacción se permitió reflujar (80°C) hasta el día siguiente. Después del enfriado, la mezcla se diluyó con H_2O (2 ml), se extrajo con EtOAc (2 x 10 ml), se secó sobre $MgSO_4$, se concentró y se secó para proporcionar el compuesto en bruto **214**. Se purificó mediante TLC prep (10% MeOH/DCM) para proporcionar el compuesto **214**.

EJEMPLO DE PREPARACIÓN 219



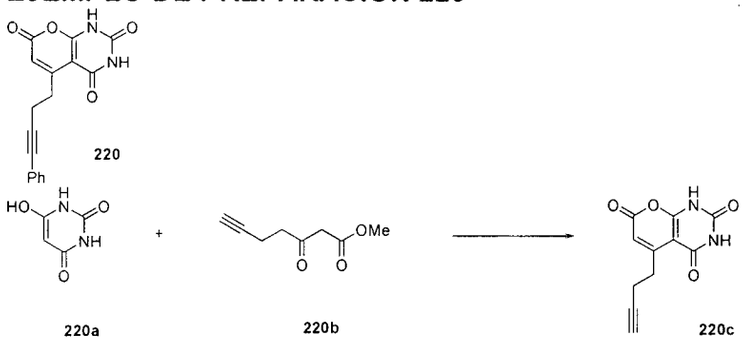
219



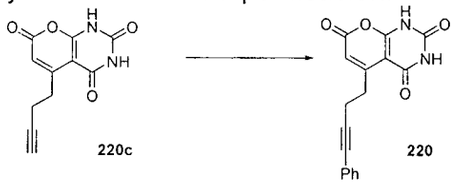
214b 219

Se agregó el Compuesto **214b** (0,1 g, 0,3 mmol) a DMF (3,0 ml) en un balón de 10 ml. Se agregó $PdCl_2(PPh_3)_2$ (0,011 g, 0,015 mmol), fenilacetileno (0,061 g, 0,6 mmol), CuI (0,006 g, 0,03 mmol), y trietilamina (0,091 g, 0,9 mmol) y la mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se diluyó con EtOAc (5 ml), se neutralizó con HCl 1N, y se extrajo con EtOAc (2 x 10 ml), se secó sobre $MgSO_4$, se concentró y se secó para proporcionar el producto en bruto **219**. El producto en bruto se tomó con éter y se filtró para proporcionar el compuesto **219** puro.

EJEMPLO DE PREPARACIÓN 220



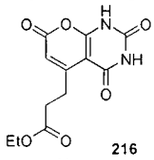
Se agregó ácido barbitúrico **220a** (1,0 g, 7,81 mmol) y ceto éster **220b** (1,45 g, 9,4 mmol) a ácido acético glacial (8 ml) y la mezcla de reacción se calentó a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el ácido acético al vacío y se agregó agua caliente para eliminar el ácido barbitúrico en exceso. Se repitió el procedimiento varias veces hasta no quedar material de partida. Ello fue seguido de lavado con éter. El producto **220c** se secó y no necesitó otra purificación.



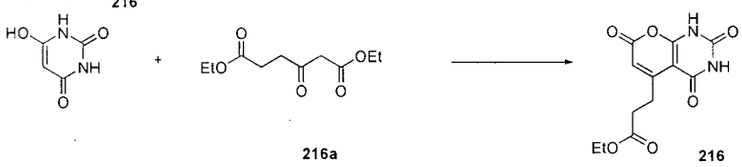
Se agregó el Compuesto **220c** (0,1 g, 0,431 mmol) a DMF (1 ml) en un balón de 10 ml. Se agregó yodobenceno (0,053 g, 0,258 mmol), $PdCl_2(PPh_3)_2$ (0,003 g, 0,0043 mmol), CuI (0,002 g, 0,0086 mmol), y Et_2NH (0,157 g, 2,15

mmol) y la mezcla de reacción se agitó a temperatura ambiente hasta el día siguiente. La reacción se diluyó con EtOAc (2 ml), se neutralizó con HCl 1N y se extrajo con EtOAc (2 x 10 ml). Se secó sobre $MgSO_4$, se concentró al vacío. El producto en bruto se purificó mediante TLC prep (20 % MeOH/DCM) para proporcionar el compuesto **220**.

EJEMPLO DE PREPARACIÓN 216



216

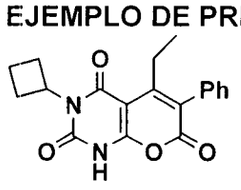


216a **216**

Se agregó ácido barbitúrico (1,0 g, 7,81 mmol) y β-cetoadipato de dietilo **216a** (2,03 g, 9,4 mmol) a ácido acético glacial (8 ml) y la mezcla de reacción se calentó a reflujo hasta el día siguiente. Luego de enfriar a temperatura ambiente, se eliminó el ácido acético al vacío y se agregó agua caliente para eliminar el exceso de ácido barbitúrico. Se repitió el procedimiento varias veces hasta no quedar material de partida. Ello fue seguido de lavado con éter. El producto **216** se secó y no requirió otra purificación.

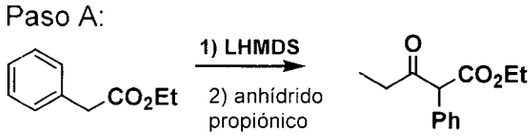
El material de partida para la preparación del Ejemplo **203** es como sigue.

EJEMPLO DE PREPARACIÓN 203



203

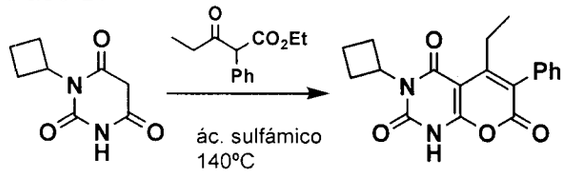
Paso A:



203a

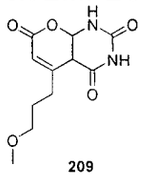
A una solución de etilfenilacetato (8,2 g, 0,05 mol) en THF a -78ºC se agregó LHMDS (1M en THF, 100 ml, 0,10 mol) y se agitó durante 20 min. Se agregó rápidamente anhídrido propiónico (6,5 ml, 0,05 mol). La mezcla se permitió calentar hasta 0^0C y se agitó durante 30 min. Se desactivó con NH_4Cl (ac.) y se extrajo con EtOAc. El procesamiento usual proporcionó el producto en bruto, que se cromatografió en gel de sílice para obtener el producto.

Paso B:



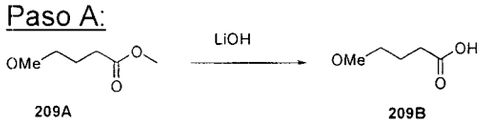
El Compuesto **203** se obtuvo mediante un procedimiento de condensación normal con ácido ciclobutilbarbitúrico.

EJEMPLO DE PREPARACIÓN 209



209

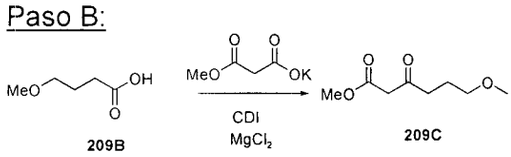
Paso A:



209A 209B

El material de partida **209a** (9,9 g, 75 mmol) se disolvió en THF (100 ml) y agua (25 ml). LiOH (3,4 g, 80,9 mmol), la mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. Se agregó HCl 1N (100 ml) y se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$) para dar el Compuesto **209b** (8,8 g, 93%).

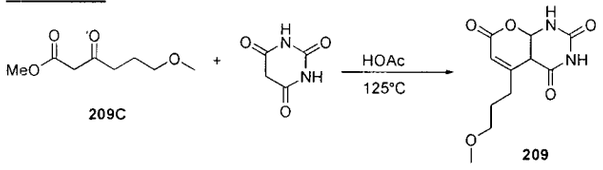
Paso B:



209B 209C

Se agregó el **Compuesto 209c** (1,9 g, 16,1 mmol) disuelto en THF (50 ml), CDI (12,3 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 h. Se agregaron $MgCl_2$ (1,5 g, 16,1 mmol) y $KOCOCH_2CO_2Me$ (3,8 g, 24,2 mmol), la mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. Se agregaron EtOAc (100 ml) y agua (50 ml). La capa acuosa se separó y se extrajo con EtOAc. La capa acuosa se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se separó mediante cromatografía con gel de sílice, con una columna Biotage 40S+, se eluyó con EtOAc: hexanos, 1:10, para dar 2,1 g (74%) de un líquido amarillo como el **Compuesto 209d**.

Paso B:

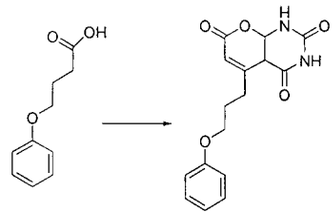


209C 209

Se mezclaron el **Compuesto 209c** (1,13 g, 6,49 mmol) y ácido barbitúrico (0,5 g, 3,90 mmol) con HOAc (2 ml) en un tubo sellado, y se calentó en un baño de aceite a 125°C hasta el día siguiente. La mezcla se enfrió a temperatura

ambiente, se eliminó el HOAc y el MeOH residual, y se filtró. Se redujo el volumen del líquido madre hasta que comenzó a aparecer el sólido, el sólido color beige se recolectó para dar el **Compuesto 209** (153 mg, 10%). Electroaspersión MS [M+1]: 253,1.

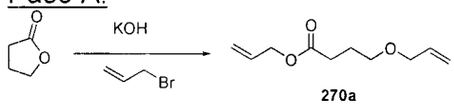
Compuesto 208 se preparó en un modo similar como en **Compuesto 209**, a partir del **Compuesto 208 a** disponible en el mercado.



compuesto 208 A Compuesto 208

EJEMPLO DE PREPARACIÓN 270

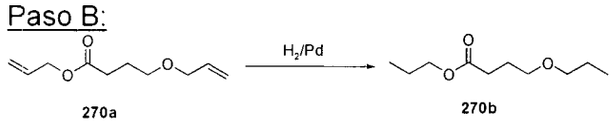
Paso A:



270a

La lactona de partida (10 g, 116 mmol) se mezcló con bromuro de alilo (30 ml, 346 mmol), tolueno (75 ml), y KOH (19,5 g, 348 mmol). La mezcla se calentó 110°C hasta el día siguiente. La mezcla se enfrió a temperatura ambiente; se agregó agua (100 ml). La capa acuosa se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró para dar un líquido color amarillo como el **Compuesto 270a** deseado (11,8 g, 55,2%).

Paso B:

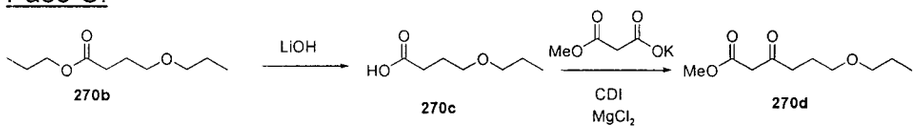


270a 270b

El **Compuesto 270a** (3,0 g, 16,3 mmol) se disolvió en EtOH (20 ml), se agregó 10 % Pd/C (300 mg). La solucion se agitó bajo H_2 hasta el día siguiente.

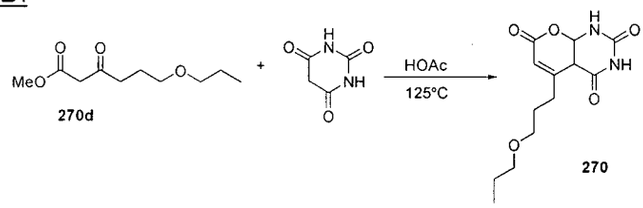
La mezcla se filtró a través de Celite, y el filtrado se concentró para dar un líquido color amarillo como el deseado **Compuesto 270b** (2,5 g, 81%).

Paso C:



El **Compuesto 270b** (3,0 g, 16,3 mmol) se disolvió en THF (20 ml)-H_2O (7 ml), se agregó LiOH (1,66 g, 39,5 mmol). La mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. Se agregó HCl 1 N (75 ml) y se extrajo con Et_2O. Se combinaron los extractos orgánicos, se secó ($MgSO_4$) se filtró y se concentró. El residuo se disolvió en THF (50 ml), se agregó CDI (12,3 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 h. Se agregaron MgCl2 (1,3 g, 13,6 mmol) y $KOCOCH_2CO_2Me$ (2,9 g, 18,5 mmol), la mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. Se agregaron EtOAc (100 ml) y agua (50 ml). La capa acuosa se separó y se extrajo con EtOAc. La capa acuosa se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se separó mediante cromatografía con gel de sílice, con una columna Biotage 40S+, se eluyó con EtOAc: hexanos, 1:10, para dar 1,5 g (46%) un líquido amarillo como **Compuesto 270d**.

Paso D:

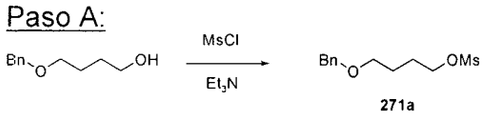


El **Compuesto 270d** (448 mg, 2,22 mmol) y ácido barbitúrico (340 mg, 2,65 mmol) se mezcló con HOAc (2 ml) en un tubo sellado, y se calentó en un baño de aceite a 125ºC hasta el día siguiente. La mezcla se enfrió a temperatura ambiente, se eliminó HOAc y el MeOH residual, y se filtró. El líquido madre se

concentró y se separó mediante TLC prep, se eluyó con 1:10:10, HOAc:DCM:EtOAc, para dar el deseado **Compuesto 270** (72 mg, 11,4%) como un sólido blanco. Electroaspersión MS [M+1]: 281,2.

EJEMPLO DE PREPARACIÓN 271

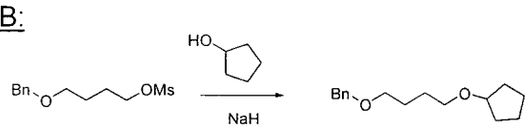
Paso A:



271a

El alcohol de partida (5,2 g, 28,0 mmol) se disolvió en DCM (100 ml), trietilamina (6 ml, 42,7 mmol) y se agregó MsCl (2,6 ml, 33,6 mmol). La solución resultante se agitó a temperatura ambiente durante 1 h. La mezcla se diluyó con EtOAc y se lavó con HCl 1N (50 ml x 2). Se combinaron las capas acuosas, se extrajo con EtOAc. Se combinaron las capas orgánicas, se lavó con salmuera, se secó (MgSO4), se filtró, y se concentró para dar el C**ompuesto 271a** (7,26 g, 100%).

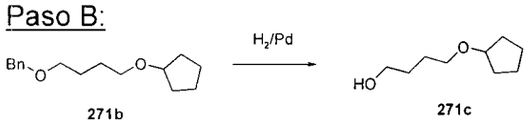
Paso B:



271a **271b**

Se disolvió ciclopentanol (3,8 ml, 42 mmol) en THF (50 ml) bajo nitrógeno. Se agregó NaH (0,85 g, 95% de dispersión oleosa, 33,7 mmol). La solución resultante se agitó a temperatura ambiente durante 1 h. Una solución de mesilato **271a** (7,26 g, 28 mmol) en DMF (30 ml) se agregó mediante una jeringa. La mezcla resultante se calentó a 85°C hasta el día siguiente. La mezcla se enfrió a temperatura ambiente, y se diluyó con EtOAc, y se lavó con agua (50 ml x 3). Se combinaron las capas acuosas y se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. El residuo se purificó sobre una columna de gel de sílice, se eluyó con EtOAc-hexanos (1:10) para dar 4,95 g (71%) del **Compuesto 271b** como un líquido ámbar.

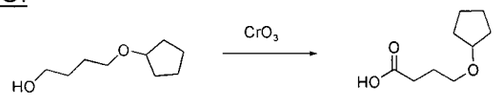
Paso B:



271b 271c

Compuesto 271b (4,95 g, 20 mmol) se disolvió en EtOH (100 ml), se agregó 10% Pd/C (0,55 g) y se agitó bajo 1 atm. de hidrógeno hasta el día siguiente. Se filtró a través de Celite, el filtrado se concentró al vacío. El residuo se purificó sobre una columna de gel de sílice, se eluyó con EtOAc-hexanos (1:3) para dar 3,1 g (98%) del **Compuesto 271c** como un líquido incoloro.

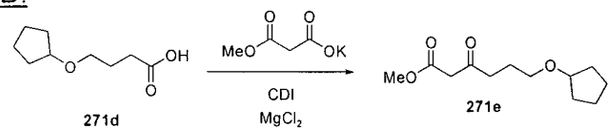
Paso C:



271c 271d

CrO_3 se mezcló con 4,7 ml del H_2SO_4 conc. La mezcla se diluyó con agua a 36 ml. **Compuesto 271c** se disolvió en acetona (30 ml), y se agregó el reactivo de Jones. La mezcla se agitó a temperatura ambiente durante 1 h, se diluyó con agua y se extrajo con DCM. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró para dar 1,99 g (71%).

Paso D:

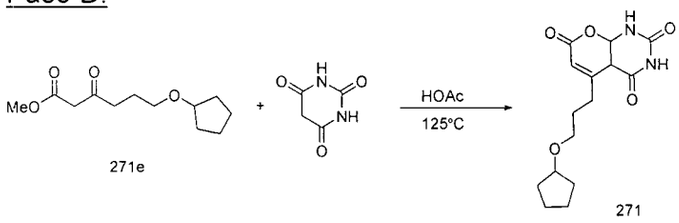


271d 271e

El **Compuesto 271d** (2,40 g, 14,0 mmol) se disolvió en THF (50 ml), se agregó CDI (2,48 g, 15,3 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 h. Se agregaron $MgCl_2$ (1,5 g, 15,3 mmol) y $KOCOCH_2CO_2Me$ (3,3 g, 20,9 mmol), la mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. Se agregó EtOAc (100 ml) y agua (50 ml). La capa acuosa se separó y se extrajo con EtOAc. La capa acuosa se extrajo con EtOAc. Se combinaron los extractos orgánicos, se lavó con salmuera, se secó ($MgSO_4$), se filtró y se concentró. El residuo se filtró a través de un taco de gel de

sílice, se eluyó con EtOAc: hexanos, 1:3, para dar 2,2 g (69%) un líquido amarillo como **Compuesto 270e.**

Paso D:

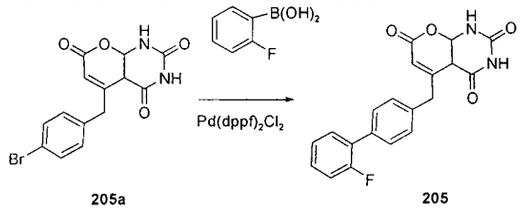


271e 271

El **Compuesto 271e** (448 mg, 2,22 mmol) y ácido barbitúrico (340 mg, 2,65 mmol) se mezcló con HOAc (2 ml) en un tubo sellado, y se calentó en un baño de aceite a 125°C hasta el día siguiente. La mezcla se enfrió a temperatura ambiente, se eliminó el HOAc y el MeOH residual, y se filtró. El líquido madre se concentró y se separó mediante TLC prep, se eluyó con 1:10:10, HOAc:DCM:EtOAc, para dar el deseado **Compuesto 271** (55 mg, 4%) como un sólido blanco. Electroaspersión MS [M+1]: 307,2.

Compuesto 273, Compuesto 287 y el compuesto 290 se prepararon en un modo similar al **Compuesto 271** a partir de los correspondientes alcoholes.

EJEMPLO DE PREPARACIÓN 205

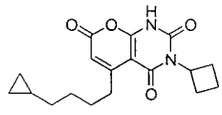
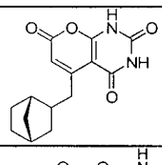
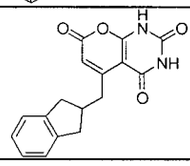
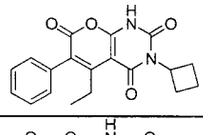
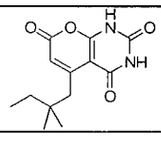
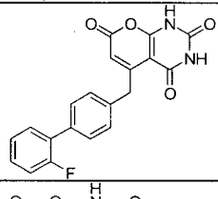
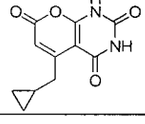


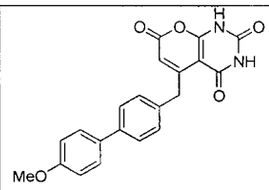
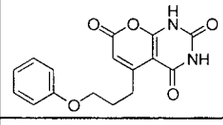
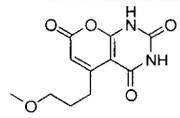
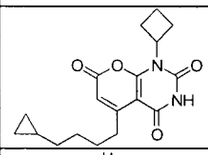
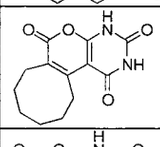
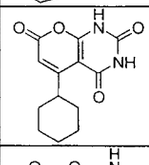
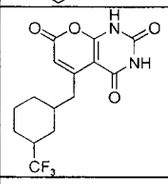
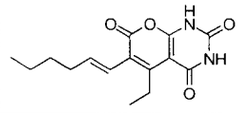
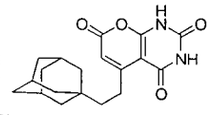
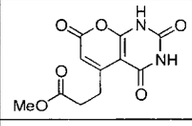
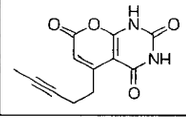
205a 205

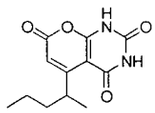
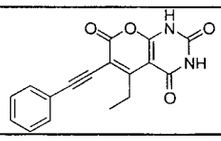
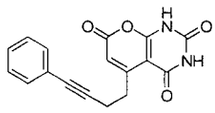
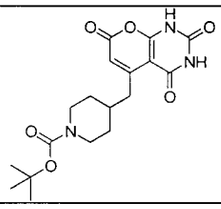
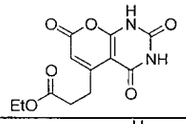
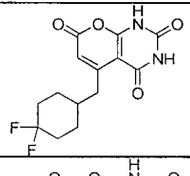
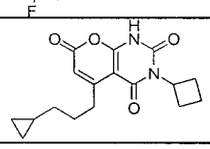
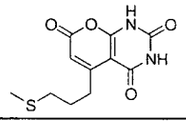
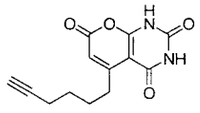
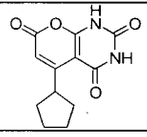
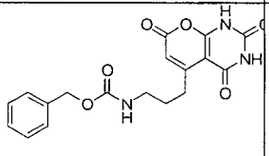
El **Compuesto 205a** (50 mg, 0,14 mmol) se disolvió en DMF (2 ml) y H_2O (2 ml), se agregaron $Pd(dppf)_2Cl_2$ y K_2CO_3. La mezcla resultante se calentó a 85°C bajo nitrógeno durante 5 h. La mezcla se enfrió a temperatura ambiente y se filtró a través de Celite. El filtrado se concentró. El residuo se disolvió en MeOH, y DCM se agregó mientras continuaba la precipitación. El sólido se recolectó como el deseado **Compuesto 205** (21 mg, 40%). Electroaspersión MS [M+1]: 481,5.

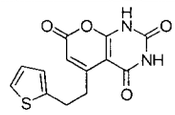
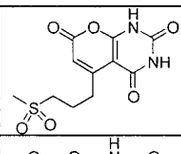
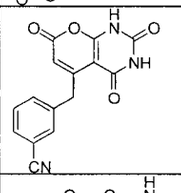
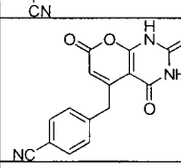
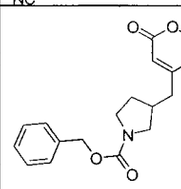
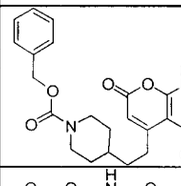
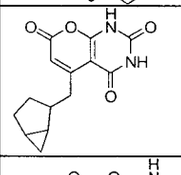
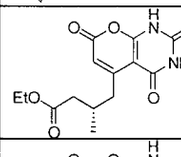
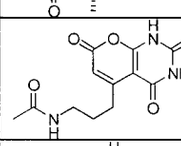
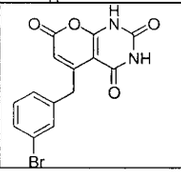
Compuesto 207 se preparó en un modo similar al **Compuesto 205**, utilizando el correspondiente ácido borónico.

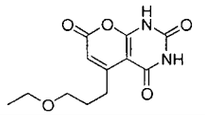
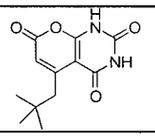
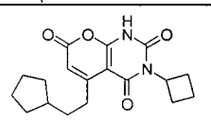
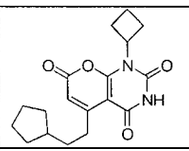
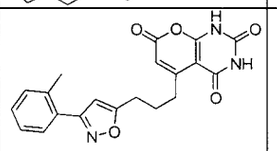
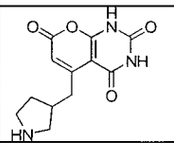
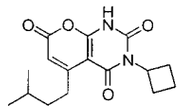
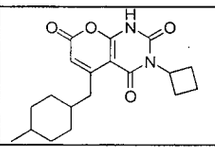
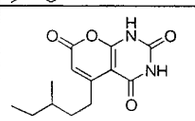
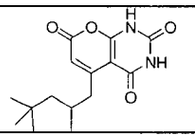
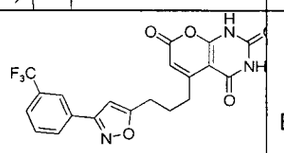
Se muestran diversos compuestos de la invención en la Tabla a continuación, así como en las Tablas que se presentan luego en esta especificación. Los datos de LCMS también se muestran en cualquier lugar disponible. También se muestran los datos de actividad (EC50), en cualquier lugar que pueden medirse y estén disponibles, y se designan A, B o C, donde A = 0,001 nM a 100 nM; B es >100 <1000 nM y C es >1000 nM.

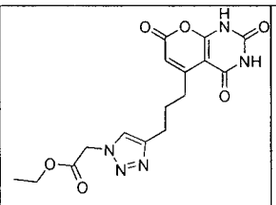
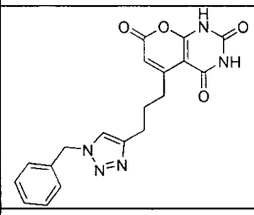
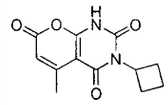
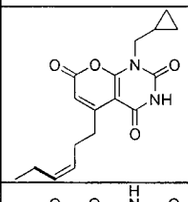
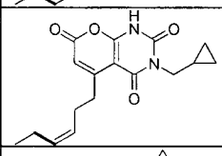
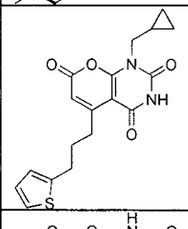
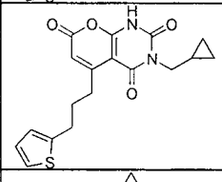
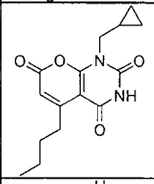
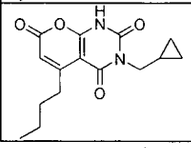
Compuesto Nº	**ESTRUCTURA**	**ND EC50 AMPc (nM)**	**Electroaspersión LCMS [M+1]+**
200		B	331,2
201		C	289,2
202		B	311,2
203		C	339,1
204		C	265,1
205		B	365,2
206		B	235,1

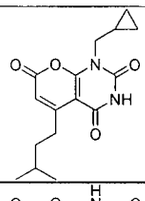
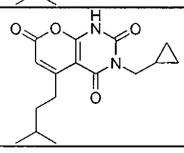
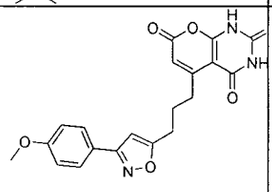
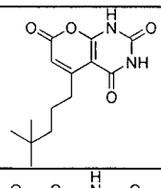
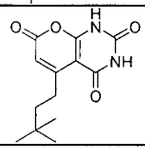
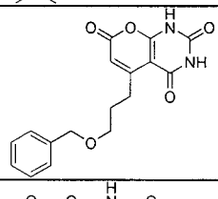
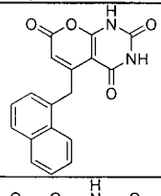
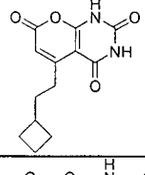
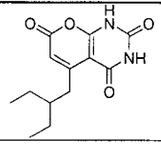
207		C	377,2
208		C	316,2
209		B	253,1
210		B	331,2
211		C	263,1
212		B	263,1
213		B	345,2
214		C	291,2
215		C	343,2
216		B	267,1
217		C	247,1

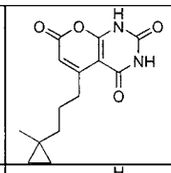
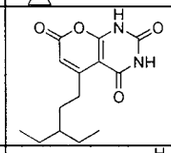
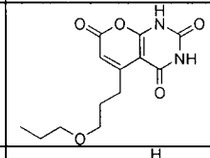
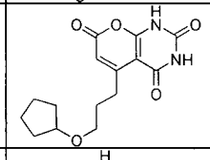
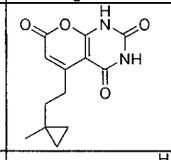
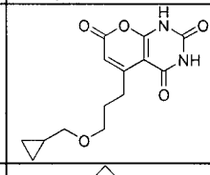
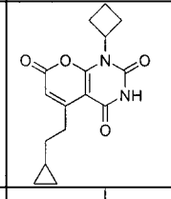
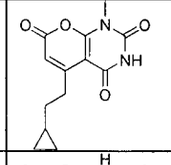
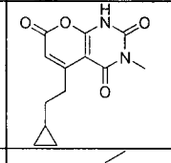
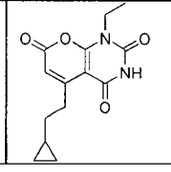
218		B	251,1
219		C	309,2
220		C	309,2
221		C	378,2
222		C	281,2
223		A	313
224		A	317,2
225		A	269,1
226		A	261,1
227		C	249,1
228		C	372,2

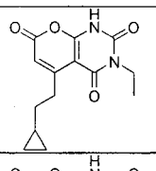
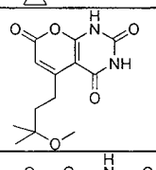
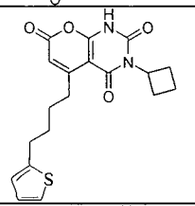
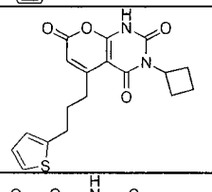
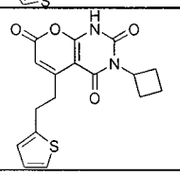
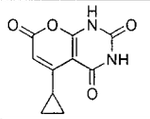
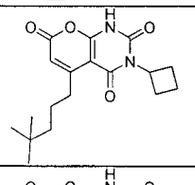
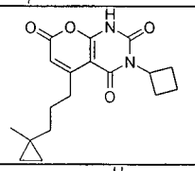
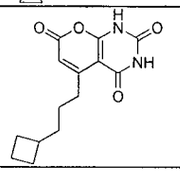
229		A	391,2
230		B	301,2
231		C	318,2 (M+Na)
232		C	368,2 (M+Na)
233		C	398
234		C	426
235		A	275,2
236		C	309,2
237		C	280,2
238		B	349,2

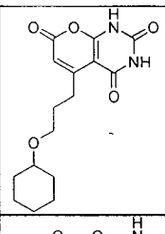
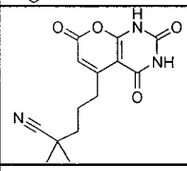
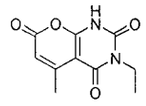
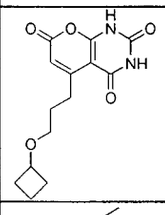
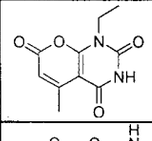
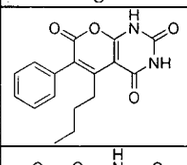
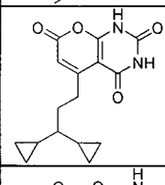
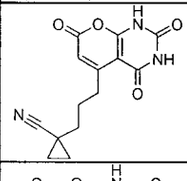
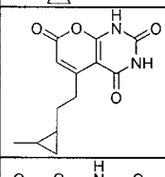
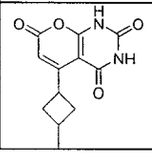
239		A	267,1
240		C	251
241		A	331,2
242		C	331,2
243		B	380
244		C	264
245		A	305,2
246		C	345,2
247		A	265,1
248		C	293,2
249		B	434

250		C	376
251		B	380
252		A	249,1
253		C	317,2
254		C	317,2
255		C	359,2
256		C	359,2
257		C	291,2
258		B	291,2

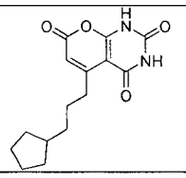
259		C	305,2
260		C	305,2
261		B	396
262		A	279,2
263		C	265,1
264		C	329,2
265		C	321,2
266		A	263,1
267		C	265,1

268		A	277,2
269		B	279,2
270		A	281,2
271		B	307,2
272		B	263,1
273		B	293,2
274		B	303,2
275		B	263,1
276		B	263,1
277		C	277,2

278		B	277,2
279		C	281,2
280		C	373,2
281		B	359,2
282		B	345,2
283		B	221,1
284		B	333,1
285		B	331,2
286		A	277,2

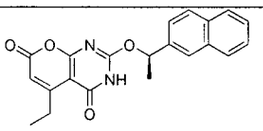
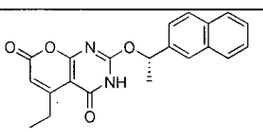
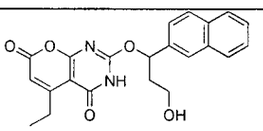
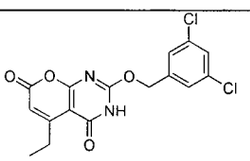
287		C	321,2
288		C	290,2
289		C	223,1
290		B	315,2 (M+Na)
291		C	223,1
292		B	313,2
293		B	303,2
294		B	288,2
295		B	263,1
296		B	249,1

503

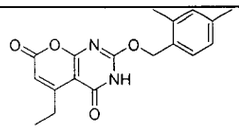
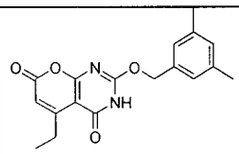
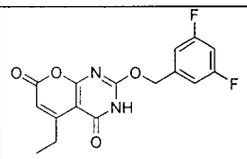
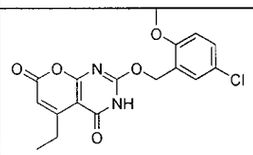
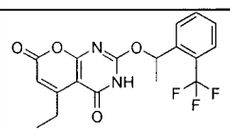
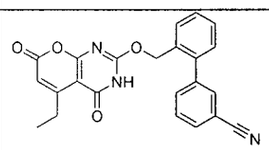
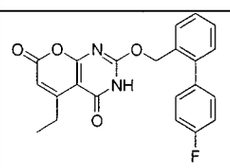
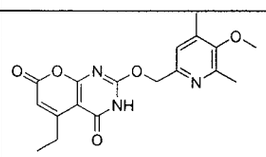
297		A	291,2

Los compuestos **500 a 690** se prepararon mediante un procedimiento similar a aquel utilizado para la preparación del Ejemplo 49, utilizando el Ejemplo 10, y el correspondiente alcohol apropiado.

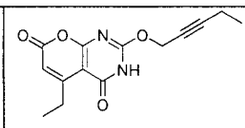
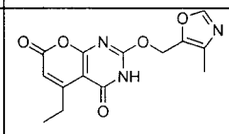
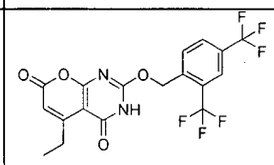
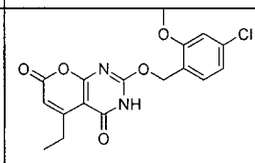
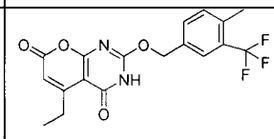
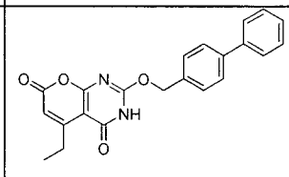
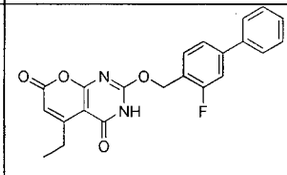
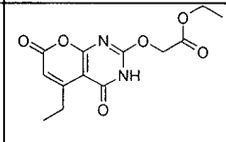
Los compuestos **691** y **698** se prepararon mediante un procedimiento similar al Ejemplo 49, utilizando el oxiaminocarbamato apropiado y el sulfóxido que se preparó utilizando el Ejemplo 10.

Compuesto Nº	**Estructura**	**ND EC50 AMPc (nM)**	**Electroaspersión LCMS [M+1]+**
500		B	363,1
501		A	363,1
502		B	343
503		B	368

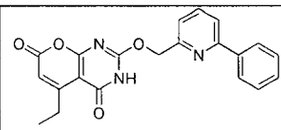
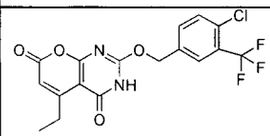
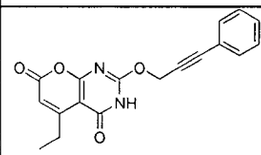
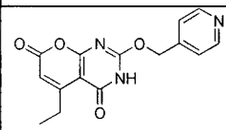
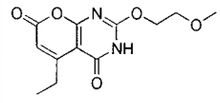
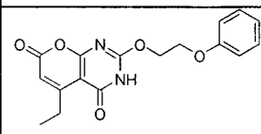
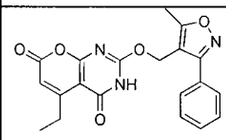
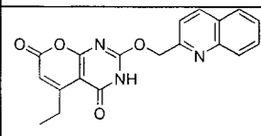
504

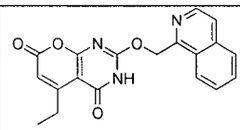
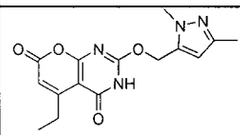
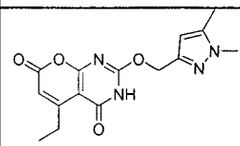
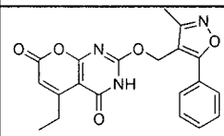
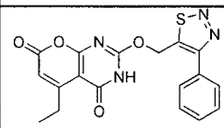
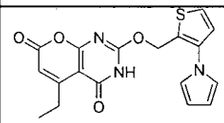
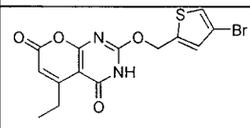
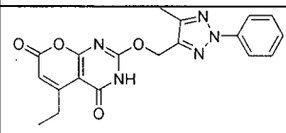
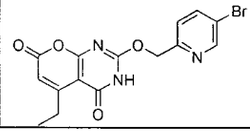
504		B	327
505		B	327
506		C	335
507		A	363
508		C	381,1
509		B	400
510		C	393
511		C	358,2

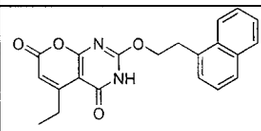
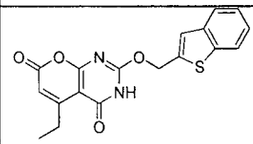
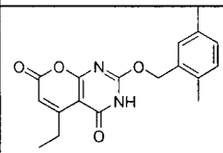
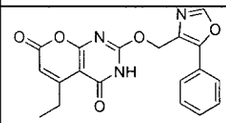
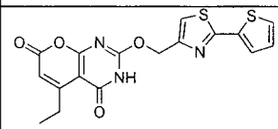
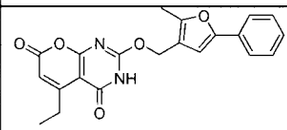
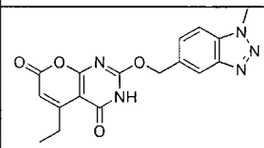
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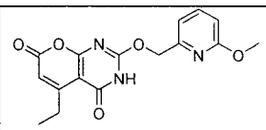
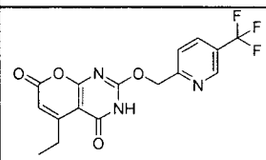
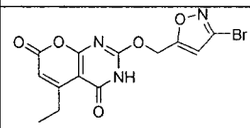
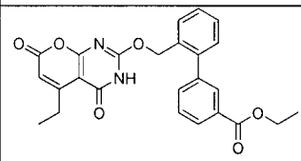
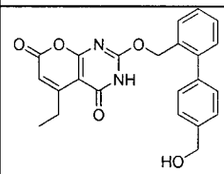
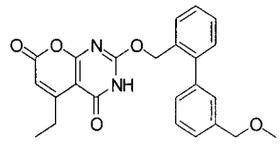
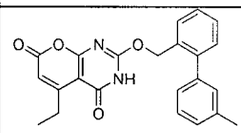
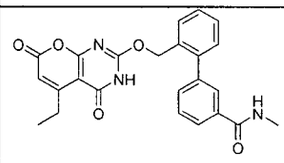
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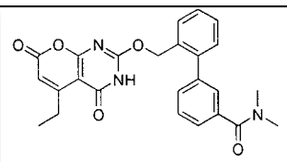
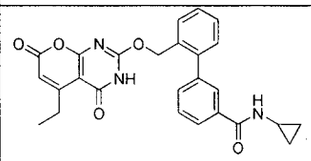
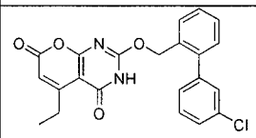
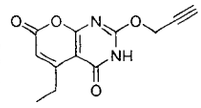
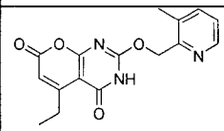
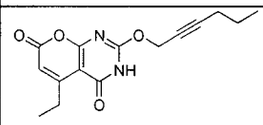
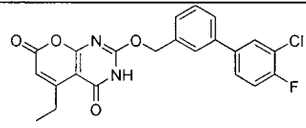
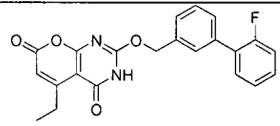
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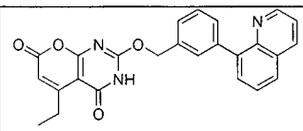
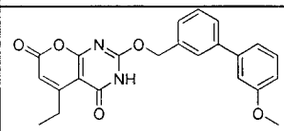
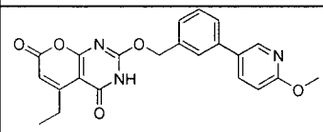
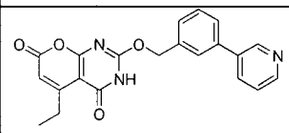
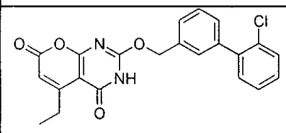
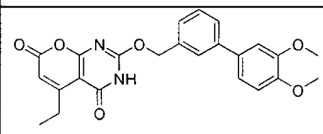
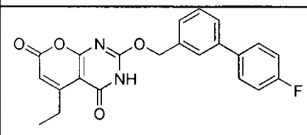
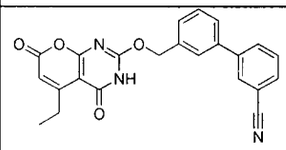
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527		B	350

528		B	350
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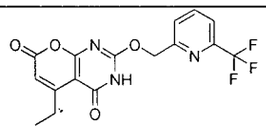
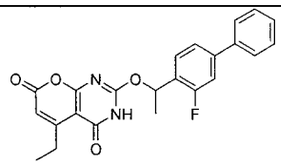
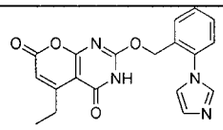
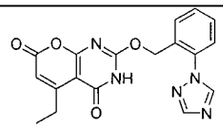
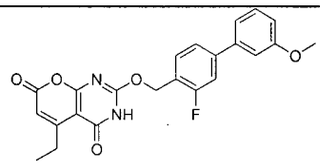
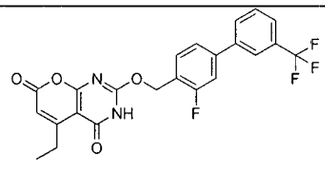
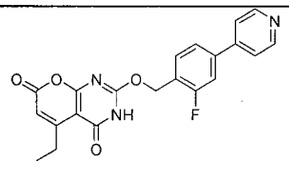
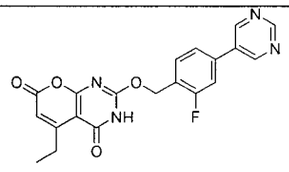
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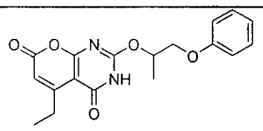
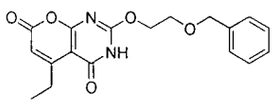
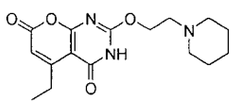
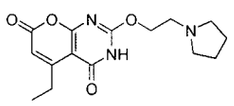
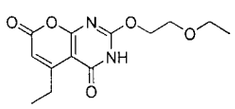
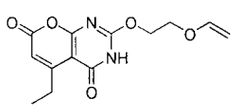
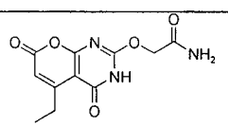
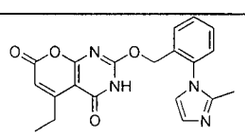
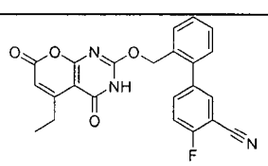
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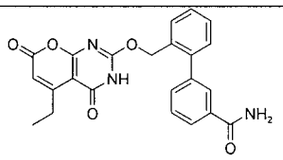
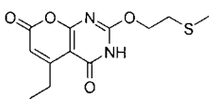
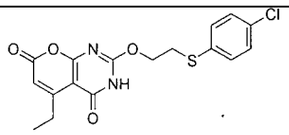
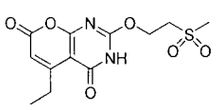
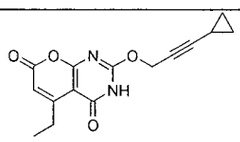
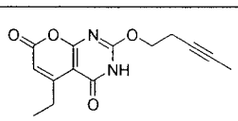
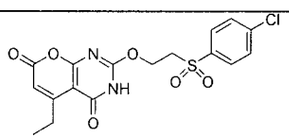
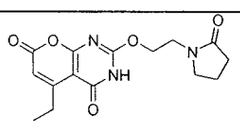
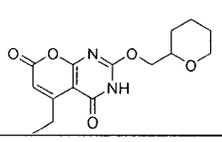
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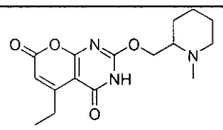
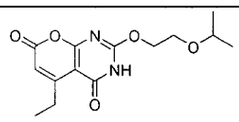
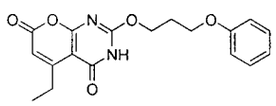
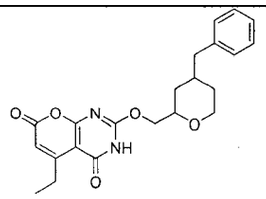
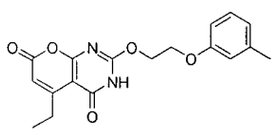
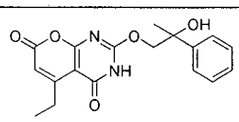
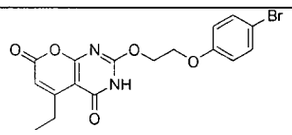
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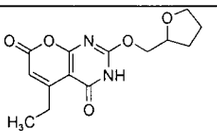
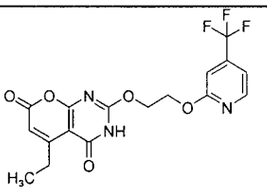
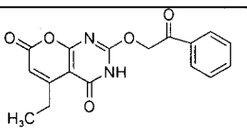
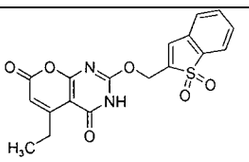
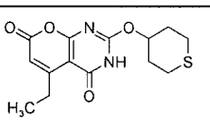
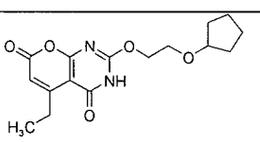
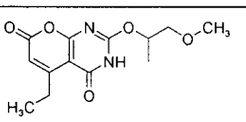
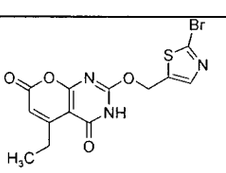
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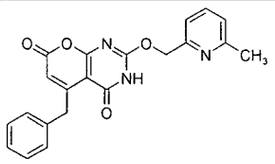
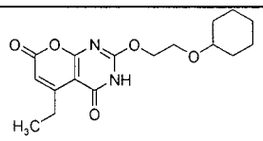
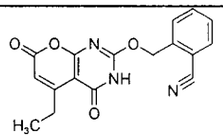
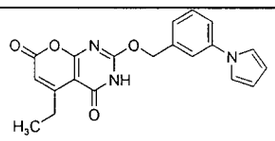
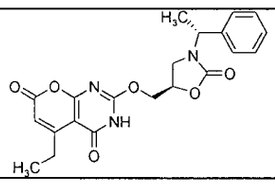
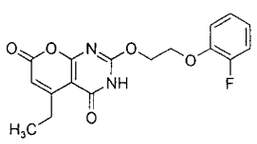
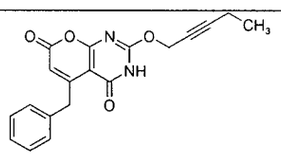
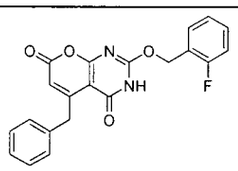
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569		A	407,2
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572		B	423,1
573		B	461,1
574		B	394,1
575		B	395,1

576		C	343,2
577		B	343,2
578		C	320,2
579		C	306,2
580		C	281,2
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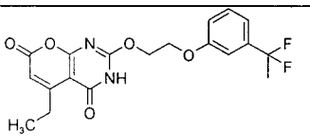
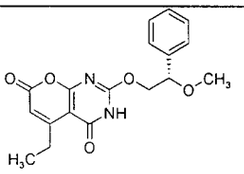
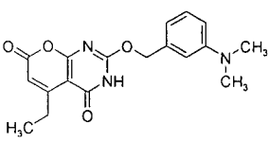
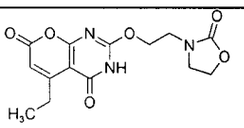
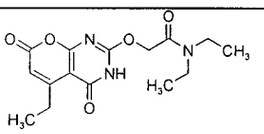
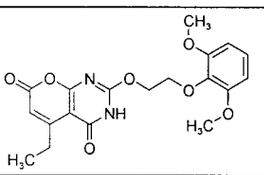
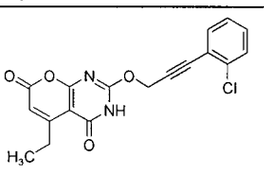
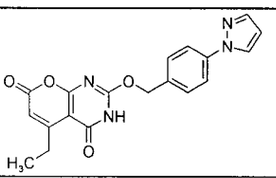
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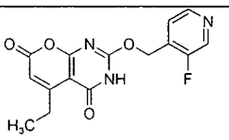
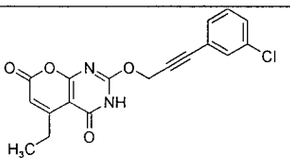
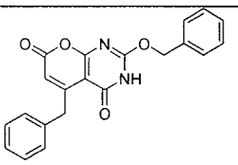
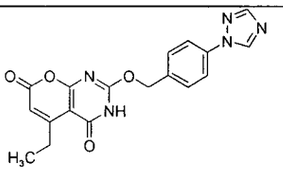
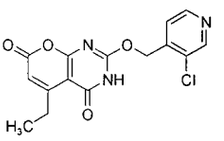
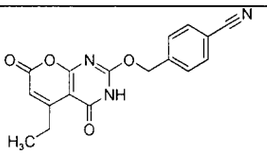
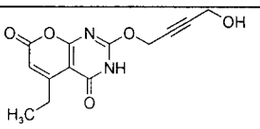
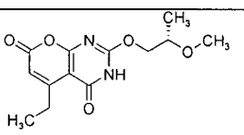
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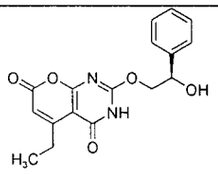
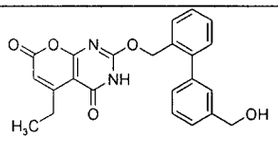
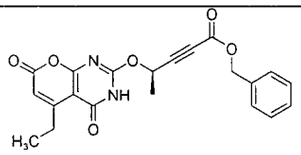
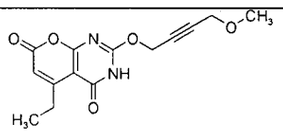
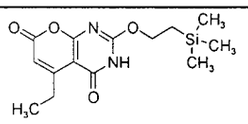
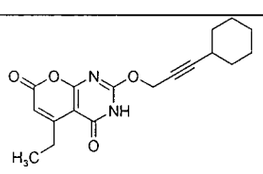
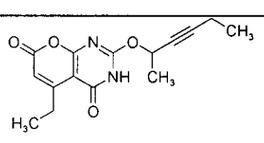
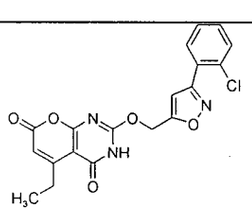
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602		B	398,1
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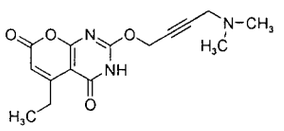
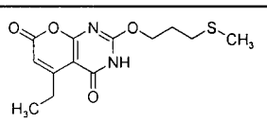
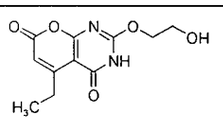
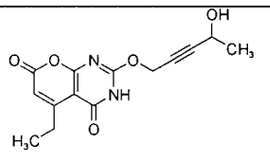
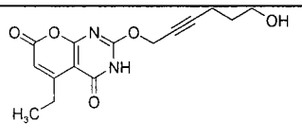
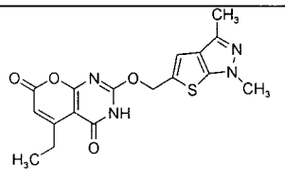
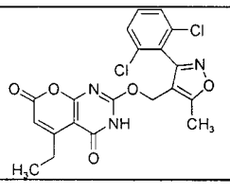
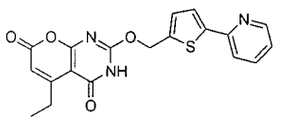
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610		C	335
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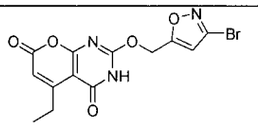
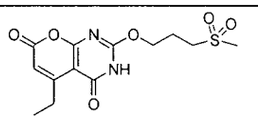
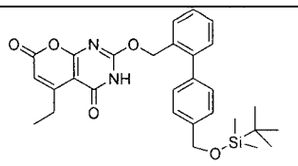
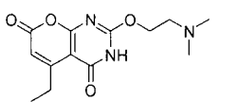
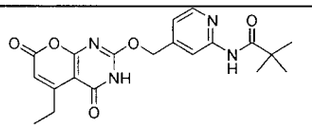
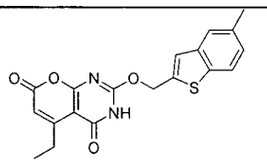
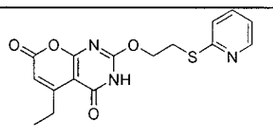
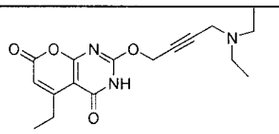
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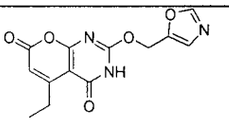
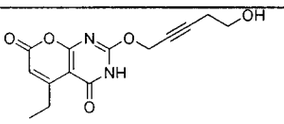
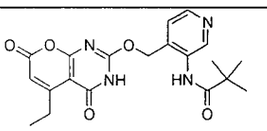
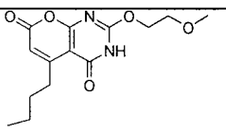
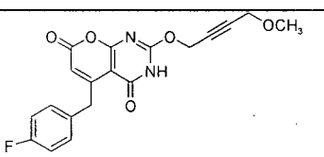
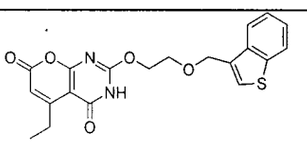
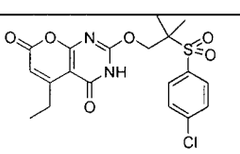
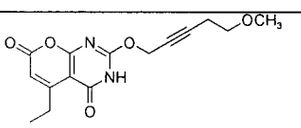
617		B	397,2
618		B	343,2
619		B	342,2
620		C	322,2
621		B	322,2
622		B	389,2
623		A	357,2
624		B	365,2

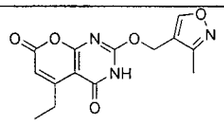
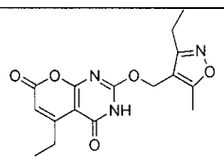
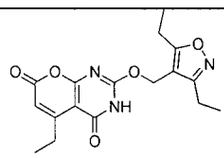
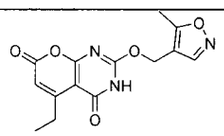
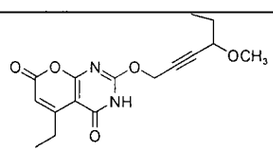
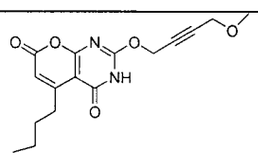
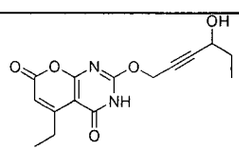
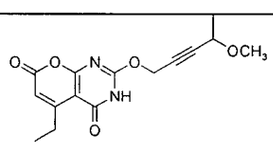
625		B	318,2
626		A	358
627		C	361,2
628		C	366,2
629		B	334,2
630		C	324,2
631		B	277
632		B	281,2

633		B	329,2
634		B	405
635		C	395
636		B	291
637		B	309,2
638		B	329
639		B	283
640		B	400,1

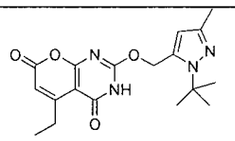
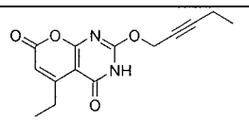
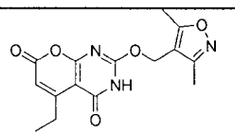
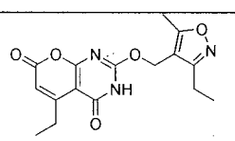
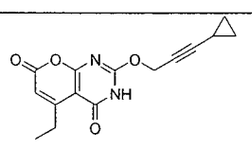
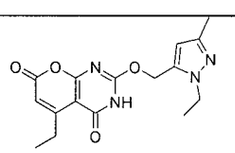
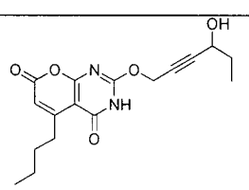
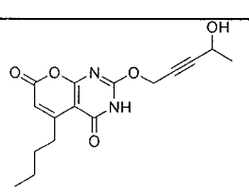
641		A	304
642		B	297,2
643		B	253,1
644		A	291
645		A	305
646		C	373,2
647		B	448,2
648		B	382,2

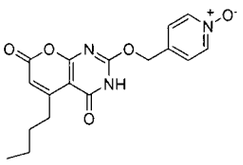
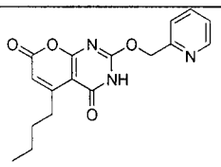
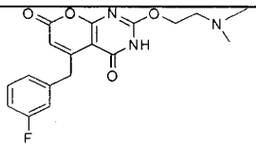
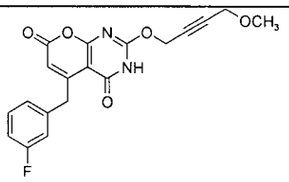
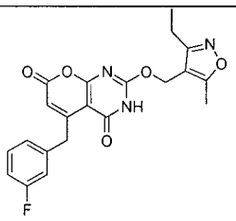
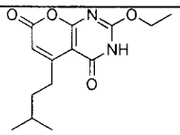
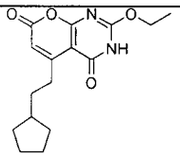
649		B	368
650		B	329,2
651		B	520
652		A	280,1
653		C	399,2
654		A	M+Na 391,2
655		B	346,2
656		C	332

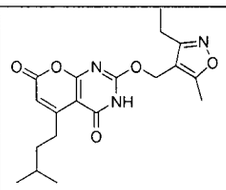
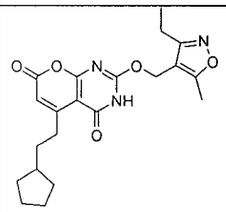
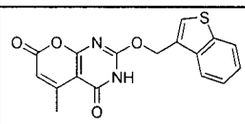
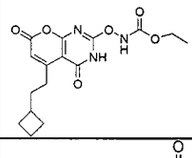
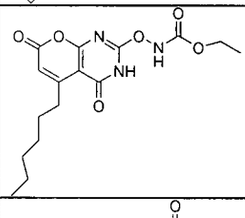
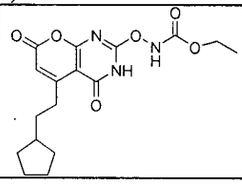
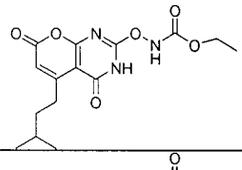
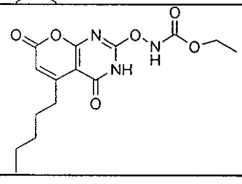
657		C	290
658		B	291
659		C	399,2
660		C	317,2 (M+Na)
661		B	371,2
662		A	399,2
663		C	439,2
664		B	305

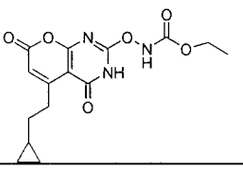
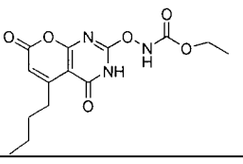
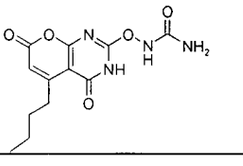
665		C	304
666		A	332
667		B	346
668		C	304
669		B	319
670		A	319,2
671		A	305
672		B	305

525

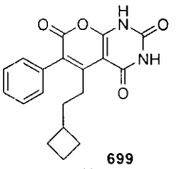
673		B	359
674		A	303
675		B	346
676		B	360
677		A	315
678		B	331
679		A	333
680		A	319

681		C	344,2
682		C	328,2
683		C	360,2
684		A	371,2
685		B	412,2
686		B	279,2
687		B	305,2

688		B	374,2
689		B	400,2
690		C	241,1
691		A	350,2
692		A	352,2
693		B	364,2
694		C	338,2
695		A	338,2

696		B	336,2
697		--	324,2
698		--	295,2

EJEMPLO DE PREPARACIÓN 699



699



699a 699b

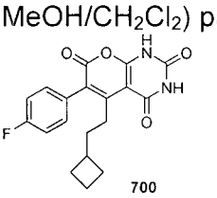
Se agregó el compuesto **699a** (0,925 g, 3,53 mmol) a DMF (10 ml) en un balón equipado con una barra agitadora magnética. Se agregó *N*-yodosuccinimida (1,59 g, 7,05 mmol) en porciones y la mezcla de reacción se calentó a 50°C hasta el día siguiente. Después del enfriado a temperatura ambiente, se agregó H_2O (25 ml). El producto se filtró, se lavó con agua seguido de éter para dar una mezcla blanca polvorienta (> 95% rendimiento). El producto **699b** se usó como tal en el próximo paso sin otra purificación.



699b 699

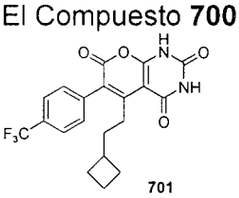
Se agregó el compuesto **699b** (0,1 g, 0,258 mmol) a 5 ml de DME/H_2O (4:1) en un balón de 10 ml. Se agregó $PdCl_2(PPh_3)_2$ (0,018 g, 0,0258 mmol),

Na_2CO_3 (0,082 g, 0,774 mmol), y ácido fenilborónico (0,057 g, 0,464 mmol) y la mezcla de reacción se reflujó (80°C) durante 6 h. Después del enfriado, la mezcla se concentró y se purificó mediante cromatografía flash (CH_2Cl_2 a 5% MeOH/CH_2Cl_2) para proporcionar el compuesto **699**.



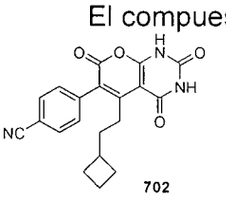
700

El Compuesto **700** se preparó de la misma manera que en el ejemplo **699**.



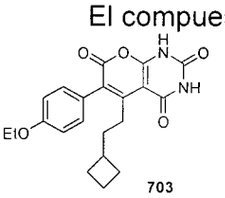
701

El compuesto **701** se preparó de la misma manera que en el ejemplo **699**.



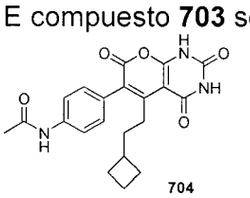
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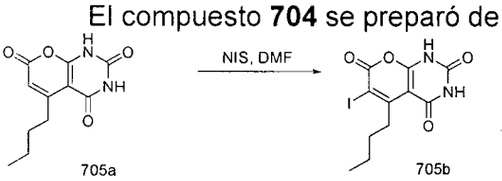
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E compuesto **703** se preparó de la misma manera que en el ejemplo **699**.



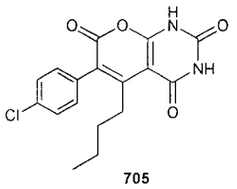
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El compuesto **704** se preparó de la misma manera que en el ejemplo **699**.



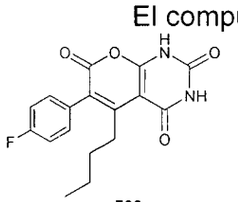
705a 705b

El compuesto **705b** se preparó de la misma manera que en el ejemplo **699b**.



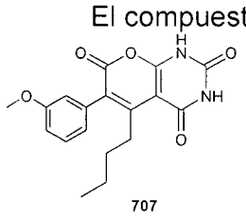
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El compuesto **705** se preparó del mismo modo que el compuesto **699.**



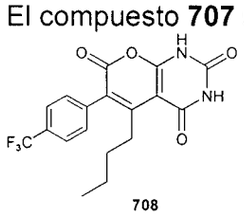
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El compuesto **706** se preparó del mismo modo que el compuesto **699.**



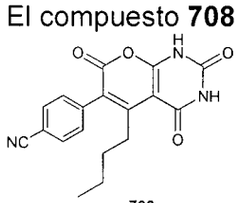
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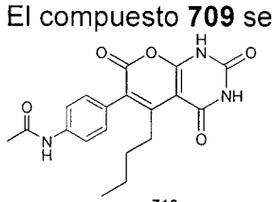
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709

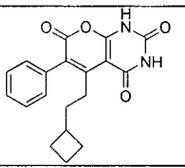
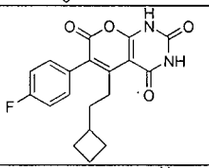
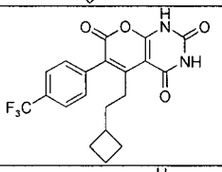
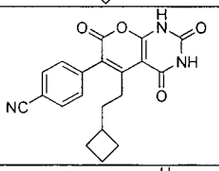
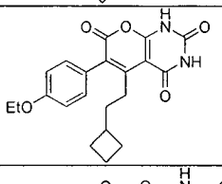
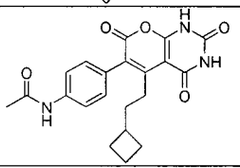
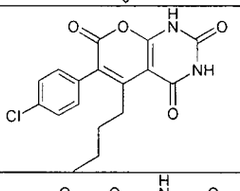
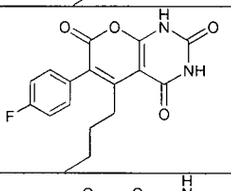
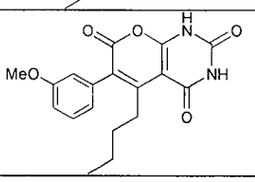
El compuesto **709** se preparó del mismo modo que el compuesto **699.**

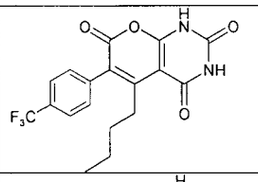
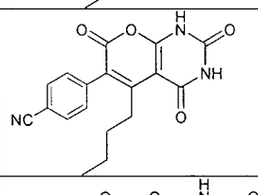
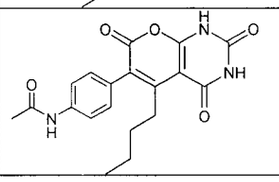


710

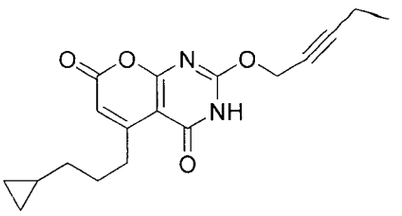
El compuesto **710** se preparó del mismo modo que el compuesto **699.**

Compuesto	ESTRUCTURA	ND EC_{50}	Electroaspersión

Nº		AMPc (nM)	LCMS [M+1]+
699		C	339,2
700		C	357,2
701		C	407,2
702		C	364,2
703		C	383,2
704		C	396,2
705		C	347,2
706		C	331,2
707		C	343,2

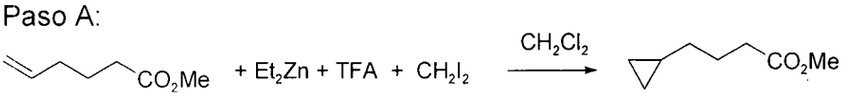
708		B	381,2
709		C	338,2
710		C	370,2

EJEMPLO DE PREPARACIÓN 711



711

Paso A:

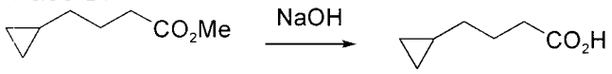


711 A

A una solución de dietil zinc (3,0 eq, 1,0 M en THF) en CH_2Cl_2 (0,2 M) a 0°C, se agregó TFA (3,0 equiv, gota a gota mediante un embudo de adición). La mezcla resultante se agitó a 0ºC durante 15 minutos después de haberse completado el agregado. Luego se agregó CH_2I_2 (3,0 equiv) a la mezcla de reacción gota a gota mediante una jeringa y la reacción resultante se agitó a 0ºC durante 10 minutos. A la reacción resultante se agregó metiléster del ácido hex-5-enoico (1,0 equiv) y la mezcla de reacción se agitó durante aproximadamente 15 horas, permitiendo que la mezcla llegue a temperatura ambiente. La reacción luego se desactivó mediante el cuidadoso gregado de HCl 1N acuoso y se extrajo

la capa acuosa con CH_2Cl_2 (3x). Las fases orgánicas combinadas se lavaron con agua, luego con salmuera, luego se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el compuesto **711A** en rendimiento cuantitativo.

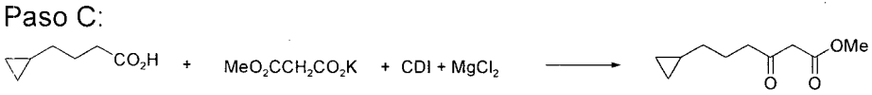
Paso B:



711A **711B**

Se agregó una solución NaOH acuosa (2,0 equiv, 2,0 N) a una solución de **711A** (1,0 equiv) en THF y MeOH (v/v = 2/1, 0,2 M) a temperatura ambiente. La mezcla se agitó durante 4 horas y el solvente luego se eliminó al vacío. La solución acuosa resultante se extrajo con éter y la solución resultante luego se acidificó utilizando HCl 5 M. La capa acuosa se extrajo con éter (3x) y las fases orgánicas combinadas se lavaron con agua, luego con salmuera, luego se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el compuesto **711B** en rendimiento cuantitativo.

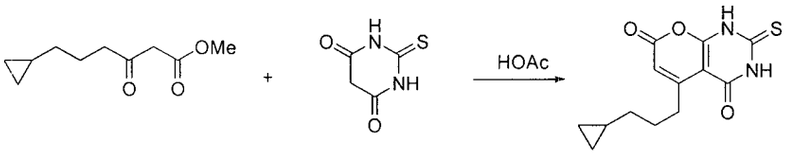
Paso C:



711B **711C**

Se agregó CDI (1,2 equiv) a una solución de **711B** en THF (0,5 M) a temperatura ambiente. La mezcla de reacción se agitó durante 1 hora, luego se agregaron monometiléster de melonato, sal potásica (1,5 equiv) y $MgCl_2$ (1,0 equiv). La reacción resultante se agitó durante aproximadamente 15 horas y luego se desactivó con HCl acuoso (1,0 N). La capa acuosa se extrajo con EtOAc (3x). Las fases orgánicas combinadas se lavaron con agua, luego con salmuera, luego se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el compuesto **711C** en rendimiento cuantitativo.

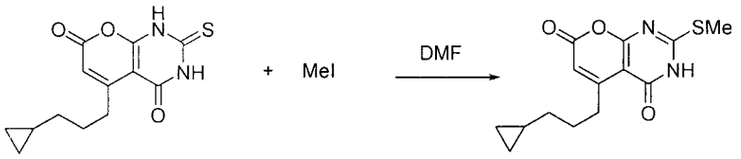
Paso D:



711C **711D**

Una mezcla de 4,6-dihidroxi-2-mercapto-pirimidina (1,0 eq) y **711C** (1,25 equiv) en HOAc (1,0 M) se calentó a reflujo y se agitó a esta temperatura durante aproximadamente 15 horas. La mezcla de reacción luego se enfrió y se concentró al vacío y el residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice para proporcionar el compuesto **711D** (37% rendimiento).

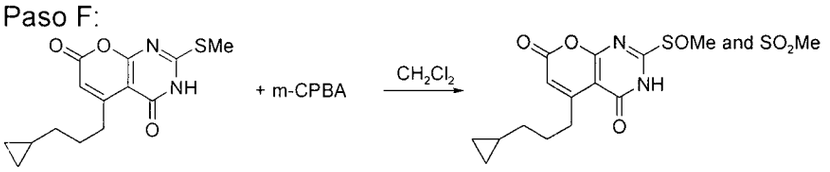
Paso E:



711D **711E**

Se agregó MeI (1,8 equiv) a una suspensión de **711D** (4,0 g, 17,86 mmol) en DMF (0,3 M) a temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente durante aproximadamente 15 horas, luego se vertió en agua y la solución resultante se filtró a través de un embudo sinterizado. El material sólido recolectado se lavó con agua y se secó bajo vacío para proporcionar el compuesto **711E** (96% rendimiento).

Paso F:

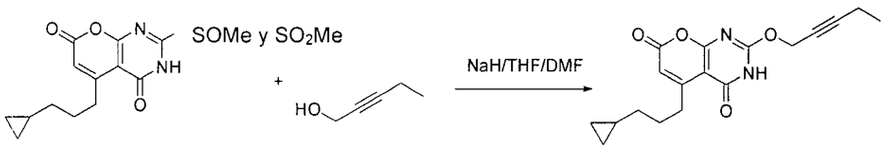


711E **711F**

Se agregó *m*-CPBA (2,0 equiv) a una suspensión de **711E** (1,0 equiv) en CH_2Cl_2 (0,15 M) a temperatura ambiente. Después de agitar durante 3 horas, la reacción se desactivó con Me_2S (3,0 eq) y se concentró al vacío para proporcionar

el producto en bruto que se lavó con Hexano/EtOAc (v/v = 3/1) para proporcionar el compuesto **711F** como una mezcla de sulfona y sulfóxido (90% rendimiento, w/w = 1/2).

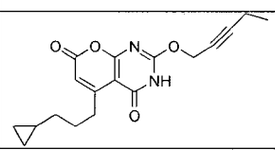
Paso G:

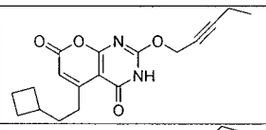
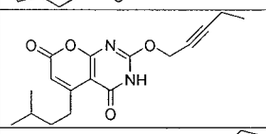
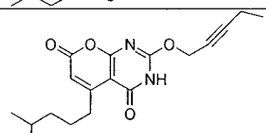
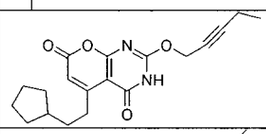
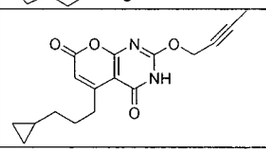
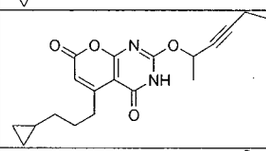
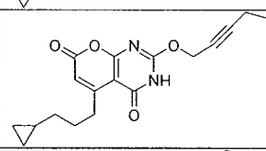
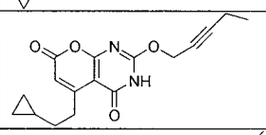
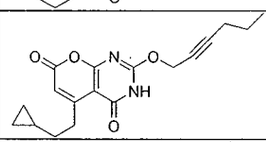
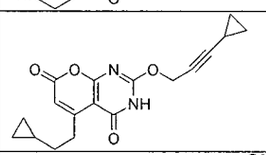
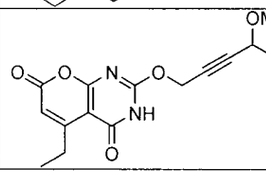


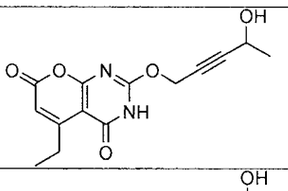
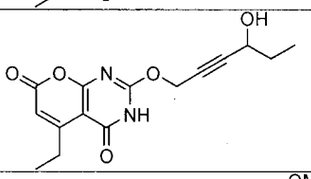
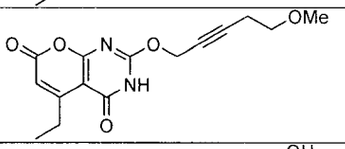
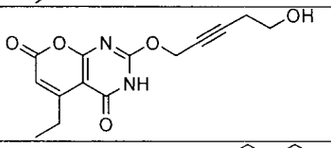
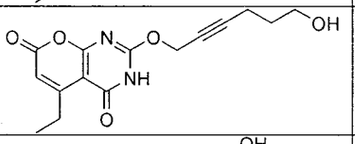
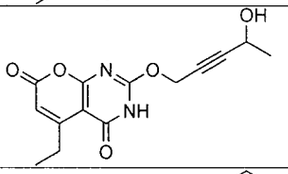
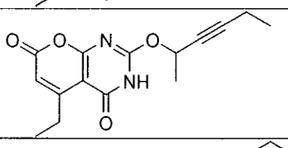
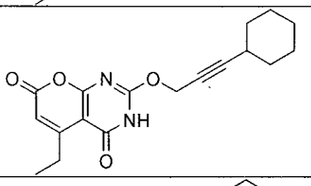
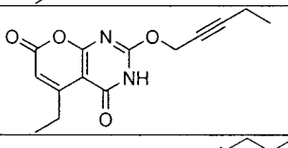
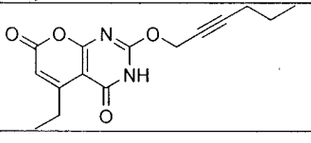
711F **711G**

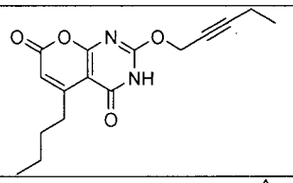
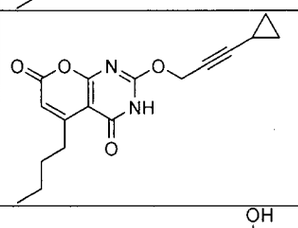
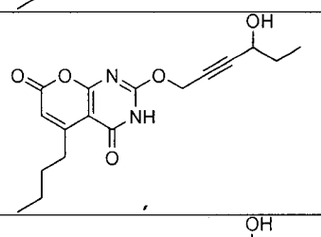
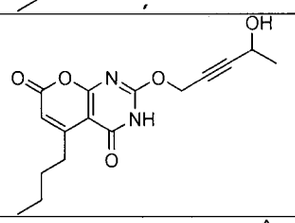
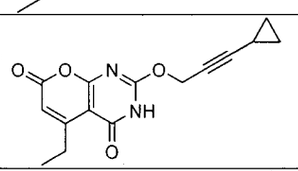
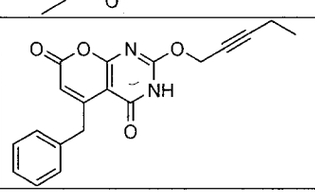
Se agregó pent-2-ine-1-ol (2,0 equiv) gota a gota a una suspensión de NaH (2,0 equiv) en THF a temperatura ambiente. La mezcla de reacción se agitó durante 1 hora para proporcionar una solución clara a la que luego se agregó gota a gota una solución de **711F** (1,0 equiv) en DMF. La mezcla de reacción se agitó durante aproximadamente 2 horas a temperatura ambiente y luego se desactivó con HOAc (2,0 equiv). La solución resultante se diluyó con EtOAc y se lavó sequencialmente con HCl 0,1 M, agua y salmuera, luego se secó sobre $MgSO_4$ y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: hexano/CH_2Cl_2/EA (v/v/v = 7/3/2)) para proporcionar el compuesto **711** (50% rendimiento). Electroaspersión MS $[M+1]^+$ 329,2.

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **712-739**:

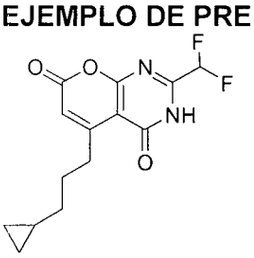
Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
712		329,2

713		329,2
714		317,2
715		331,2
716		343,2
717		315,2
718		343,2
719		357,2
720		315,2
721		329,2
722		327,2
723		305

724		305
725		319
726		305
727		291
728		305
729		291
730		289
731		329
732		275
733		289

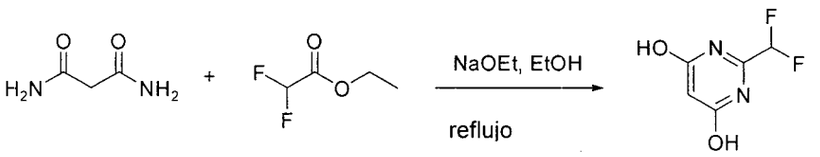
734		303
735		315
736		333
737		319
738		287
739		337,1

EJEMPLO DE PREPARACIÓN 740



740

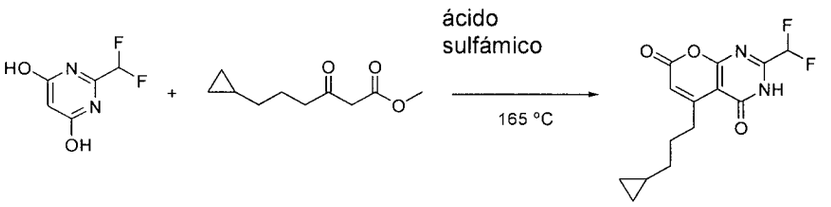
Paso:1



740A

Una mezcla de malonamida (40,00 g, 392,22 mmol) y NaOEt (21%, 292,00 ml, 784,53 mmol) en MeOH (1 l) se agitó a temperatura ambiente durante 1 hora. Luego se agregó etiléster del ácido difluoroacético (58,00 g, 467,74 mmol) a la mezcla de reacción y la reacción se calentó a reflujo y se agitó a esta temperatura durante aproximadamente 15 horas. La mezcla de reacción se enfrió a temperatura ambiente y el producto sólido se recolectó por filtración y se lavó secuencialmente con EtOH, EtOAc y hexano, luego se apiró a sequedad bajo vacío para proporcionar 45,0 g del producto como un polvo blanco (71% rendimiento).

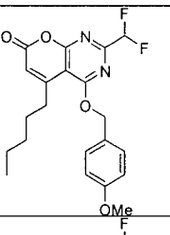
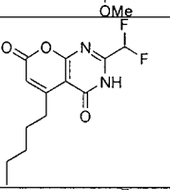
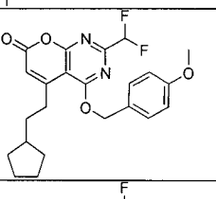
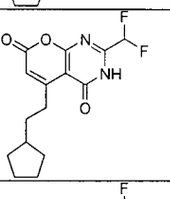
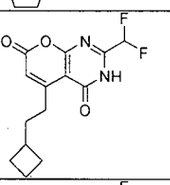
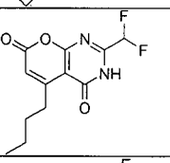
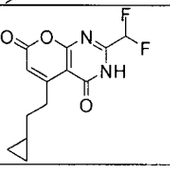
Paso:2

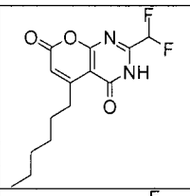
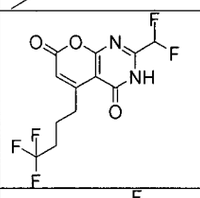
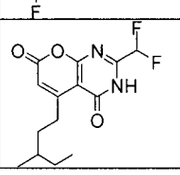


740A **740B** **740**

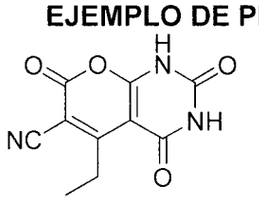
Una mezcla del Compuesto **740A** (10,50 g, 64,81 mmol), compuesto **740B** (14,90 g, 80,98 mmol), y ácido sulfámico (6,29 g, 64,84 mmol) se calentó a 165ºC y se agitó a esta temperatura durante 30 minutos. La mezcla de reacción luego se enfrió a aproximadamente 70ºC, luego se vertió en una mezcla de CH_2Cl_2/MeOH (1:1, 50 ml) y la solución resultante se filtró. El sólido recolectado por filtración luego se lavó repetidamente con CH_2Cl_2/MeOH (1:1) y se combinaron los eluatos y se concentró al vacío para proporcionar el compuesto **740** como cristales blancos (3,30 g, 17%).

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **742**, **743**, **745**, **746**, **748**, **750**, **752**, **754**, **757** y **812**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
742		405,2
743		285,1
745		431,2
746		311,2
748		297,2
750		271,1
752		283,2

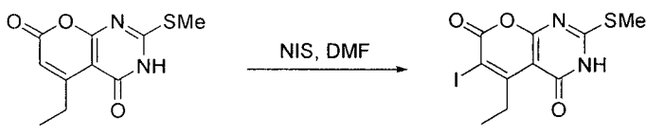
754		299,2
757		325,2
812		299,2

EJEMPLO DE PREPARACIÓN 758



758

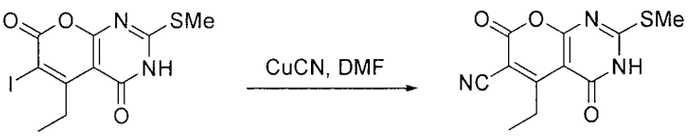
Paso A:



758A **758B**

Se agregó NIS (6,72 g, 29,9 mmol) a una solución de **758A** (5 g, 21 mmol) en DMF (70 ml). La mezcla de reacción se calentó a 50 °C y se agitó a esta temperatura durante aproximadamente 15 horas. La mezcla de reacción luego se enfrió a temperatura ambiente y se agregó agua (100 ml). La solución resultante se filtró, y el sólido recolectado se lavó con agua luego éter para proporcionar el compuesto **758B** como un polvo amarillo (65% rendimiento) que se utilizó sin otra purificación.

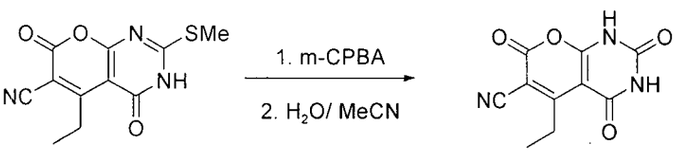
Paso B:



758B **758C**

Se agregó CuCN (0,246 g, 2,75 mmol) a una solución de **758B** (1,0 g, 2,75 mmol) en DMF (10 ml). La reacción se reflujó durante 2 h, bajo N_2. Luego de enfriar a temperatura ambiente, se agregó H_2O (50 ml). El producto precipitado se filtró, se lavó con agua, luego con éter para proporcionar **16** (95% rendimiento).

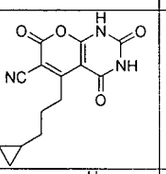
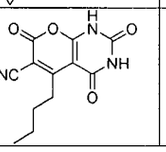
Paso C:



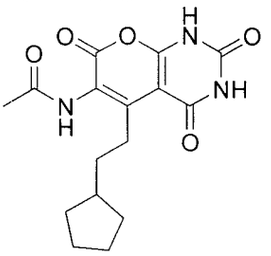
758C **758**

Se agregó *m*-CPBA (0,936 g, 4,18 mmol) a una solución de **758C** (0,55 g, 2,09 mmol) en CH_2Cl_2 (15 ml). La reacción resultante se agitó a temperatura ambiente durante 4 horas, luego se agregó Me_2S y la solución resultante se agitó durante otros 10 minutos y se concentró al vacío. El residuo resultante se diluyó con 10 ml CH_3CN/ H_2O (1:1) y la solución resultante se agitó a temperatura ambiente durante 12 horas luego se concentró al vacío y se purificó mediante TLC prep (15% MeOH/DCM) para proporcionar el compuesto **758**. Electroaspersión MS: $[MH^+]$ = 262,1

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **759** y **760**:

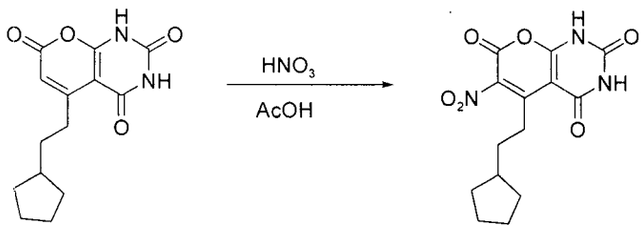
Compuesto Nº	Estructura	Electroaspersión LCMS $[M+1]^+$
759		288,2
760		262,1

EJEMPLO DE PREPARACIÓN 761



761

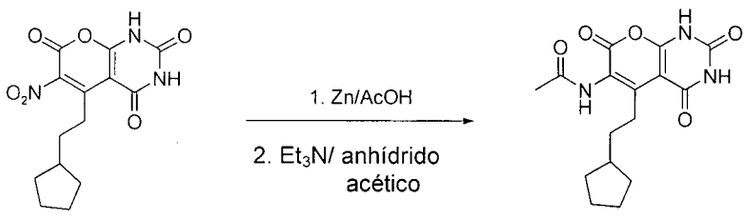
Paso A:



761A **761B**

Se agregó HNO_3 humeante (0,9 ml) gota a gota a una solución de **761A** (0,5 g, 1,81 mmol) en HOAc (1,8 ml) bajo N_2. La reacción se calentó a 100 °C y se agitó a esta temperatura durante 30 minutos, luego la mezcla de reacción se vertió en agua fría (5 ml). El precipitado formado se aisló y se lavó con acetonitrilo (1 ml) para proporcionar el compuesto **761B** (0,3 g, 51%). Electroaspersión MS: $[MH^+]$ = 322,2

Paso B:

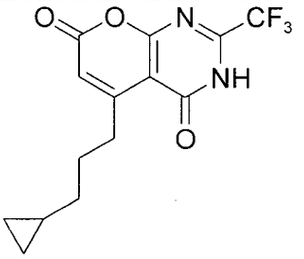


761B **761**

Se agregó Zn en polvo (0,47 g, 7,2 mmol) a una solución de **761B** (0,23 g, 0,72 mmol) en HOAc (3 ml) y MeOH (2 ml), y la reacción resultante se agitó a temperatura ambiente durante aproximadamente 18 horas. La reacción se filtró y el filtrado se concentró al vacío para proporcionar el residuo que se disolvió en CH_2Cl_2 (2 ml). A la solución resultante se agregó Et_3N (2 ml) seguido de anhídrido acético (2 ml). La reacción resultante se agitó a temperatura ambiente durante 24 horas, luego se concentró al vacío y el residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: $MeOH/CH_2Cl_2$ (v/v =

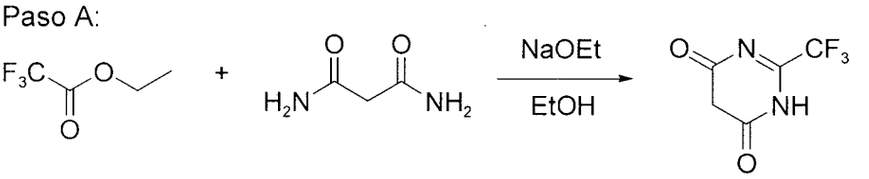
10/97)) para proporcionar el compuesto **761** (0,15 g, 62%). Electroaspersión MS: $[MH^+]$ = 334,2

EJEMPLO DE PREPARACIÓN 762



762

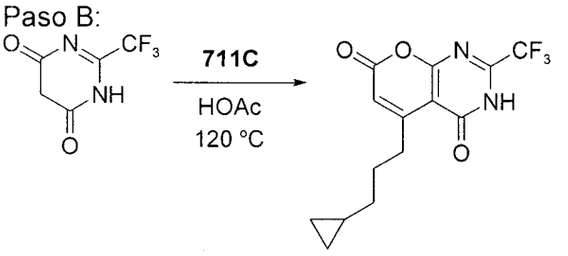
Paso A:



762A

Se agregó etiléster del ácido trifluoroacético (8,8 ml, 73,5 mmol) lentamente a una suspensión de malonamida (5 g, 49 mmol) y NaOEt (21% en EtOH, 36,5 ml, 98 mmol) en EtOH (50 ml). La reacción resultante se colocó bajo atmósfera de nitrógeno, se calentaron a reflujo y se agitó a esta temperatura durante aproximadamente 20 horas. La mezcla de reacción luego se filtró y el sólido color amarillo recolectado se lavó con EtOAc, luego con EtOH para proporcionar el compuesto **762A**.

Paso B:

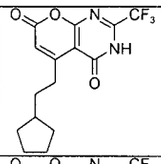
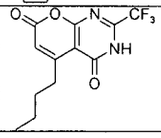


762A **762**

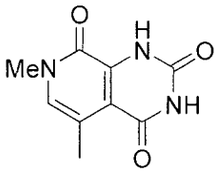
El compuesto **711C** (0,8 g, 4,2 mmol, preparado como se describió antes en el EJEMPLO DE PREPARACIÓN 711, paso C) se agregó a una solución de

762A (0,5 g, 2,8 mmol) en HOAc (1,5 ml). La reacción resultante se calentó a 120°C y se agitó a esta temperatura durante 20 horas, luego la reacción se enfrió a temperatura ambiente y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: 3% $MeOH/CH_2Cl_2$) seguido de TLC prep (5% $MeOH/CH_2Cl_2$) para proporcionar el compuesto **762**.

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **763** y **764**:

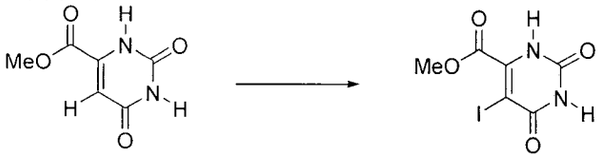
Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
763		329,2
764		289,2

EJEMPLO DE PREPARACIÓN 765



765

Paso A:

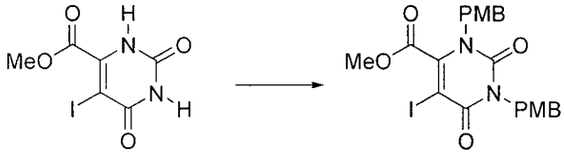


765A **765B**

Se agregó N-yodosuccinimida (40 g, 177 mmol) a una solución de **765A** (15 g, 88 mmol) en una mezcla de TFA-TFAA (300 ml, 30 ml) y la reacción

resultante se calentó a 85 °C y se agitó a esta temperatura durante aproximadamente 15 horas. La reacción luego se enfrió a temperatura ambiente y se concentró al vacío. El residuo resultante se distribuyó entre 200 ml de H_2O y 100 ml de EtOAc. El precipitado se recolectó y se lavó con H_2O y EtOAc, luego se secó al vacío para proporcionar el compuesto **765B** (20,2 g, 78%).

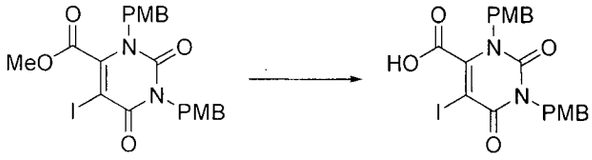
Paso B:



765B **765C**

Se agregaron Na_2CO_3 (27 g, 300 mmol) y PMBCl (34 ml, 300 mmol) a una solución de **765B** (20 g, 100 mmol) en DMF (300 ml). La solución resultante se calentó a 50 °C y se agitó a esta temperatura durante aproximadamente 15 horas. La reacción luego se enfrió a temperatura ambiente y se distribuyó entre H_2O (250 ml) y EtOAc (500 ml). La capa orgánica se separó y se lavó con H_2O, luego con salmuera, luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío. El residuo resultante se filtró a través de un taco de gel de sílice, se eluyó con EtOAc-heaxanos (1:10) seguido de EtOAc-hexanos (1:1). El filtrado se concentró al vacío y el residuo se recristalizó de DCM y hexanos para proporcionar **765C** (16,6 g, 31%).

Paso C:

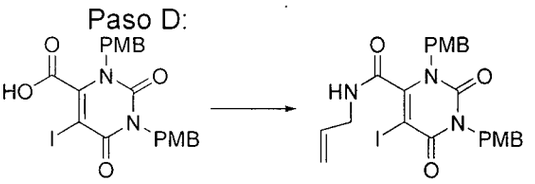


765C **765D**

Se agregó yoduro de litio (15,3 g, 114 mmol) a una solución de **765C** (15,3 g, 28,5 mmol) en EtOAc (300 ml). La solución resultante agitada se calentó a 85°C y se agitó a esta temperatura durante aproximadamente 15 horas. La

mezcla de reacción se enfrió a temperatura ambiente; luego se agregó agua (100 ml) y la solución resultante se transfirió a un embudo separador. La capa acuosa se separó y se llevó a un pH básico mediante el agregado de NaOH 1N, luego la solución basificada se lavó con éter. La capa acuosa luego se ajustó a un pH = 1 mediante el agregado de HCl 1N y la solución ácida resultante se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron con una solución 1 N de tiosulfato de sodio, se secó sobre $MgSO_4$, luego se filtró y se concentró al vacío para proporcionar el compuesto **765D** (13,5 g, 90%).

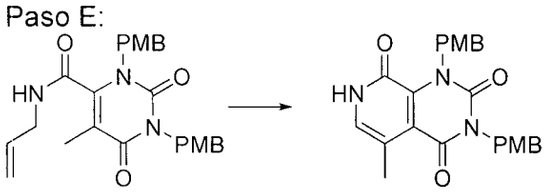
Paso D:



765D **765E**

Se agregó cloruro de oxalilo (0,2 ml, 2,32 mmol) a una solución de **765D** (1,0 g, 1,91 mmol) en CH_2Cl_2 (10 ml), seguido del agregado de una gota de DMF. La mezcla resultante se agitó a temperatura ambiente durante 30 minutos, luego se concentró al vacío. El residuo resultante se disolvió en CH_2Cl_2 (10 ml), y a la solución resultante se agregó alilamina (0,2 ml, 19,8 mmol) . La reacción resultante se agitó a temperatura ambiente durante aproximadamente 15 horas, luego la mezcla de reacción se diluyó con CH_2Cl_2 (10 ml) y se lavó con HCl 1N. La capa orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: EtOAc-hexanos, 1:1), para proporcionar el compuesto **765E** (0,61 g, 60%).

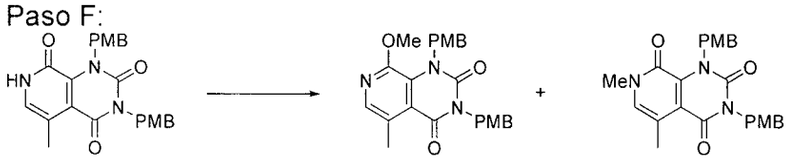
Paso E:



765E **765F**

En un tubo sellado, se agregaron Et_3N (0,42 ml, 2,99 mmol) y $Pd(OAc)_2$ (38 mg, 0,17 mmol) a una solución de **765E** (1,0 g, 1,91 mmol) en DMF (6 ml). La reacción resultante se calentó a 85°C y se agitó a esta temperatura durante aproximadamente 15 horas, luego se enfrió a temperatura ambiente y se filtró a través de Celite. El filtrado se concentró al vacío y el residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: EtOAc-hexanos, 1:1) para proporcionar el compuesto **765F** (0,27 g, 36%).

Paso F:



765F **765G** **765H**

Una solución de **765F** (262 mg, 0,60 mmol) en DMF/THF (1:1, 12 ml) se enfrió a 0°C y se agregó NaH (30 mg, 1,18 mmol, 95% de dispersión en aceite). La reacción resultante se agitó a 0ºC durante aproximadamente 30 minutos, luego se agregó yodometano (0,1 ml, 1,60 mmol) y la reacción se agitó a temperatura ambiente durante aproximadamente 15 horas. La reacción se desactivó con agua, y la capa acuosa se separó y se extrajo con CH_2Cl_2. Los extractos orgánicos combinados se secaron sobre $MgSO_4$ y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (eluyente: EtOAc-hexanos, 1:1) para proporcionar el compuesto **765G** (5 mg, 4% rendimiento) y **765H** (121 mg, 90%).

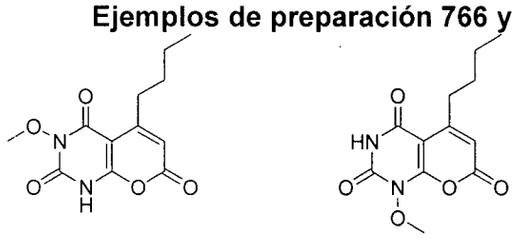
Paso G:



765H **765**

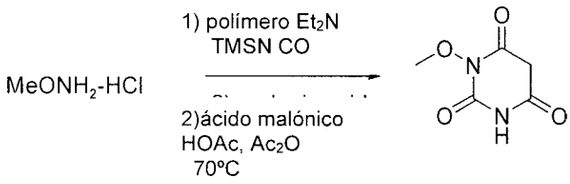
Se agregó TFA (0,5 ml) y TfOH (0,1 ml) a una solución de **765H** (100 mg, 0,22 mmol) en CH_2Cl_2 (6 ml). La reacción resultante se agitó a temperatura ambiente durante aproximadamente 15 horas, luego se concentró al vacío para proporcionar el residuo en bruto que se purificó utilizando TLC prep (eluyente: ácido acético/CH_2Cl_2/EtOAc, 1:10:10) para proporcionar el compuesto **765** (12 mg, 26%). Electroaspersión MS $[M+1]^+$ 208,1

Ejemplos de preparación 766 y 767



766 **767**

Paso A:

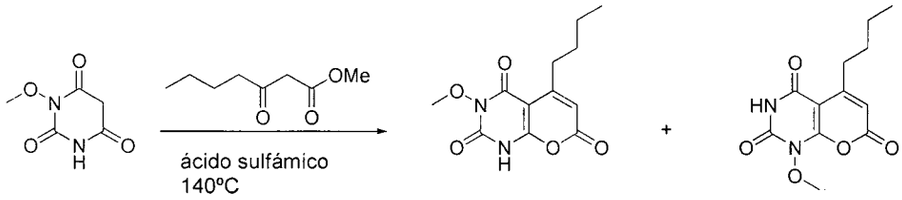


766A

Se agregó dietilaminometil-poliestireno (40 g, 3,2 mmol/g,128 mmol) a una solución de clorhidrato de metoxilamina (5,0 g, 60 mmol) en MeOH (300 ml). La mezcla de reacción se agitó durante 1 h. Luego, se agregó TMSNCO (8,1 ml, 60 mmol) y la solución se agitó durante 4 h. El polímero se filtró y se lavó dos veces

con MeOH (50 ml, each). Se eliminaron los volátiles y el residuo se disolvió en ácido acético (40 ml), luego se agregó ácido malónico (5,1 g, 60 mmol) y Ac_2O (40 ml). La mezcla se calentó a 70°C durante 10h. La reacción se concentró al vacío y el residuo se disolvió en MeOH (100 ml), se agitó durante 10 min. y se concentró. El residuo resultante se trituró en 1:1 EtOAc/Et2O y se filtró para obtener **34** (4,2 g).

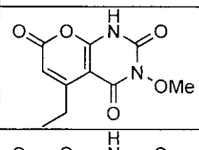
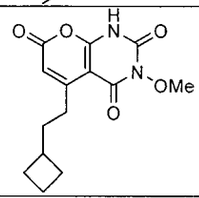
Paso B:

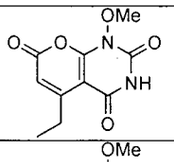
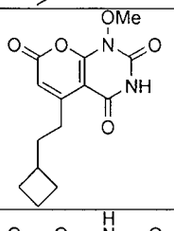
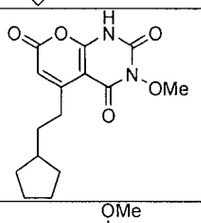
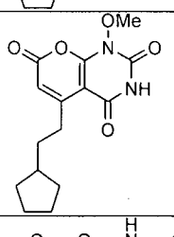
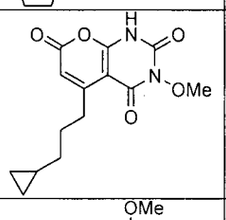
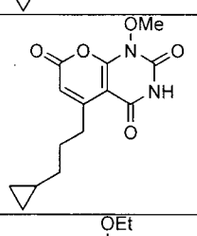
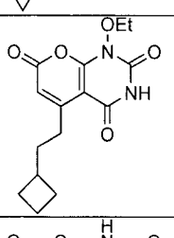
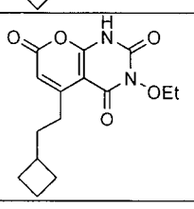


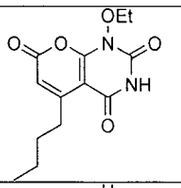
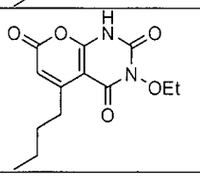
766A **766** **767**

Se agregó ácido sulfámico (613 mg, 6,32 mmol) a una mezcla de metiléster de ácido 3-oxo-heptanoico (2,0 g, 12,6 mmol) y **766A** (1,0 g, 6,32 mmol). La mezcla se calentó a 140 °C durante 4 horas. El residuo resultante se disolvió en 10 ml de MeOH, se filtró y se separó utilizando HPLC Gilson para obtener los compuestos **766** y **767** puros. Electroaspersión MS $[M+1]^+$ 267,1

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **768-779**:

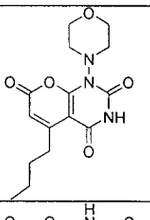
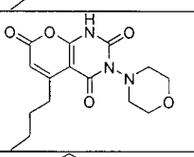
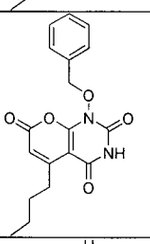
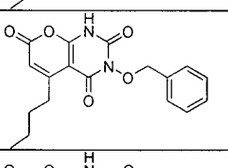
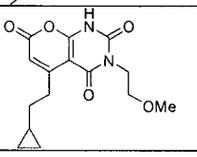
Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
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769		293,1

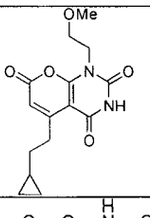
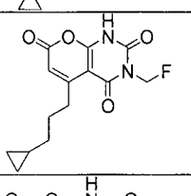
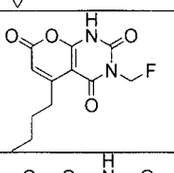
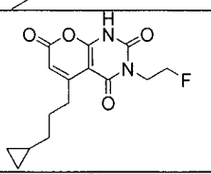
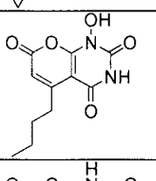
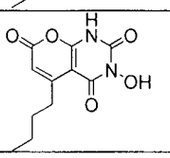
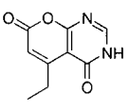
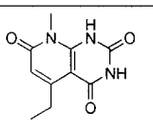
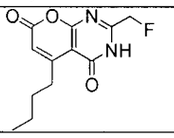
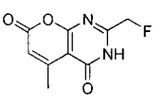
770		293,1
771		292,2
772		306,3
773		306,31
774		ND
775		ND
776		307,1
777		307,1

778		281,1
779		281,1

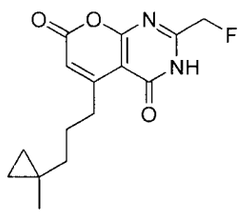
ND = no disponible

Otros compuestos ilustrativos de fórmula (I), incluyen pero sin ser limitativo los compuestos **796-810**, que se detallan a continuación:

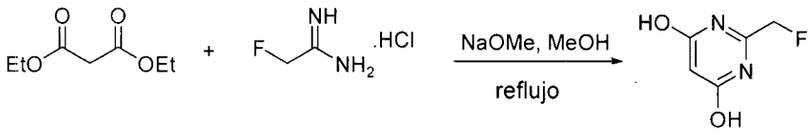
Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
796		322,2
797		322,2
798		343,2
799		343,2
800		307,2

801		307,2
802		295,2
803		269,1
804		309,2
805		253,1
806		253,1
807		193,1
808		222,2
809		253,1
810		211,1

EJEMPLO DE PREPARACIÓN 811



811

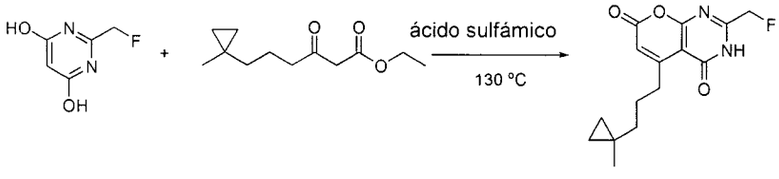


811A

Paso A:

Una solución de dietilmalonato (2,96 g, 18,48 mmol) y NaOMe (25% en peso en MeOH, 10,75 g, 49,76 mmol) se agregó a una solución de clorhidrato de 2-fluoroacetamidina (2,0 g, 17,77 mmol) en MeOH (20 ml). La reacción resultante se calentó a reflujo y se agitó a esta temperatura durante aproximadamente 15 horas. La mezcla de reacción se enfrió a temperatura ambiente, se concentró al vacío, y el residuo resultante se diluyó con agua (20 ml). La solución resultante se neutralizó utilizando HCl conc. y el sólido formado se recolectó por filtración, se lavó secuencialmente con H_2O y Et_2O, luego se aspiró a sequedad para proporcionar el compuesto **811A** como un polvo color marrón pálido (1,8 g, 69%).

Paso B

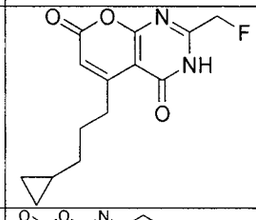
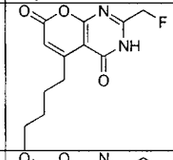
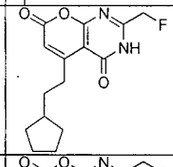
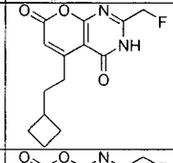
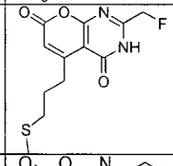
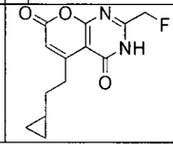


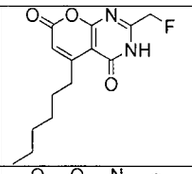
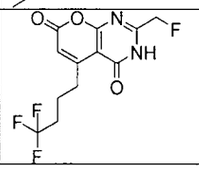
811A **811B** **811**

Una mezcla del Compuesto **811A** (0,1 g, 0,694 mmol), compuesto **811B** (0,295 g, 1,39 mmol) y ácido sulfámico (0,034 g, 0,347 mmol) se calentó a 130°C y se agitó a esta temperatura durante aproximadamente 2 horas. Las mezclas de reacción luego se enfriaron a temperatura ambiente y se vertieron en una mezcla

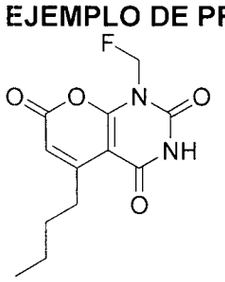
de CH_2Cl_2/MeOH (1:1, 1 ml). La solución resultante se purificó utilizando cromatografía flash en columna (eluyente: gradiente de 20% a 50% EtOAc/hexanos) para proporcionar el compuesto **811** como un sólido blanco.

Utilizando el método que se describió previamente, y los materiales apropiados, se prepararon los compuestos **741**, **744**, **747**, **749**, **751**, **753**, **755** y **756**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
741		279
744		267,1
747		293,2
749		279,2
751		285,2
753		265,1

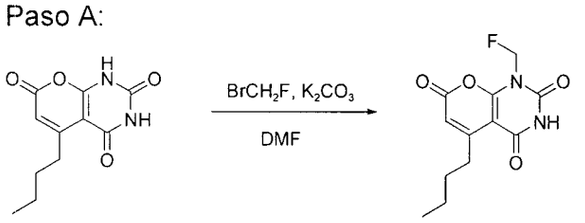
755		281,2
756		307,2

EJEMPLO DE PREPARACIÓN 813



813

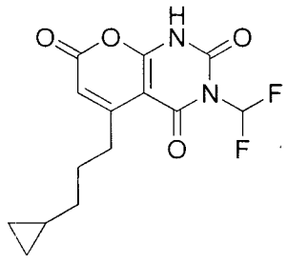
Paso A:



102 **813**

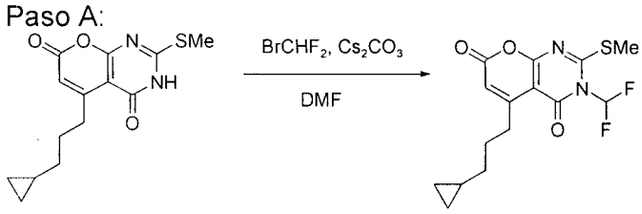
Se agregó K_2CO_3 (0,35 g, 2,54 mmol) a una solución de compuesto **102** (0,4 g, 1,69 mmol) y $BrCH_2F$ (0,21 g, 1,86 mmol) en DMF (5,0 ml) a temperatura ambiente. La mezcla resultante se agitó hasta el día siguiente. La mezcla de reacción se diluyó con acetato etílico y se neutralizó con solución acuosa HCl (0,5 N). La fase orgánica se lavó con agua (3x), se secó (Mg_2SO_4), y se concentró al vacío para proporcionar el producto en bruto que se purificó con PTLC (CH2Cl2/MeOH = 20/1) para dar el producto **813** (5 mg), Electroaspersión MS $[M+1]^+$ 269,1.

EJEMPLO DE PREPARACIÓN 814



814

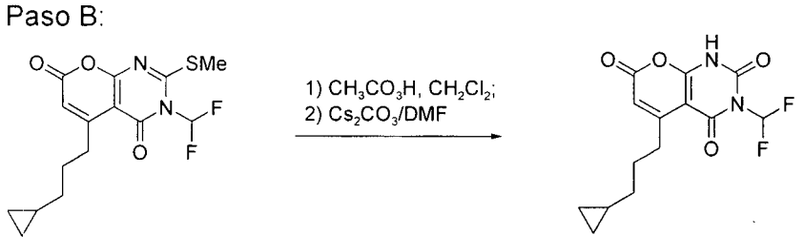
Paso A:



711E **814A**

Se agregó Cs_2CO_3 (1,30 g, 3,99 mmol) a una solución de compuesto **711E** (0,39 g, 1,33 mmol) y $BrCHF_2$ (0,79 g, 6,05 mmol) en DMF (5,0 ml) a temperatura ambiente. La mezcla resultante se agitó hasta el día siguiente. La mezcla de reacción se diluyó con acetato etílico y se neutralizó con solución acuosa HCl (0,5 N). La fase orgánica se lavó con agua (3x), se secó (Mg_2SO_4), y se concentró al vacío para proporcionar el producto en bruto que se purificó con cromatografía en columna de gel de sílice (gradiente EtOAc/hexano) para proporcionar el compuesto **814A** (0,15 g).

Paso B:

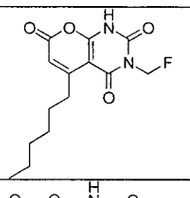
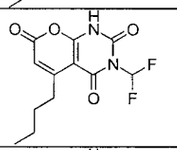
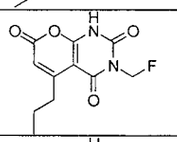
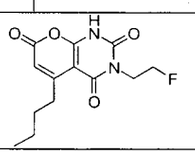
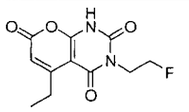


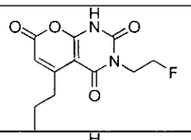
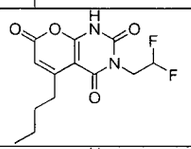
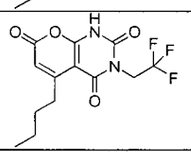
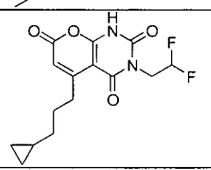
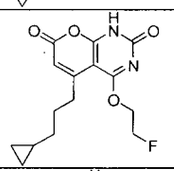
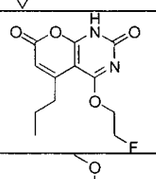
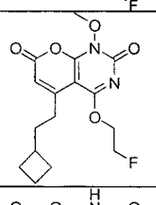
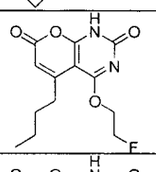
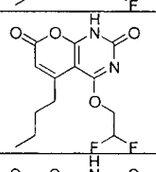
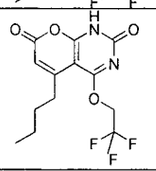
814A **814**

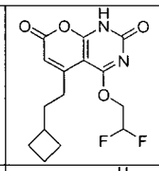
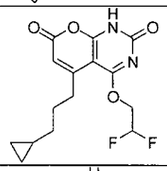
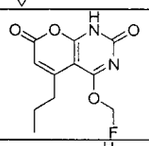
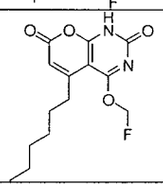
Se agregó CH_3CO_3H (0,30 ml, 1,4 mmol) a temperatura ambiente a una solución de **814A** (80 mg, 0,234 mmol) en CH_2Cl_2 (2,0 ml). La mezcla se agitó

durante 3 horas antes de ser desactivada con Me_2S (10,0 eq.). La mezcla de reacción se diluyó con acetato etílico y se lavó con agua (3x). La fase orgánica se lavó con salmuera, se secó (Mg_2SO_4), y se concentró al vacío para proporcionar el producto en bruto DMF (2,0 ml) y se trató con Cs_2CO_3 (91,6 mg, 0,281 mmol). La mezcla se agitó durante 1 hora antes de que se diluyó con acetato etílico y se neutralizó con solución acuosa HCl (0,5 N). La fase orgánica se lavó con agua (3x), se secó (Mg_2SO_4), y se concentró al vacío para proporcionar el producto en bruto que se purificó con separación Gilson de fase reversa para proporcionar el compuesto **814** (60 mg), Electroaspersión MS $[M+1]^+$ 313,2.

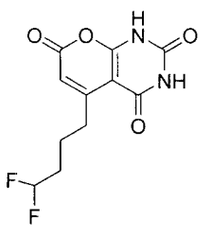
Utilizando el método que se describió previamente en los Ejemplos de preparación 813 y 814, y sustituyendo el compuesto bromo apropiado en el Paso A, se prepararon los Compuestos **815-833**:

Compuesto Nº	**Estructura**	**Electroaspersión LCMS $[M+1]^+$**
815		297,2
816		287,2
817		255,1
818		283,2
819		255,1

820		269,1
821		301,2
822		319,2
823		327,2
824		309,2
825		269,1
826		339,2
827		283,2
828		301,2
829		319,2

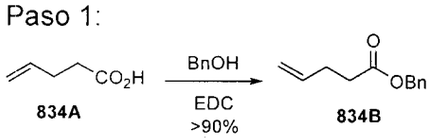
830		327,2
831		327,2
832		255,1
833		297,2

EJEMPLO DE PREPARACIÓN 834



834

Paso 1:

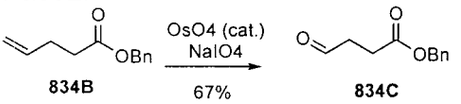


834A **834B**

A una solución de ácido 4-pentenoico (**834A**, 60 g, 0,594 mol) y alcohol bencílico (56 ml, 0,54 mol) en diclorometano (1 l) se agregó EDC (207 g, 1,08 mol) a 0°C y la reacción se agitó hasta que se volvió homogénea (~5 min). Luego se agregó DMAP (6,7 g, 0,054 mol) y la mezcla de reacción se permitió calentar a temperatura ambiente, luego se agitó bajo nitrógeno por otras 2 horas. La mezcla de reacción se lavó con HCl 1N (aq.), luego con $NaHCO_3$ sat. (ac.), luego se secó

sobre sulfato de sodio y se concentró al vacío para proporcionar el compuesto **834B** en un rendimiento aproximadamente cuantitativo (>95%).

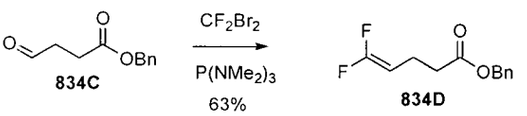
Paso2:



834B **834C**

A una solución de compuesto **834B** (2,3 g, 0,012 mol) y 4% de tetraóxido de osmio en agua (3 ml, 0,04 eq) en 3:1 (v/v) THF/H_2O (45 ml:15 ml) se agregó peryodato de sodio (7,7 g, 0,036 mol) y la reacción resultante se agitó bajo nitrógeno a temperatura ambiente hasta el día siguiente. Luego se agregó peryodato de sodio y se formó un precipitado de la reacción exotérmica resultante. La mezcla de reacción se filtró, se secó sobre sulfato de sodio y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (0-20% EtOAc/Hexano) para proporcionar el compuesto **834C** (1,6 g, 0,083 mol, 67%).

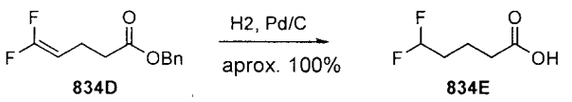
Paso 3:



834C **834D**

A una solución de triamida de hexametilo fosfórica (25,4 g, 0,156 mol) en THF (300 ml) a -78°C se agregó dibromodifluorometano (16,4 g, 0,078 mol) y la suspensión resultante se permitió calentar a temperatura ambiente. Se agregó el compuesto **834C** (7,5 g, 0,039 mol) y RM se reflujó a 66°C bajo nitrógeno hasta el día siguiente. La mezcla de reacción se filtró, se secó sobre sulfato de sodio y se concentró al vacío. El residuo resultante se purificó utilizando cromatografía flash en columna en gel de sílice (0-10% EtOAc/Hexano) para proporcionar el compuesto **834D** (5,5 g, 0,024 mol, 62 %).

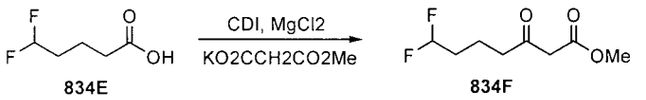
Paso 4:



834D 834E

A una solución de compuesto **834D** (5,5 g, 0,024 mol) en EtOAc (120 ml) se agregó 10% Pd/C (1,3 g, 0,05 eq) y la solución resultante se colocó en un agitador Parr bajo gas hidrógeno a 50 psi hasta el día siguiente. La mezcla de reacción luego se filtró y el filtrado se concentró al vacío para proporcionar el compuesto **834E** (3,3 g, 0,024 mol, >99%).

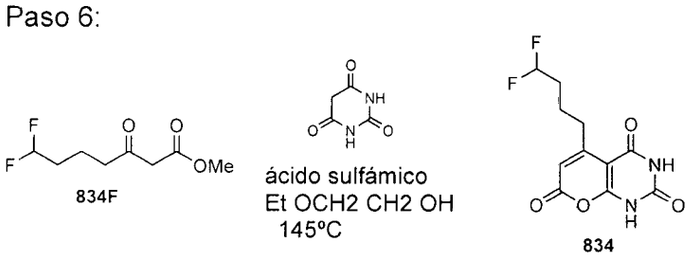
Paso 5



834E 834F

A la solución del compuesto **834E** (6 g, 0,0434 mol) en THF (150 ml) se agregó CDI (8,5 g, 1,2 eq) y la reacción resultante se agitó a temperatura ambiente bajo nitrógeno durante 1 hora. Luego se agregaron MgCl2 (4,1 g, 1 eq) y malonato de monometilo sal de potasio (10,2 g, 1,5 eq) y la reacción resultante se agitó a temperatura ambiente bajo nitrógeno hasta el día siguiente. La mezcla de reacción luego se distribuyó entre HCl 1N (ac.) (200 ml) y EtOAc (200 ml). Se colectó la capa acuosa y se extrajo con EtOAc (3 x 100 ml) y las capas orgánicas combinadas se lavaron con salmuera (50 ml), se secaron sobre sulfato de sodio, se filtró y se concentró al vacío. El residuo en bruto obtenido se purificó usando cromatografía flash en gel de sílice (0-20% EtOAc/Hexano) para proporcionar el compuesto **834F** (6,7 g, 0,0347, 80%)

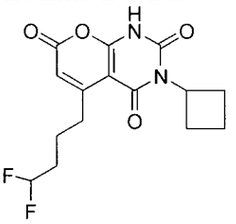
Paso 6:



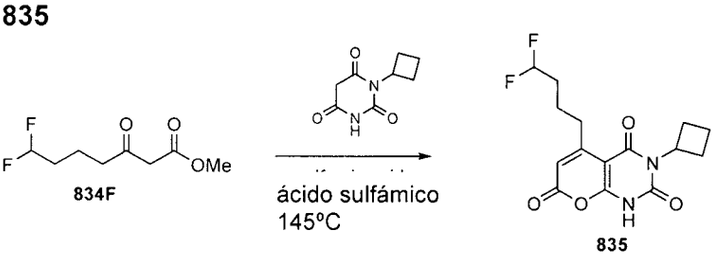
834F 834

A una solución de ácido barbitúrico (7 g, 1,1 eq) y el compuesto **834F** (9,7 g, 0,05 mol) en EtOEtOH (15 ml) se agregó ácido sulfámico (2,4 g, 0,5 eq) y la reacción resultante se agitó a 147°C durante 4 horas. La mezcla de reacción se concentró al vacío y el residuo resultante se trituró con agua caliente tres veces para proporcionar el compuesto **834** (2 g, 0,007 mol, 15 %).

EJEMPLO DE PREPARACIÓN 835

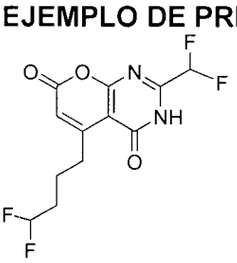


835

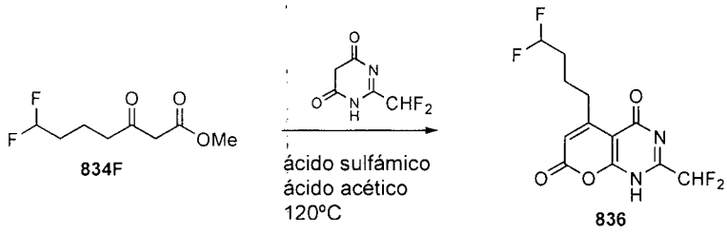


Se calentó ácido N-ciclobutilbarbitúrico (782, 4,3 mmol) y el compuesto **834F** (1 g, 1,2 eq) a 140°C durante 2 horas en presencia de ácido sulfámico (417 mg, 1 eq). La mezcla se suspendió en 10 ml de DMF y la suspensión luego se filtró. El filtrado se inyectó en una HPLC Gilson en veinte inyecciones y se purificó en una columna C18 eluyendo con 0,1% TFA en agua/acetonitrilo (gradiente 10-100% agua/acetonitrilo a un caudal de 25 ml/min) para proporcionar el compuesto **835** (tiempo de retención: 10,1 min; 120 mg, 0,037 mmol, 9%).

EJEMPLO DE PREPARACIÓN 836

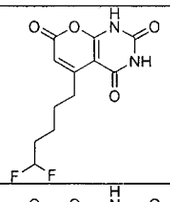
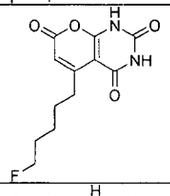
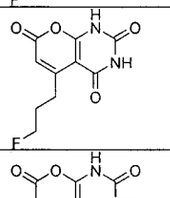
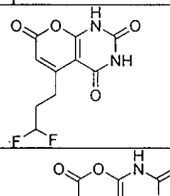
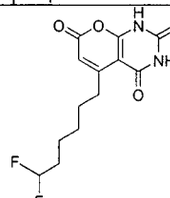
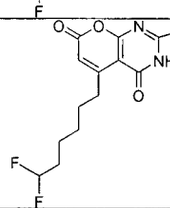
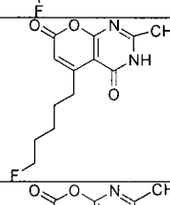
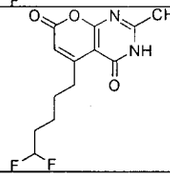


836



A una mezcla de ácido difluorobarbitúrico (1 g) y el compuesto **834F** (1 g) en un vial para microondas de 15 ml se agregó ácido acético (3 ml). El vial se selló y la solución resultante so procesó con microondas a 180°C durante 20 minutos. La mezcla de reacción luego se concentró al vacío *y* se purificó utilizando cromatografía flash en gel de sílice (gradiente de elución de 0-80% EtOAC/Hexano). El UV azul resultante de la elución de la columna se recolectó y se concentró al vacío y el residuo resultante se purificó utilizando TLC prep (2:1 EtOAc/Hexano) para proporcionar el compuesto **836** (40 mg, 3%).

Utilizando los métodos que se describieron antes en Ejemplos de preparación **834-836** con el difluoro β-ceto éster adecuado y ácido barbitúrico o un derivado de ácido barbitúrico, se prepararon los Compuestos **837-844**:

Compuesto Nº	Estructura
837	
838	
839	
840	
841	
842	
843	
844	

Ensayo del receptor del ácido nicotínico

La actividad agonista del receptor del ácido nicotínico de los compuestos de la invención se determinó siguiendo la inhibición de la acumulación de AMPc estimulada por forscolina en las células, utilizando el kit de detección de AMPc MesoScale Discovery de acuerdo con las instrucciones del fabricante. En resumen, se recolectaron enzimáticamente células ováricas de hámster chino (CHO) que expresan el receptor recombinanate humano del ácido nicotínico (NDR), se lavaron 1 vez en solución salina bufferizada con fosfato (PBS) y se resuspendieron en PBS que contiene IBMX 0,5 mM a $3x10^6$ células/ml. Se agregaron 10 µl de la suspensión con células a cada cavidad de una placa de 384-cavidades que contenía 10 µl del compuesto de ensayo. Los compuestos de ensayo se diluyeron con PBS que contenía 6 µM de forscolina. Las placas se incubaron durante 30 minutos a temperatura ambiente después de la adición de células. Se agregó el buffer de lisis que contenía AMPc-Tag a cada cavidad (10 µl/cavidad) como se indica en las instrucciones del fabricante. Luego las placas se incubaron de 45 minutos hasta el día siguiente. Previo a la lectura, se agregaron 10 µl de buffer reconocido a cada cavidad, y se leyó la placa en un dispositivo de imagen 6000 plate imager. La señal se convertió a la concentración de AMPc utilizando una curva estándar en cada placa. Los valores EC_{50} del compuesto se determinaron a partir de gradientes de concentración de los compuestos de ensayo.

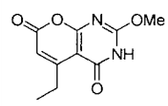
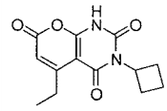
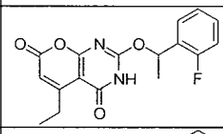
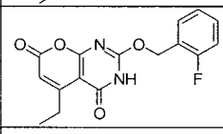
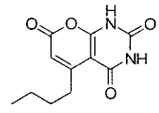
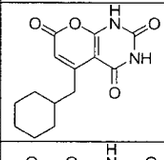
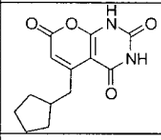
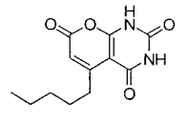
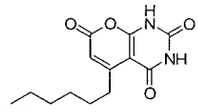
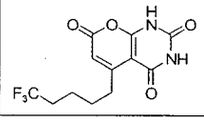
Los compuestos de fórmula (I) de la presente invención, y las sales, solvatos o ésteres de los mismos, presentan valores EC_{50} de AMPc inferiores que aproximadamente 10.000 nM, de preferencia aproximadamente 1000 nM o inferior, de mayor preferencia aproximadamente 500 nM o inferior, incluso de mayor preferencia aún de aproximadamente 100 nM o inferior.

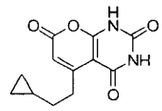
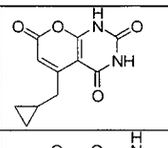
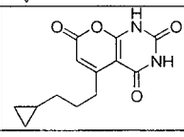
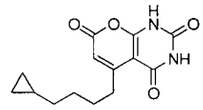
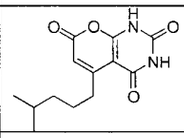
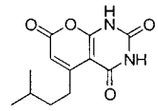
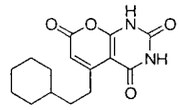
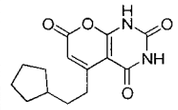
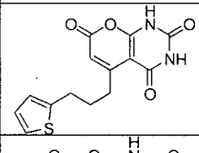
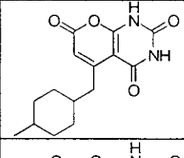
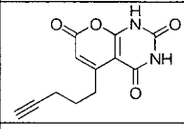
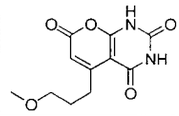
Los ejemplos 1, 5, 10, 29, 39, 71, 101-116, y 118-135 presentan valores EC_{50} de AMPc de 100 nM o inferiores.

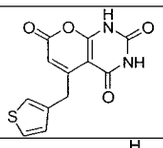
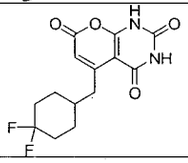
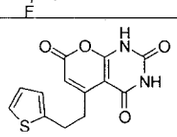
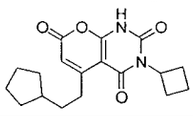
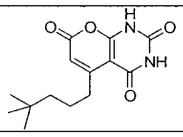
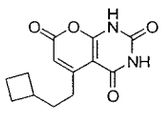
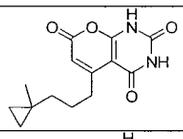
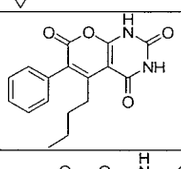
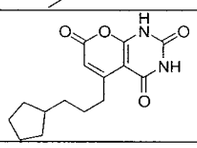
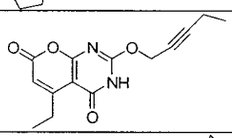
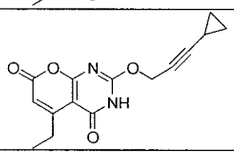
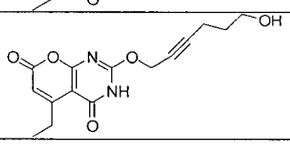
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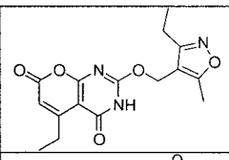
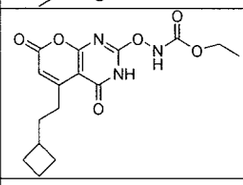
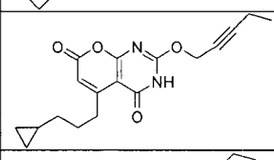
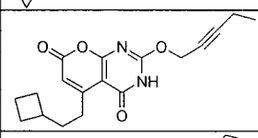
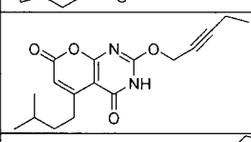
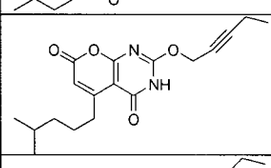
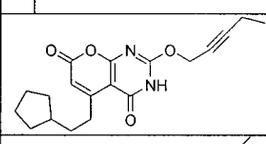
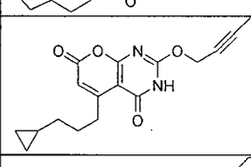
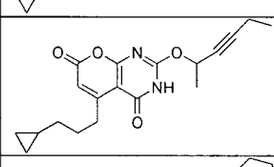
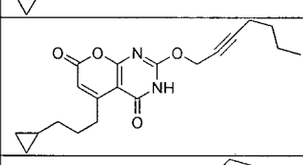
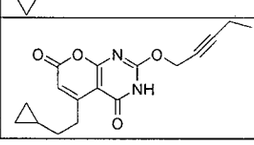
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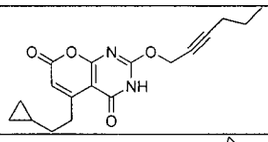
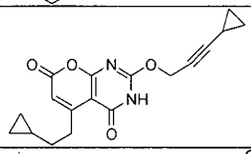
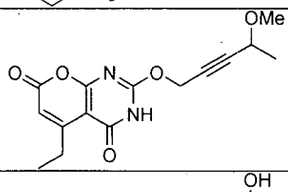
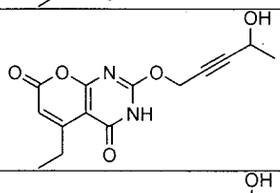
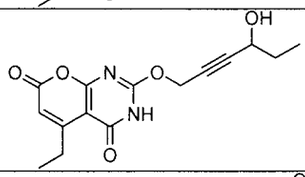
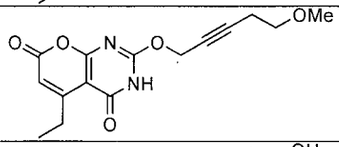
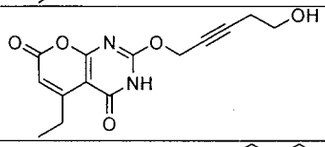
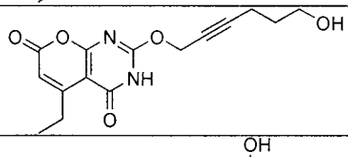
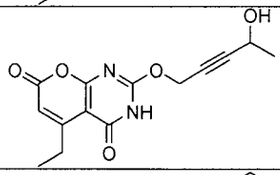
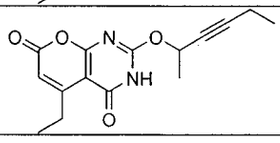
Actividad del agonista del receptor nicotínico del Compuestos ilustrativos seleccionados de la invención

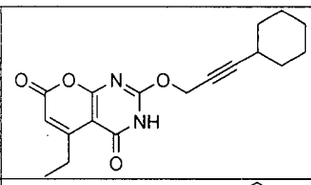
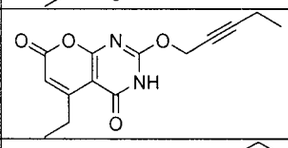
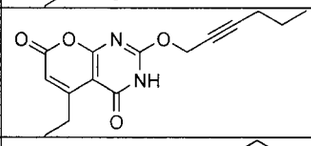
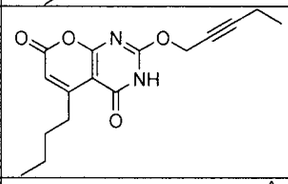
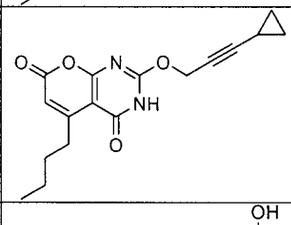
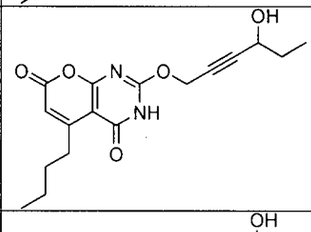
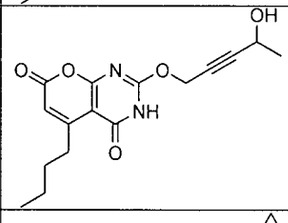
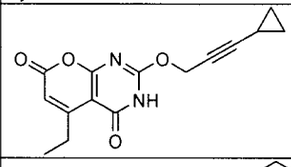
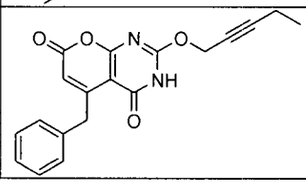
Compuesto Nº	Estructura	ND EC_{50} campo (nM)
11		125,0
35		9,0
90		475,3
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102		31,0
103		74,3
104		47,0
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108		28,0
112		14,4

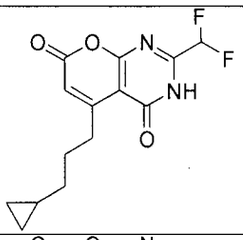
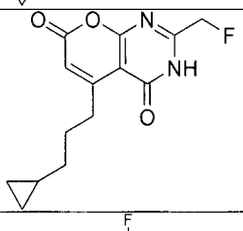
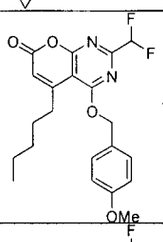
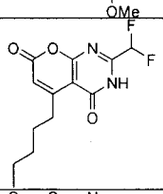
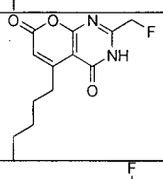
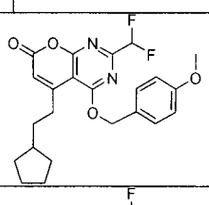
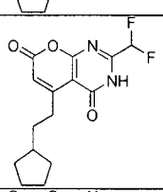
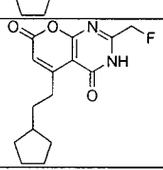
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119		10,1
122		5,3
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124		78,5
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126		26,5
127		57,3
128		6,3
129		106,5

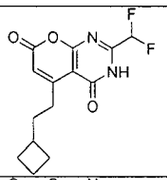
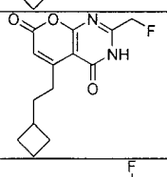
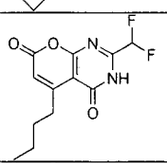
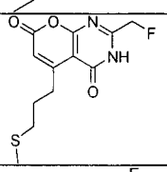
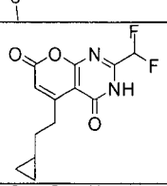
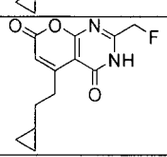
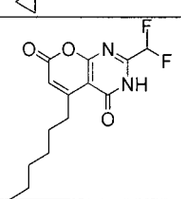
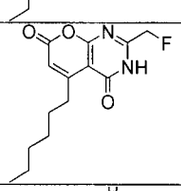
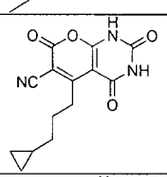
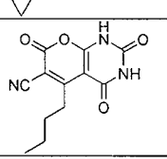
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268		2,1
292		300
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645		26,2

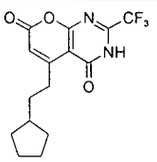
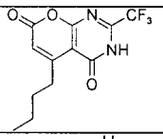
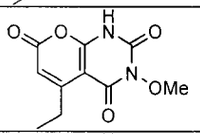
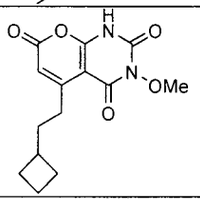
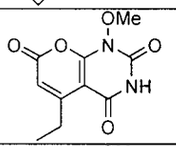
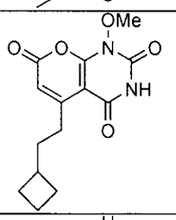
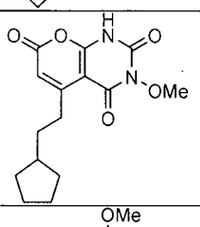
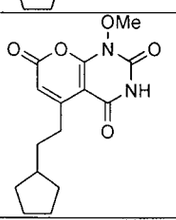
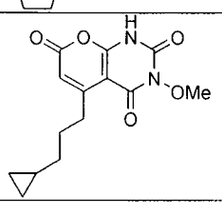
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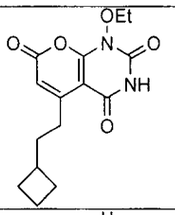
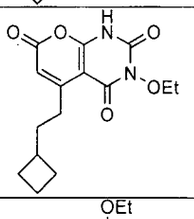
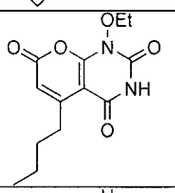
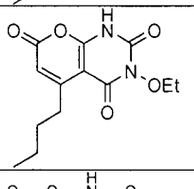
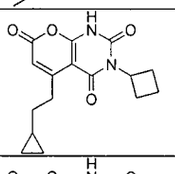
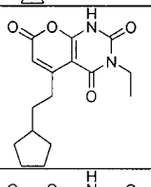
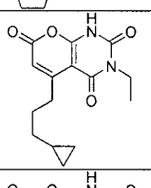
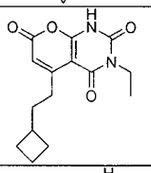
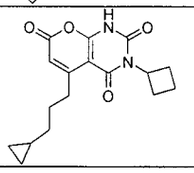
721		225,5
722		111,5
723		296
724		59,5
725		675
726		219
727		179
728		26,2
729		49,9
730		155,8

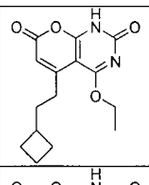
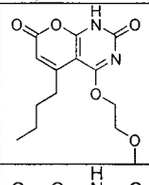
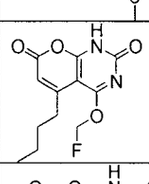
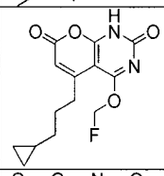
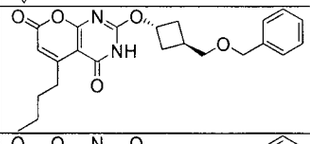
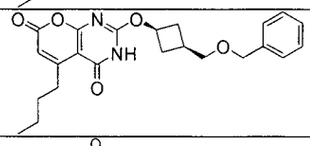
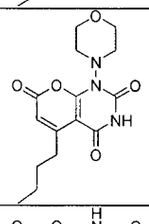
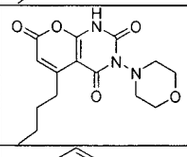
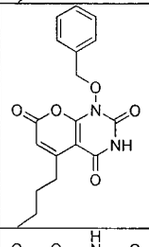
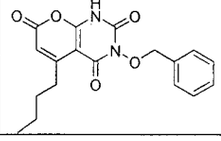
731		177,4
732		95,5
733		52,6
734		71,8
735		94
736		32,9
737		59,5
738		33,8
739		136,8

740		130
741		123
742		1068
743		212,5
744		128
745		10000
746		1402
747		1233

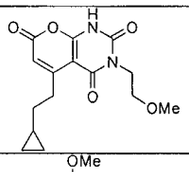
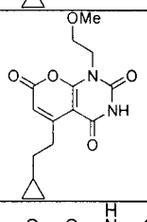
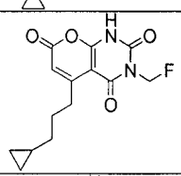
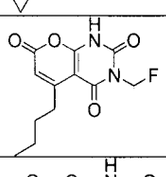
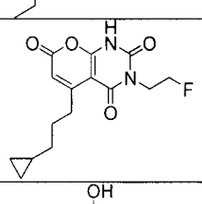
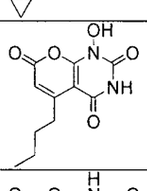
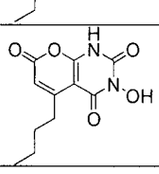
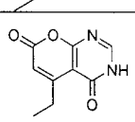
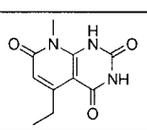
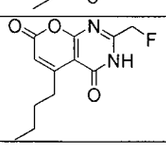
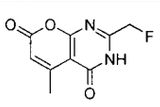
748		286
749		182,5
750		1892,5
751		487
752		248
753		228
754		308
755		286
759		2326
760		10000

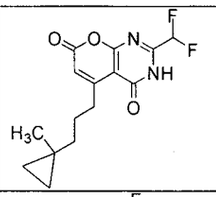
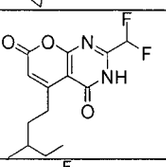
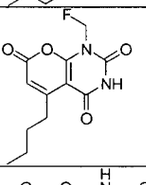
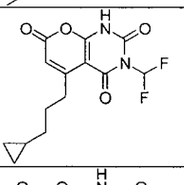
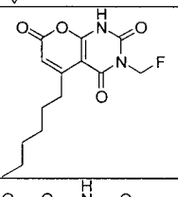
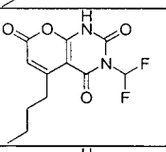
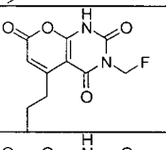
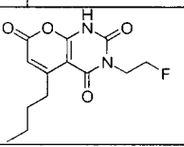
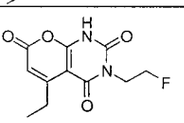
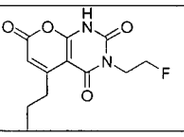
763		7734
764		8922
768		383,5
769		19
770		908
771		17
772		39
773		48,5
774		28,0

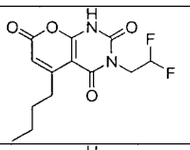
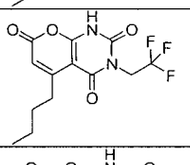
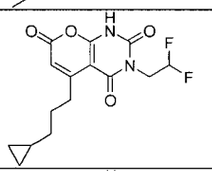
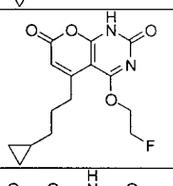
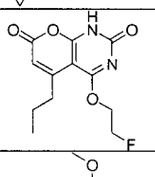
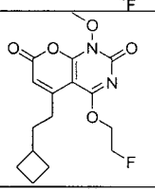
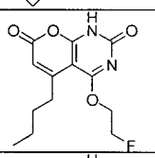
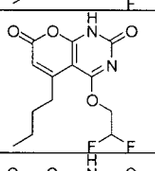
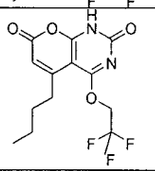
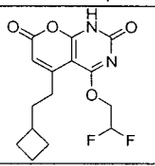
776		10000
777		5600
778		9150
779		2851
780		36
781		68
782		94
783		64
784		17,9

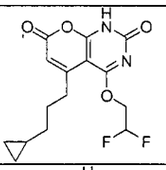
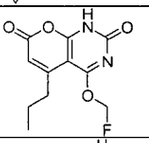
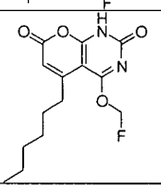
786		5331
787		681,5
788		38,5
789		88
791		50
792		44
796		>10000
797		>1000
798		>10000
799		>10000

580

800		>10000
801		>10000
802		12
803		3450
804		178
805		2063
806		256
807		>10000
808		>10000
809		187
810		>10000

811		22
812		40
813		256
814		161
815		10000
816		291
817		1450
818		308
819		1536
820		10000

821		142
822		10000
823		10000
824		91
825		616
826		3251
827		690
828		407
829		882
830		112

831		531
832		304
833		511

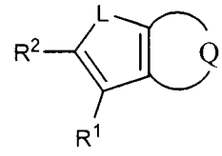
También se determinó la actividad de los compuestos **834-844** aplicando el ensayo que se describió previamente y los valores EC_{50} medidos se ubicaron en un rango de aproximadamente 3 nM a aproximadamente 1600 nM.

La actividad de varios otros compuestos de la presente invención se mostró antes en esta especificación como A, B o C. Los especialistas en el arte podrán apreciar que los compuestos de la invención que se describieron aquí, presentan una excelente actividad agonista del receptor del ácido nicotínico. Mientras que la presente invención fue descrita conjuntamente con las realizaciones específicas indicadas anteriormente, un especialista en el arte conocerá diversas alternativas, modificaciones y otras variaciones de la misma. Se pretende que todas esas alternativas, modificaciones y variaciones estén incluidas dentro del espíritu y alcance de la presente invención.

REIVINDICACIONES

Habiendo así especialmente descripto 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.

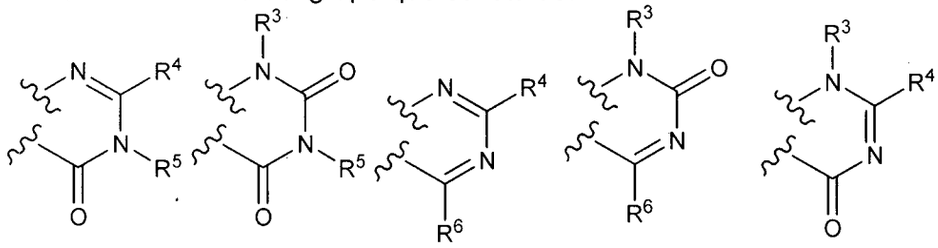
1. Un compuesto que presenta la fórmula:



(I)

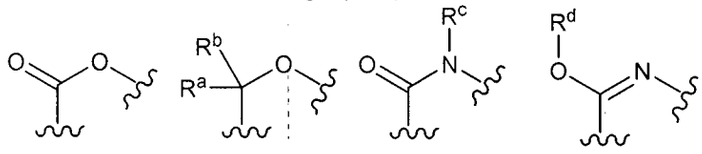
o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico, donde:

Q se selecciona del grupo que consta de:



(a) , (b) , (c) , (d) y (e) ;

L se selecciona del grupo que consta de:



(f) , (g) , (h) , y (i) ;

R^1 se selecciona del grupo que consta de H, alquilo, arilalquilo, -alquilen-S-alquilo, alquenilo, alquinilo, haloalquilo, donde un grupo alquilo puede estar sustituido opcionalmente con uno o más de los siguientes grupos, que pueden ser iguales o diferentes: -OH, cicloalquilo, -C(O)-alquilo, -alquilen-C(O)-O-alquilo, $-O-R^{10}$, -alquilen-O-alquilo, arilo, -alquilen-arilo, heteroarilo, -alquilen-heteroarilo, halógeno, $-(CH_2)_n-N(R^7)_2$, -alquilen-cicloalquilo, o -alquilen-cicloalquenilo,

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donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^1 no está sustituida o está sustituida con uno o más grupos X, dicho arilo o la porción arilo de dicho -alquilen-arilo de R^1 no está sustituido o está sustituido con uno o más grupos Y, y dicho heteroarilo o la porción heteroarilo de dicho –alquilen-heteroarilo de R^1 no está sustituido o está sustituido con uno o más grupos Y;

R^2 se selecciona del grupo que consta de H, halógeno, alquilo, haloalquilo, alquilo sustituido con uno o más -OH, -C(O)-alquilo, -C(O)-O-alquilo, -C(O)-OH, -O-R^{10}, -alquilen-O-alquilo, arilo no sustituido, arilo sustituido con uno o más grupos Y, heteroarilo no sustituido, heteroarilo sustituido con uno o más grupos Y, y halógeno; o

R^1 y R^2 junto con los átomos de carbono anulares a los que están unidos según se muestra, forman un anillo cicloalquenilo de 5 o 6 miembros o un anillo heterocíclico de 5 o 6 miembros que presenta 1 o 2 heteroátomos;

R^3 se selecciona del grupo que consta de H, alquilo, alquilo sustituido con uno o más grupos hidroxilo, -alquilen-O-alquilo, cicloalquilo, -alquilen-cicloalquilo, -alquilen-C(O)-O-alquilo, -alquilen-O-C(O)-alquilo, alquenilo, arilo, y heteroarilo,

donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^3 no está sustituido o está sustituido con uno o más grupos X, dicho arilo de R^3 no está sustituido o está sustituido con uno o más grupos Y, y dicho heteroarilo de R^3 no está sustituido o está sustituido con uno o más grupos Y;

R^4 se selecciona del grupo que consta de H, halógeno, alquilo, haloalquilo, -O-cicloalquilo, -O-alquinilo, -O-R^{10}, -C(O)-O-alquilo, -$S(O)_m$-R^9, -$N(R^7)_2$, -$N(R^7)$-NH-C(O)-alquilo, -$N(R^7)$-NH-C(O)-O-alquilo, -O-N=$C(R^{12})_2$, -$N(R^7)$-N=$C(R^{12})_2$, -C(O)-alquilo, heterociclilo no sustituido, heterociclilo sustituido

con uno o más grupos X, -O-N(R^7)-C(O)-O-alquilo, -C(O)-N(R^7)$_2$, -CN, -N_3, y -O-C(O)-alquilo;

R^5 se selecciona del grupo que consta de H, alquilo, -OH, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo -alquilen-C(O)-R^8, -alquilen-C(O)-N(R^{11})$_2$, -alquilen-C(=N-O-alquil)-arilo, cicloalquilo, -alquilen-cicloalquilo, -alquilen-C(O)-O-alquilo, -alquilen-O-C(O)-alquilo, -alquilen-C(O)-heterociclilo y alquenilo,

donde el cicloalquilo o la porción cicloalquilo de dicho -alquilen-cicloalquilo de R^5 no está sustituido o está sustituido con uno o más grupos X, y la porción arilo de dicho -alquilen-C(=N-O-alquil)-arilo de R^5 no está sustituida o está sustituida con uno o más grupos Y;

R^6 se selecciona del grupo que consta de H, alquilo, alquenilo, alquilo sustituido con uno o más grupos hidroxilo, -alquilen-O-alquilo, -O-R^{10}, halógeno, arilo, heteroarilo y -N(R^7)$_2$,

donde el arilo de R^6 no está sustituido o está sustituido con uno o más grupos Y, y dicho heteroarilo de R^6 no está sustituido o está sustituido con uno o más grupos Z;

cada R^7 se selecciona de manera independiente del grupo que consta de H, alquilo, cicloalquilo, arilo, -C(O)-alquilo, y -C(O)-arilo,

donde el cicloalquilo de R^7 no está sustituido o está sustituido con uno o más grupos X, y la porción arilo de dicho -C(O)-arilo o dicho arilo de R^7 no está sustituido o está sustituido con uno o más grupos Y;

dos grupos R^7 junto con el átomo de N al que están unidos forman un heterociclilo;

R^8 se selecciona del grupo que consta de arilo, -OH y heterociclilo,

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donde el heterociclilo de R^8 no está sustituido o está sustituido con uno o más grupos X, y dicho arilo de R^8 no está sustituido o está sustituido con uno o más grupos Y;

R^9 se selecciona del grupo que consta de alquilo, -alquilen-cicloalquilo, alquenilo, $-N(R^{11})_2$ y -alquilen-arilo,

donde la porción cicloalquilo de dicho –alquilen-cicloalquilo de R^9 no está sustituida o está sustituida con uno o más grupos X, y la porción arilo de dicho -alquilen-arilo de R^9 no está sustituida o está sustituida con uno o más grupos Y, y

con la salvedad que cuando R^9 es $-N(R^{11})_2$, m es 1 o 2;

R^{10} se selecciona del grupo que consta de H, alquilo, cicloalquilo, arilalquilo, haloalquilo, -alquilen-O-alquilo, -alquilen-arilo, -alquenilen-arilo, -alquilen-heteroarilo, alquenilo, -C(O)-alquilo, alquinilo y -alquilen-cicloalquilo,

donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con –OH o alcoxi; la porción cicloalquilo de un grupo -O-cicloalquilo puede estar sustituida de manera opcional con un grupo -alquilen-O-alquilen-arilo; la porción cicloalquilo de dicho –alquilen-cicloalquilo de R^{10} no está sustituida o está sustituida con uno o más grupos X; la porción arilo de dicho -alquilen-arilo o -alquenilen-arilo de R^{10} no está sustituida o está sustituida con uno o más grupos Y; y la porción heteroarilo de dicho -alquilen-heteroarilo de R^{10} no está sustituida o está sustituida con uno o más grupos Z;

R^{11} se selecciona del grupo que consta de H, alquilo y arilo,

donde el arilo de R^{11} no está sustituido o está sustituido con uno o más grupos Y; o

dos grupos R^{11} junto con el átomo de N al que están unidos, forman un heterociclilo;

cada R^{12} se selecciona de manera independiente del grupo que consta de alquilo, arilo y heteroarilo,

donde el arilo de R^{12} no está sustituido o está sustituido con uno o más grupos Y y dicho heteroarilo de R^{12} no está sustituido o está sustituido con uno o más grupos Z; o donde ambos grupos R^{12}, junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo;

R^a y R^b se seleccionan cada uno de manera independiente del grupo que consta de H, alquilo, arilo y heteroarilo,

donde el arilo de R^a y R^b no está sustituido o está sustituido con uno o más grupos Y, y dicho heteroarilo de R^a y R^b no está sustituido o está sustituido con uno o más grupos Z;

R^c se selecciona del grupo que consta de H, alquilo, alquilen-arilo, y -C(O)-alquilo,

donde la porción arilo de dicho alquilen-arilo de R^c no está sustituida o está sustituida con uno o más grupos Y;

R^d se selecciona del grupo que consta de H, alquilo y alquilen-arilo,

donde la porción arilo de dicho alquilen-arilo de R^d no está sustituida o está sustituida con uno o más grupos Y;

cada X se selecciona de manera independiente del grupo que consta de halógeno, alquilo, haloalquilo, -O-alquilo, -O-haloalquilo y -OH;

cada Y se selecciona de manera independiente del grupo que consta de halógeno, alquilo, haloalquilo, -O-alquilo, -O-haloalquilo, -CN, $-NO_2$, -OH, $-S(O_2)$-alquilo, $-S(O_2)$-arilo, $-S(O_2)-NH_2$, $-S(O_2)$-NH-alquilo, $-S(O_2)$-NH-arilo, $-S(O_2)-N(\text{alquilo})_2$, $-S(O_2)-N(\text{arilo})_2$, $-S(O_2)$-N(alquil)(arilo) y arilo;

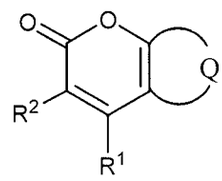
cada Z se selecciona de manera independiente del grupo que consta de alquilo, haloalquilo, halógeno, -O-alquilo, -O-haloalquilo, -CN, -OH, arilo y N-óxido;

n es 0, 1, 2 o 3;

m es 0, 1 o 2; y

con la salvedad que cuando L es (f), y R^2, R^3 y R^5 son cada uno H, entonces R^1 no es $-CH_3$.

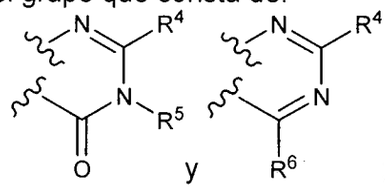
2. El compuesto de la reivindicación 1, que presenta la fórmula:



(II)

o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico, donde:

Q se selecciona del grupo que consta de:



;

R^1 es -H, alquilo, haloalquilo, arilalquilo, -alquilen-S-alquilo o -alquilen-cicloalquilo;

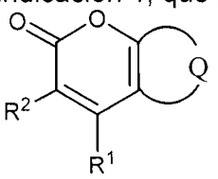
R^2 es -H, -CN o -NHC(O)-alquilo;

R^4 es -O-cicloalquilo, –O-alquinilo, -O-alquinilen-cicloalquilo, haloalquilo u $-O-N=C(R^{12})_2$, donde ambos grupos R^{12} junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo, y donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con -OH o alcoxi; y donde la porción cicloalquilo de un grupo -O-cicloalquilo puede estar sustituida de manera opcional con un grupo -alquilen-O-alquilen-arilo;

R^5 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo; y

R^6 es alcoxi, -O-alquilen-O-alquilo, -O-arilalquilo u -O-haloalquilo.

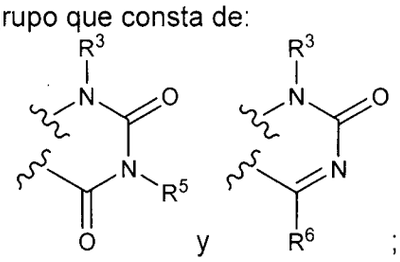
3. El compuesto de la reivindicación 1, que presenta la fórmula:



(III)

o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico, donde:

Q se selecciona del grupo que consta de:



;

R^1 es -H, alquilo, haloalquilo, arilalquilo, -alquilen-S-alquilo o -alquilen-cicloalquilo;

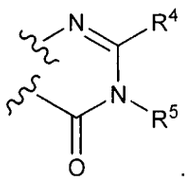
R^2 es -H, -CN o -NHC(O)-alquilo;

R^3 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo;

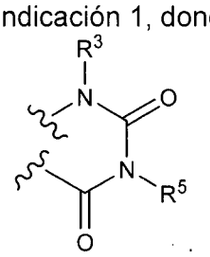
R^5 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo; y

R^6 es alcoxi, -O-alquilen-O-alquilo, -O-arilalquilo u -O-haloalquilo.

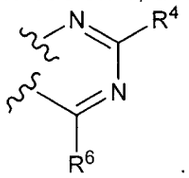
4. El compuesto de la reivindicación 1, donde Q es:



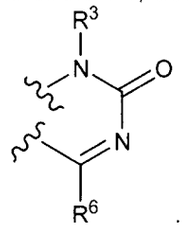
5. El compuesto de la reivindicación 1, donde Q es:



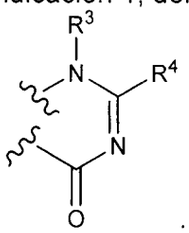
6. El compuesto de la reivindicación 1, donde Q es:



7. El compuesto de la reivindicación 1, donde Q es:



8. El compuesto de la reivindicación 1, donde Q es:



9. El compuesto de la reivindicación 1, donde

R^1 es -H, alquilo, haloalquilo, arilalquilo, -alquilen-S-alquilo o -alquilen-cicloalquilo;

R^2 es -H, -CN o -NHC(O)-alquilo;

R^3 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo;

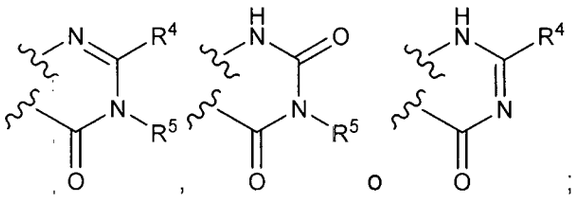
R^4 es -O-cicloalquilo, –O-alquinilo, -O-alquinilen-cicloalquilo, haloalquilo u -O-N=C(R^{12})$_2$, donde ambos grupos R^{12}, junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo, y donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con -OH o alcoxi; y donde la porción cicloalquilo de un grupo -O-cicloalquilo puede estar sustituida de manera opcional con un grupo -alquilen-O-alquilen-arilo; y

R^5 es -H, -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo; y

R^6 es alcoxi, -O-alquilen-O-alquilo, -O-arilalquilo u -O-haloalquilo.

10. El compuesto de la reivindicación 9, donde

Q es:

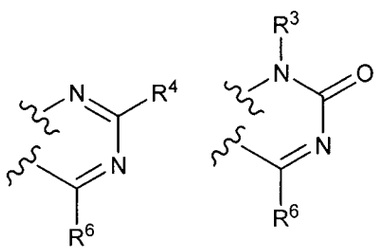


;

R^1 es alquilo, haloalquilo o -alquilen-cicloalquilo; R^2 es -H; y R^5 es -H o alquilo.

11. El compuesto de la reivindicación 9, donde

Q es:

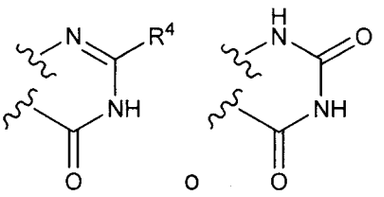


(c) o (d) ;

R^1 es alquilo, haloalquilo o -alquilen-cicloalquilo; y R^2 es -H.

12. El compuesto de la reivindicación 10, donde

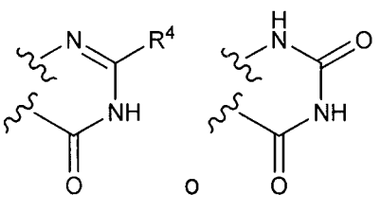
Q es:



y R^4 es -O-alquinilo u -O-alquinilen-cicloalquilo, donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con -OH o alcoxi.

13. El compuesto de la reivindicación 10, donde

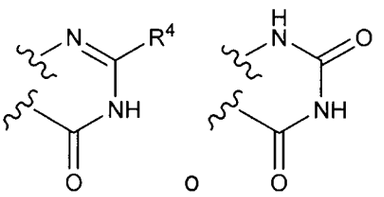
Q es:



y R^4 es haloalquilo.

14. El compuesto de la reivindicación 10, donde

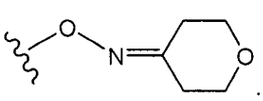
Q es:



y R^4 es -O-N=C(R^{12})$_2$, donde ambos grupos R^{12} junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo.

15. El compuesto de la reivindicación 13, donde R^4 es -CH_2F o –$CH(F)_2$.

16. El compuesto de la reivindicación 14, donde R^4 es:



17. El compuesto de la reivindicación 2, donde Q es:



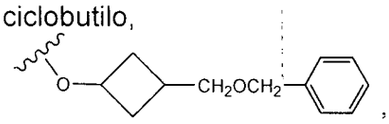
R^1 es alquilo, haloalquilo o -alquilen-cicloalquilo y R^2 es -H.

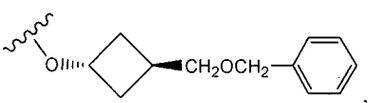
18. El compuesto de la reivindicación 17, donde R^4 es -O-alquinilo u -O-alquinilen-cicloalquilo, donde la porción alquinilo de un grupo -O-alquinilo puede estar sustituida de manera opcional con -OH o alcoxi.

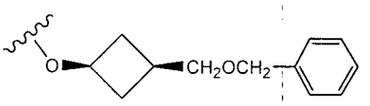
19. El compuesto de la reivindicación 17, donde R^4 es haloalquilo.

20. El compuesto de la reivindicación 17, donde R^4 es -O-N=C(R^{12})$_2$, donde ambos grupos R^{12} junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo.

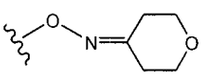
21. El compuesto de la reivindicación 17, donde R^4 es -CH_2F, –$CH(F)_2$, -CF_3, -$OCH_2C{\equiv}CCH_2CH_3$, -$OCH_2C{\equiv}C(CH_2)_3CH_3$, -$OCH_2C{\equiv}CCH_2CH_2CH_3$, -$OCH_2C{\equiv}C$-ciclopropilo, -$OCH_2C{\equiv}CCH(OCH_3)CH_3$, -$OCH_2C{\equiv}CCH(OH)CH_3$, -$OCH_2C{\equiv}CCH(OH)CH_2CH_3$, -$OCH_2C{\equiv}CCH_2CH_2OCH_3$, -$OCH_2C{\equiv}CCH_2CH_2OH$, -$OCH_2C{\equiv}C(CH_2)_3OH$, -$OCH(CH_3)C{\equiv}CCH_2CH_3$, -$OCH_2C{\equiv}C$-ciclohexilo, -O-ciclobutilo,



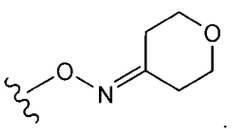




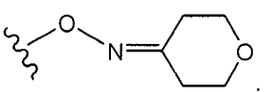
o



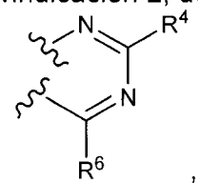
o



22. El compuesto de la reivindicación 21, donde R^4 es -CH_2F, –$CH(F)_2$ o

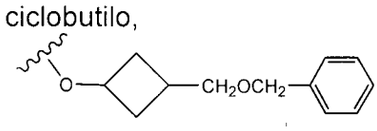


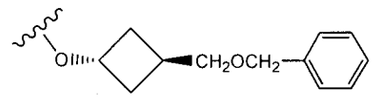
23. El compuesto de la reivindicación 2, donde Q es:

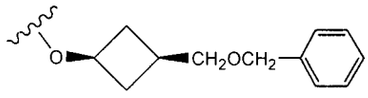


R^1 es alquilo, haloalquilo, o -alquilen-cicloalquilo, y R^2 es -H.

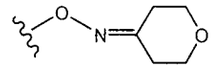
24. El compuesto de la reivindicación 23, donde R^4 es $-CH_2F$, $-CH(F)_2$, $-CF_3$, $-OCH_2C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C(CH_2)_3CH_3$, $-OCH_2C{\equiv}CCH_2CH_2CH_3$, -$OCH_2C{\equiv}C$-ciclopropilo, $-OCH_2C{\equiv}CCH(OCH_3)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$, $-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, $-OCH_2C{\equiv}C$-ciclohexilo, -O-ciclobutilo,



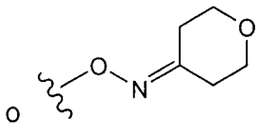




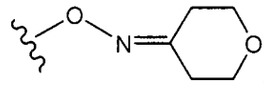
o



o



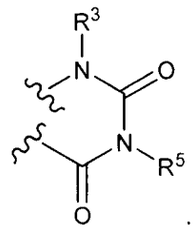
25. El compuesto de la reivindicación 24, donde R^4 es $-CH_2F$, $-CH(F)_2$ o



26. El compuesto de la reivindicación 24, donde R^1 es una cadena de alquilo lineal que presenta de 1 a 6 átomos de carbono.

27. El compuesto de la reivindicación 24, donde R^1 es $-(CH_2)_3$-ciclopropilo o $-(CH_2)_2$ciclobutilo.

28. El compuesto de la reivindicación 3, donde Q es:



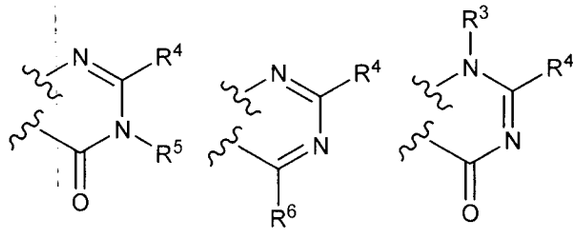
29. El compuesto de la reivindicación 28, donde R^1 es alquilo, haloalquilo, o -alquilen-cicloalquilo; y R^2, R^3 y R^5 son cada uno –H.

30. El compuesto de la reivindicación 28, donde R^1 es alquilo, haloalquilo o -alquilen-cicloalquilo; R^2 es -H y uno, pero no ambos de R^3 y R^5 es -H.

31. El compuesto de la reivindicación 29, donde R^1 es una cadena de alquilo lineal que presenta de 1 a 6 átomos de carbono.

32. El compuesto de la reivindicación 1, donde

Q es:



(a) (c) o (e),

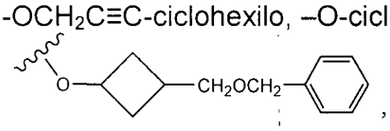
R^1 es alquilo o -alquilen-cicloalquilo y R^2 es -H.

33. El compuesto de la reivindicación 32, donde R^4 es haloalquilo u -O-N=C(R^{12})$_2$, donde ambos grupos R^{12} junto con el átomo de carbono al que están unidos, se combinan para formar un grupo heterociclilo.

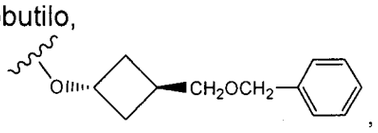
34. El compuesto de la reivindicación 33, donde R^4 es -CH_2F o -$CH(F)_2$.

35. El compuesto de la reivindicación 30, donde R^1 es metilo, etilo, n-butilo, n-fenilo, -$(CH_2)_3$-ciclopropilo o –$(CH_2)_2$-ciclobutilo, R^2 es -H y R^4 es -CH_2F, -$CH(F)_2$, -CF_3, -$OCH_2C{\equiv}CCH_2CH_3$, -$OCH_2C{\equiv}C(CH_2)_3CH_3$, -$OCH_2C{\equiv}CCH_2CH_2CH_3$, -$OCH_2C{\equiv}C$-ciclopropilo, -$OCH_2C{\equiv}CCH(OCH_3)CH_3$,

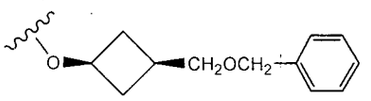
$-OCH_2C{\equiv}CCH(OH)CH_3$, $-OCH_2C{\equiv}CCH(OH)CH_2CH_3$, $-OCH_2C{\equiv}CCH_2CH_2OCH_3$, $-OCH_2C{\equiv}CCH_2CH_2OH$, $-OCH_2C{\equiv}C(CH_2)_3OH$, $-OCH(CH_3)C{\equiv}CCH_2CH_3$, -$OCH_2C{\equiv}C$-ciclohexilo, –O-ciclobutilo,



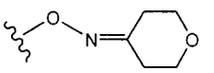
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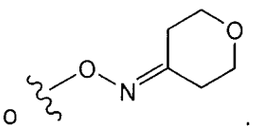


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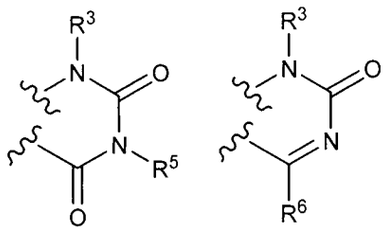




o .

36. El compuesto de la reivindicación 1, donde

Q es:



(b) o (d) ,

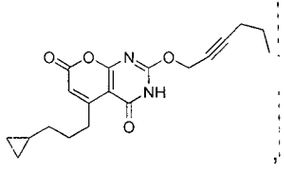
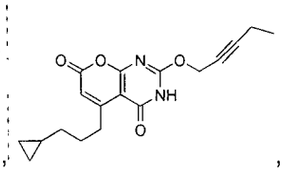
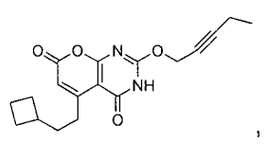
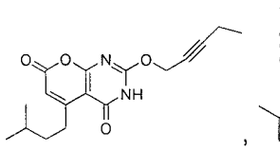
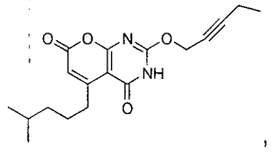
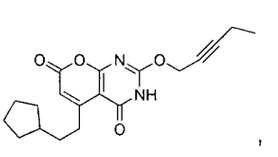
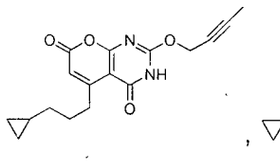
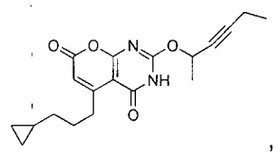
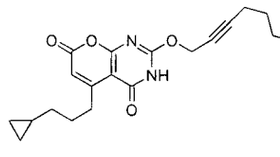
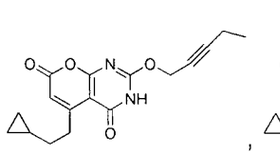
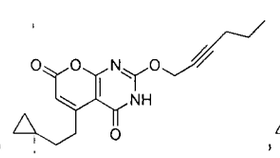
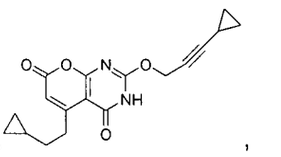
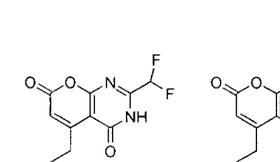
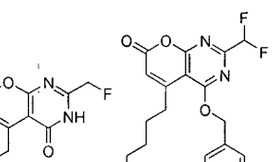
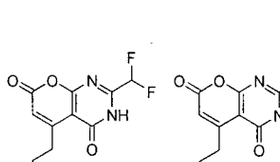
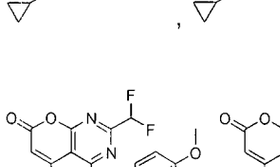
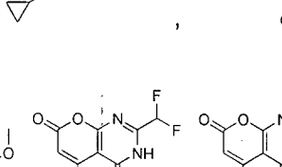
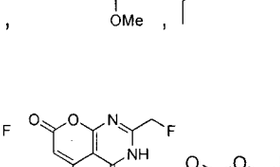
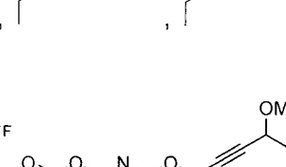
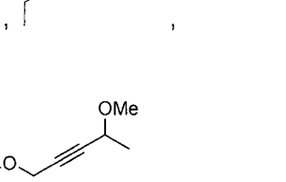
R^1 es alquilo o -alquilen-cicloalquilo y R^2 es -H.

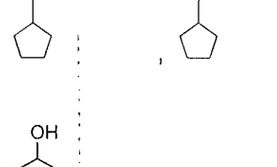
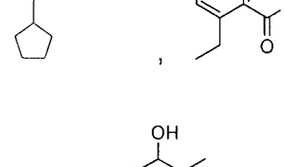
37. El compuesto de la reivindicación 36, donde uno, pero no ambos, de R^3 y R^5, es -H.

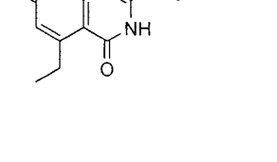
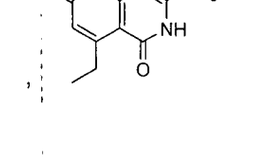
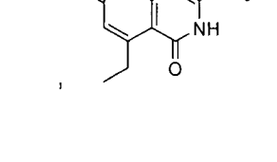
38. El compuesto de la reivindicación 37, donde uno de R^3 y R^5 es -H y el otro es -OH, alquilo, haloalquilo, arilalquilo, -O-alquilo, -O-arilo, cicloalquilo, heterociclilo, -O-cicloalquilo, -O-heterociclilo, -O-arilalquilo o -alquilen-O-alquilo.

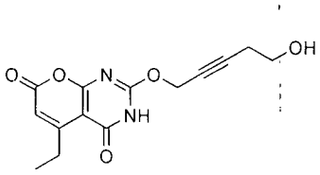
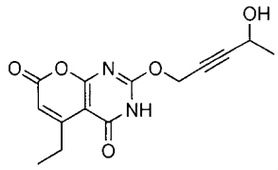
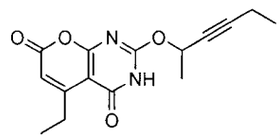
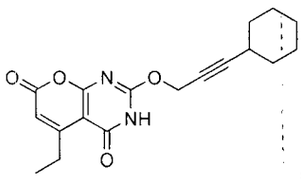
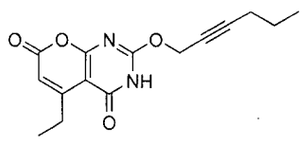
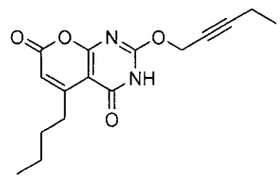
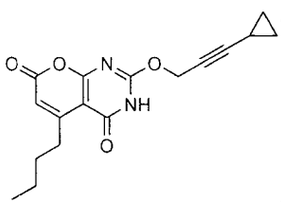
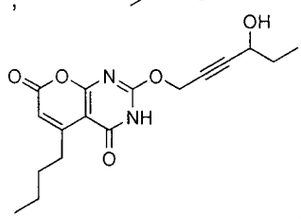
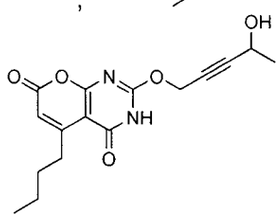
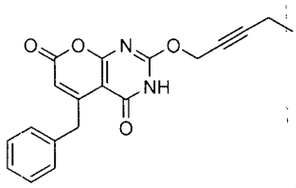
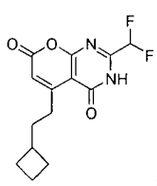
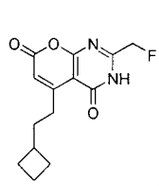
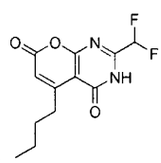
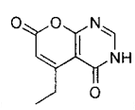
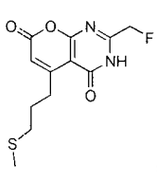
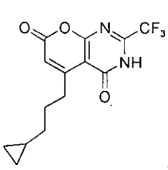
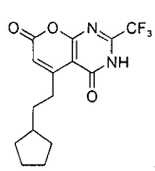
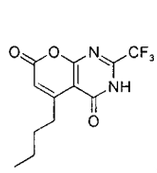
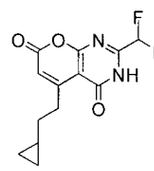
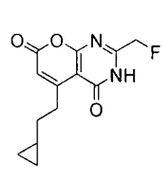
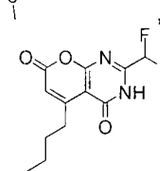
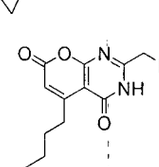
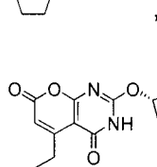
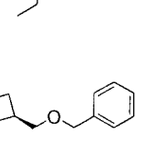
39. El compuesto de la reivindicación 38, donde uno de R^3 y R^5 es -H y el otro es $-OCH_3$, ciclobutilo, etilo, *N*-morfolinilo, -O-bencilo, $-CH_2CH_2OCH_3$, $-OCH_2CH_3$, $-CH_2F$, $-CH_2CH_2F$ u -OH.

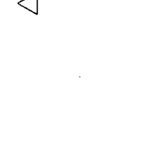
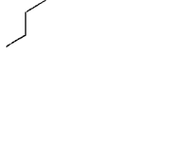
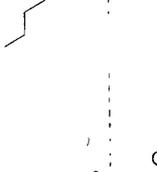
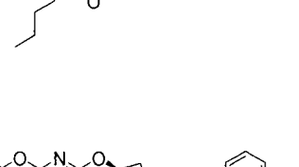
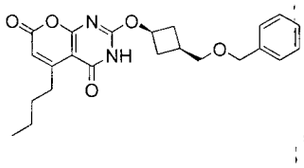
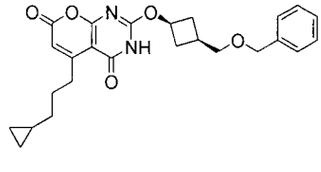
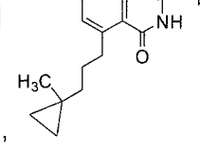
40. Un compuesto que presenta la estructura:

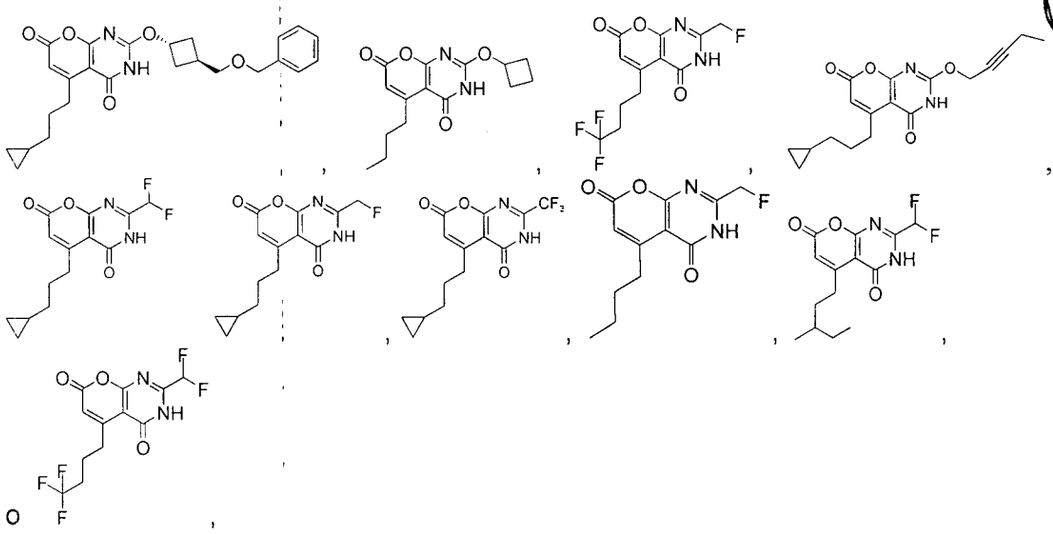





















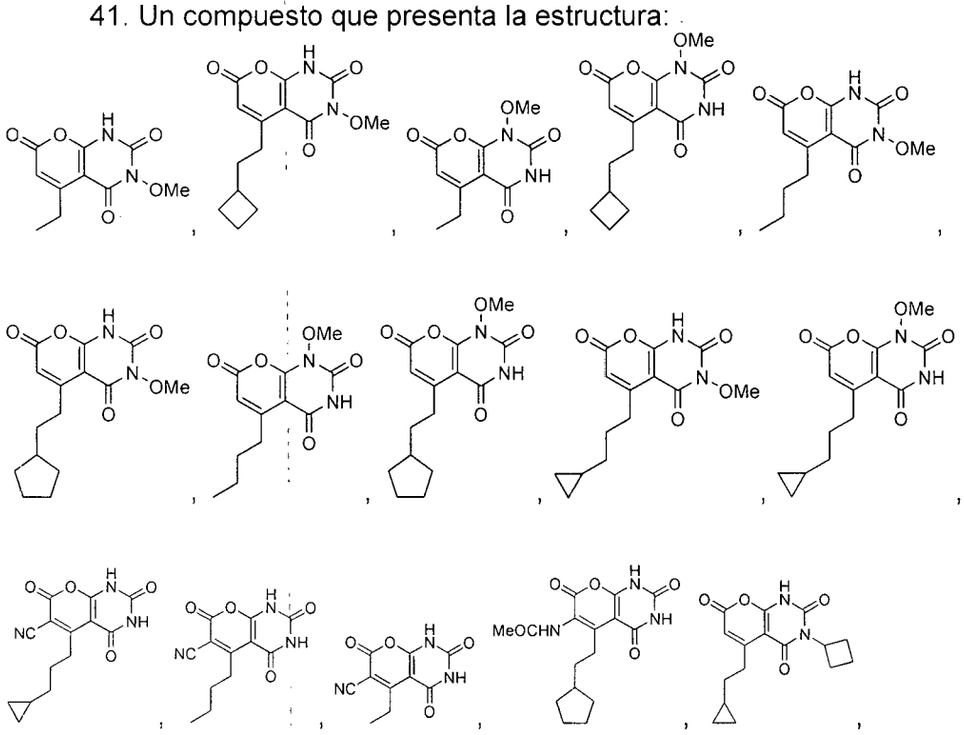

























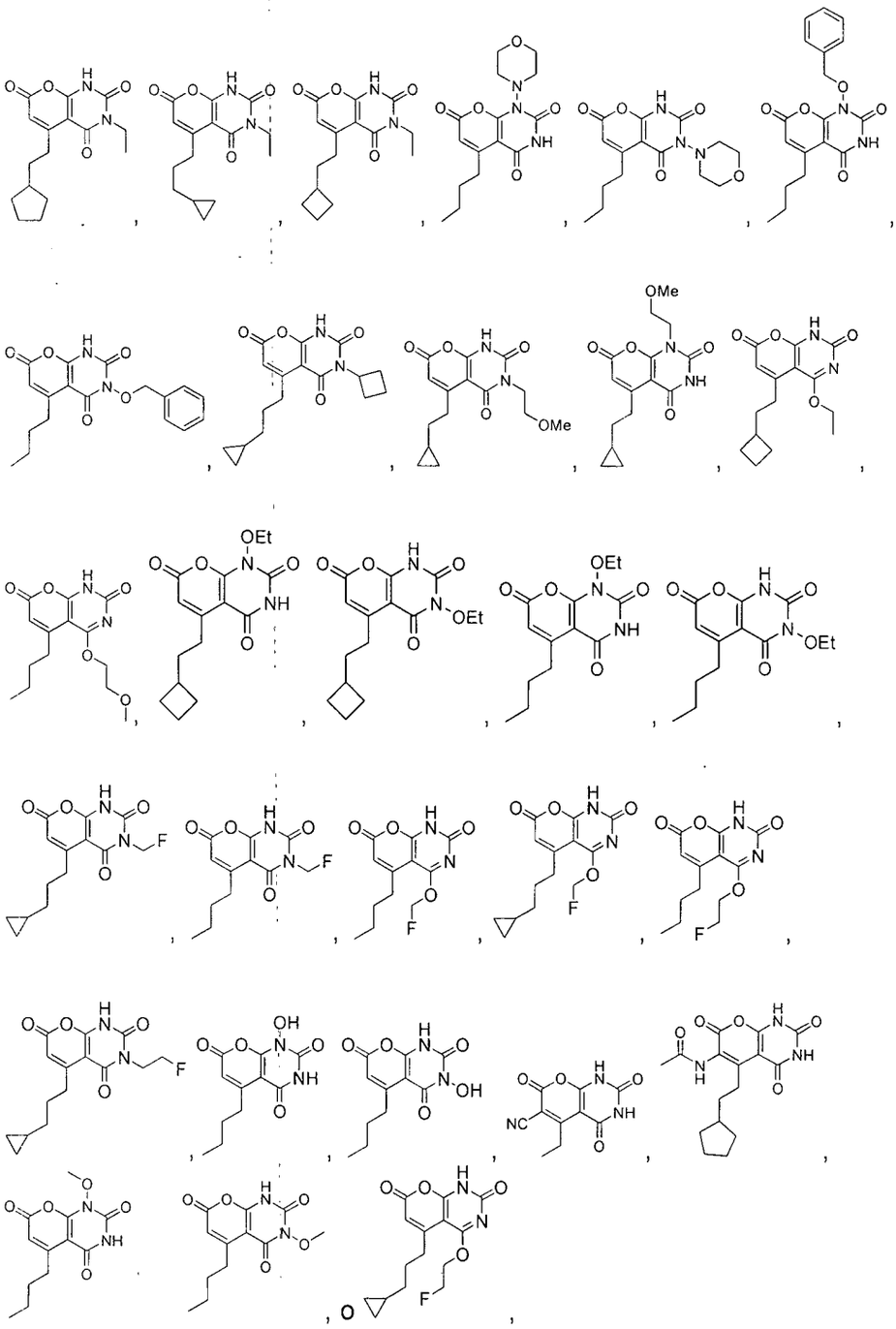







H3C



o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico.

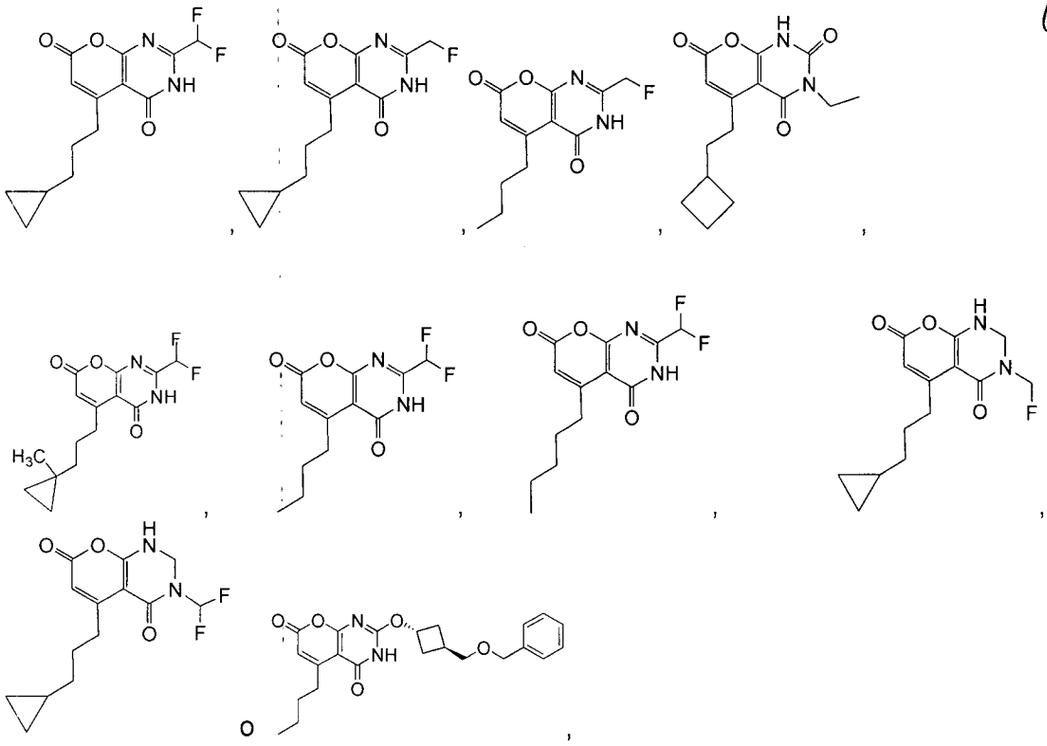
41. Un compuesto que presenta la estructura:





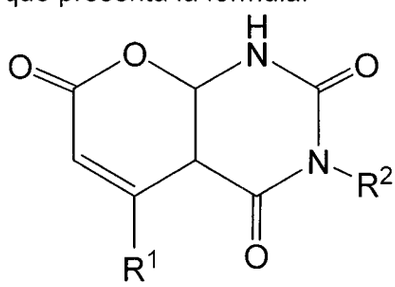
o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico.

42. Un compuesto que presenta la estructura:



o una sal, solvato, éster o tautómero del mismo aceptable para uso farmacéutico.

43. Un compuesto que presenta la fórmula:



(IV)

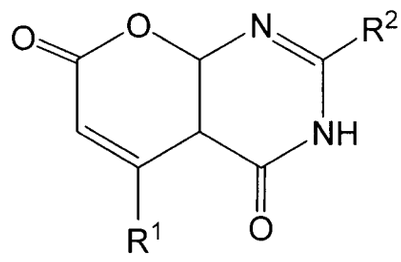
o una sal o solvato del mismo aceptable para uso farmacéutico,

donde:

R^1 es haloalquilo; y

R^2 es H o cicloalquilo.

44. Un compuesto que presenta la fórmula:



(V)

o una sal o solvato del mismo aceptable para uso farmacéutico,

donde:

R^1 y R^2 son ambos, de manera independiente, haloalquilo.

45. El compuesto de la reivindicación 43, donde R^1 es fluoroalquilo.

46. El compuesto de la reivindicación 44, donde R^1 es –alquilen-CF_2.

47. El compuesto de la reivindicación 44, donde R^1 es –alquilen-F.

48. El compuesto de la reivindicación 46, donde R^1 es $–(CH_2)_3$-CF_2, -$(CH_2)_4$-CF_2 o $–(CH_2)_5$-CF_2.

49. El compuesto de la reivindicación 43, donde R^2 es H.

50. El compuesto de la reivindicación 43, donde R^2 es cicloalquilo.

51. El compuesto de la reivindicación 50, donde R^2 es ciclobutilo.

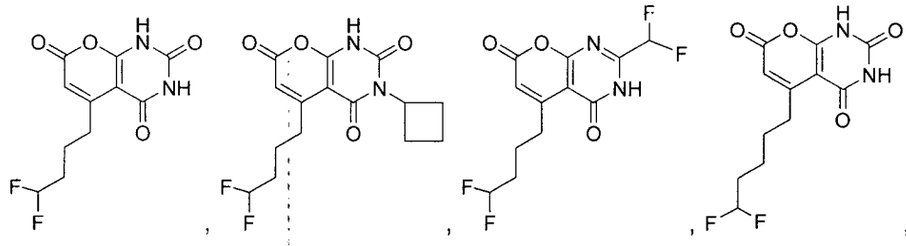
52. El compuesto de la reivindicación 44, donde R^2 es H.

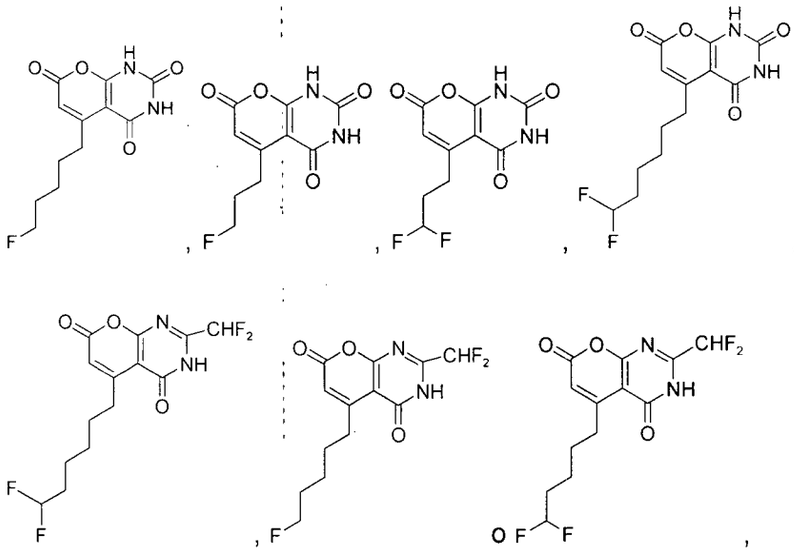
53. El compuesto de la reivindicación 45, donde R^2 es H.

54. El compuesto de la reivindicación 44, donde R^2 es cicloalquilo.

55. El compuesto de la reivindicación 45, donde R^2 es cicloalquilo.

56. Un compuesto que presenta la estructura:





o una sal o solvato del mismo aceptable para uso farmacéutico.

57. Una composición que comprende al menos un compuesto de la reivindicación 1 y un vehículo aceptable para uso farmacéutico.

58. Una composición que comprende al menos un compuesto de la reivindicación 40 y un vehículo aceptable para uso farmacéutico.

59. Una composición que comprende al menos un compuesto de la reivindicación 41 y un vehículo aceptable para uso farmacéutico.

60. Una composición que comprende al menos un compuesto de la reivindicación 42 y un vehículo aceptable para uso farmacéutico.

61. Una composición que comprende al menos un compuesto de la reivindicación 43 y un vehículo aceptable para uso farmacéutico.

62. Una composición que comprende al menos un compuesto de la reivindicación 44 y un vehículo aceptable para uso farmacéutico.

63. Una composición que comprende al menos un compuesto de la reivindicación 56 y un vehículo aceptable para uso farmacéutico.

64. La composición de cualquiera de las reivindicaciones 57-63, que comprende además al menos un agente terapéutico adicional seleccionado del grupo que consta de agentes anti-rubor, compuestos de azetidinona hidroxi-

sustituidos, compuestos β-lactama sustituidos, compuestos inhibidores de HMG CoA reductasa, inhibidores de HMG CoA sintetasa, inhibidores de la síntesis de escualeno, inhibidores de la escualeno epoxidasa, inhibidores de la biosíntesis de esteroles, derivados del ácido nicotínico, secuestrantes de ácidos biliares, aspirina, agentes NSAID, Vytorin®, ezetimibe, secuestrantes inorgánicos del colesterol, inhibidores de AcilCoA:Colesterol *O*-aciltransferasa, inhibidores de la proteína de transferencia de ésteres de colesterilo, aceites de pescado que contienen ácidos grasos Omega 3, fibras naturales solubles en agua, estanoles de plantas y/o ésteres de ácidos grasos de estanoles de plantas, anti-oxidantes, agonistas de PPAR-α, agonistas de PPAR-γ, moduladores del receptor FXR, agonistas del receptor FXR, inhibidores de la síntesis de lipoproteínas, inhibidores de renina angiotensina, inhibidores del transporte microsomal de triglicéridos, inhibidores de la reabsorción de ácidos biliares, agonistas de PPAR-δ, inhibidores de la síntesis de triglicéridos, inhibidores de la escualeno epoxidasa, inductores o activadores de receptores de lipoproteínas de baja densidad, inhibidores de la agregación plaquetaria, inhibidores de 5-LO o FLAP, agonistas δ parciales de PPAR, agonistas de niacina o del receptor de niacina, inhibidores del transportador de 5HT, inhibidores del transportador de NE, antagonistas/agonistas inversos de CB_1, antagonistas de grelina, antagonistas/agonistas inversos de H_3, antagonistas de MCH1R, agonistas/antagonistas de MCH2R, antagonistas de NPY1, antagonistas de NPY5, agonistas de NPY2, agonistas de NPY4, antagonistas de mGluR5, leptinas, agonistas/moduladores de leptinas, derivados de leptinas, antagonistas de opioides, antagonistas del receptor de orexina, agonistas de BRS3, agonistas de CCK-A, CNTF, derivados de CNTF, agonistas/moduladores de CNTF, agonistas de 5HT2c, agonistas de Mc4r, inhibidores de la recaptación de monoaminas, inhibidores de la recaptación de serotonina, miméticos de GLP-1, fentermina, topiramato, fitofarma compuesto 57,

anticuerpos de grelina, agonistas de Mc3r, inhibidores de ACC, agonistas β3, inhibidores de DGAT1, inhibidores de DGAT2, inhibidores de FAS, inhibidores de PDE, agonistas de la hormona ß tiroidea, activadores de UCP-1, activadores de UCP-2, activadores de UCP-3, acil-estrógenos, agonistas/antagonistas de glucocorticoides, inhibidores de 11β HSD-1, inhibidores de SCD-1, inhibidores de lipasas, inhibidores de transportadores de ácidos grasos, inhibidores de transportadores de dicarboxilatos, inhibidores de transportadores de glucosa, inhibidores de transportadores de fosfato, agentes antidiabéticos, agentes antihipertensivos, agentes anti-dislipidémicos, inhibidores de DPP-IV, inhibidores de la secreción de apolipoproteína-B/proteína de transferencia microsomal de triglicéridos (apo-B/MTP), agonistas simpatomiméticos, agonistas de dopamina, análogos del receptor de la hormona estimuladora de melanocitos, antagonistas de la hormona concentradora de melanina, leptonas, antagonistas del receptor de galanina, agonistas de bombesina, antagonistas del neuropéptido Y, agentes tiromiméticos, dehidroepiandrosterona, análogos de dehidroepiandrosterona, antagonistas de la proteína de unión a urocortina, agonistas del receptor del péptido-1 tipo glucagón, proteínas humanas relacionadas con agouti (AGRP), agonistas del receptor de neuromedina U, agentes anoréxicos noradrenérgicos, supresores del apetito, antagonistas de lipasas sensibles a hormonas, análogos del receptor de MSH, inhibidores de la α-glucosidasa, inhibidores del transporte inverso del colesterol apo A1 milano, inhibidores de las proteínas de unión a ácidos grasos (FABP) e inhibidores de las proteínas transportadoras de ácidos grasos (FATP).

65. La composición de la reivindicación 64, donde el al menos un agente terapéutico adicional es un inhibidor de la HMG CoA reductasa seleccionado del grupo que consta de lovastatina, simvastatina, pravastatina, atorvastatina, fluvastatina, cerivastatina, rivastatina, rosuvastatina cálcica y pitavastatina.

66. La composición de la reivindicación 65, donde el al menos un agente terapéutico adicional es simvastatina.

67. La composición de la reivindicación 64, donde el al menos un agente terapéutico adicional es un inhibidor de la proteína de transferencia de ésteres de colesterilo.

68. La composición de la reivindicación 67, donde el al menos un agente terapéutico adicional es un agente anti-rubor.

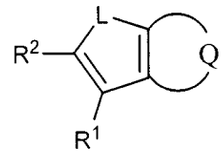
69. La composición de la reivindicación 64, donde el al menos un agente terapéutico adicional es Vytorin®, ezetimibe, aspirina, ibuprofeno o acetaminofeno o una combinación de los mismos.

70. La composición de la reivindicación 64, donde el al menos un agente terapéutico adicional es un inhibidor de DPP-IV o un mimético de GLP-1.

p. de: SCHERING CORPORATION

RESUMEN

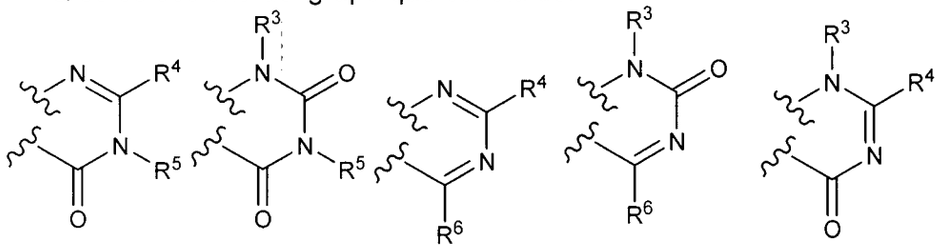
La presente invención provee compuestos de fórmula (I):



(I)

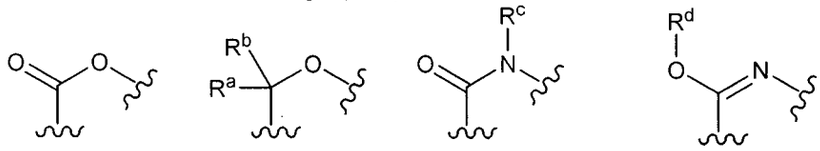
y sales, solvatos, ésteres y tautómeros de los mismos aceptables para uso farmacéutico, donde:

Q se selecciona del grupo que consta de:



(a) , (b) , (c) , (d) y (e) ; y

L se selecciona del grupo que consta de:



(f) , (g) , (h) , y (i) ; composiciones farmacéuticas que comprenden uno o más compuestos de fórmula (I) y métodos para utilizar los compuestos de fórmula (I).

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A61K 31/519 (2006.01) *A61P 3/10* (2006.01)
A61K 31/436 (2006.01)

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11/600,216 15 November 2006 (15.11.2006) US
11/771,538 29 June 2007 (29.06.2007) US

(71) Applicant *(for all designated States except US)*: **SCHERING CORPORATION** [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PALANI, Anandan** [US/US]; 25 Reinhart Way, Bridgewater, NJ 08807 (US). **SU, Jing** [US/US]; 1398 Graymill Drive, Scotch Plains, NJ 07076 (US). **XIAO, Dong** [CN/US]; 199 King George Road, Warren, NJ 07059 (US). **HUANG, Xianhai** [CN/US]; 16 Hemlock Circle, Warren, NJ 07059 (US). **RAO, Ashwin, U.** [IN/US]; 806 Evergreen Forest Boulevard, Avenel, NJ 07001 (US). **CHEN, Xiao** [US/US]; 15 Hillwood Avenue, Edison, NJ 08820 (US). **TANG, Haiqun** [CN/US]; 5 Waters Lane, Belle Mead, NJ 08502 (US). **QIN, Jun** [CN/US]; 92 Woodbury Road, Edison, NJ 08820 (US). **HUANG, Ying, R.** [US/US]; 178 River Bend Road, Berkeley Heights, NJ 07922 (US). **ASLANIAN, Robert, G.** [US/US]; 144 Philip Drive, Rockaway, New Jersey 07866 (US). **MCKITTRICK, Brian, A.** [US/US]; 14 Millbrook Road, New Vernon, New Jersey 07976 (US). **DEGRADO, Sylvia, J.** [US/US]; 6 King James Court, Scotch Plains, NJ 07076 (US).

(74) Agent: **BERGMAN, Jeffrey, P.**; Schering-Plough Corporation, 2000 Galloping Hill Road, Patent Dept. K-6-1, Kenilworth, NJ 07033-0530 (US).

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

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

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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

(88) Date of publication of the international search report:
24 December 2008

(54) Title: NITROGEN-CONTAINING HETEROCYCLIC COMPOUNDS AND METHODS OF USE THEREOF

(57) Abstract: The present invention provides compounds of Formula (I) and pharmaceutically acceptable salts, solvates, esters, and tautomers thereof, wherein: Q is selected from the group consisting of: (a), (b), (c), (d) and (e); and L is selected from the group consisting of: (f), (g), (h), and (i); pharmaceutically compositions comprising one or more compounds of formula (I), and methods of using the compounds of formula (I).

WO 2008/060476 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/023669

610

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04 C07D491/04 A61K31/519 A61K31/436 A61P3/00
A61P9/00 A61P3/10

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, BIOSIS, EMBASE, 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.
P,X	WO 2006/124490 A (SCHERING CORP [US]; PALANI ANANDAN [US]; SU JING [US]; XIAO DONG [US];) 23 November 2006 (2006-11-23) page 1, paragraph 1; claims; examples	1-5, 7-22, 28-70
P,X	WO 2007/087204 A (SCHERING CORPOORATION [US]; PALANI ANANDAN [US]; QIN JUN [US]; XIAO DO) 2 August 2007 (2007-08-02) page 1, paragraph 1; claims; examples	1-5, 7-22, 28-70
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Citation No 5735537 BRN 5954253 5959391 5975043 1994, XP002482949 abstract	1,4,8, 10,13,32

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2008	30/10/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Härtinger, Stefan

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/023669

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 233231 269065 1952, XP002482950 abstract	1,3,5, 28-31, 36,37
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; Citation No 5739692 BRN 5935847 5942970 5959486 1987, XP002482951 abstract	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 191230 1958, XP002482952 abstract	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 1037486 1965, XP002482953 abstract	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 617130 1960, XP002482954 abstract	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 1018983 1978, XP002482955 abstract	1
X	DATABASE BEILSTEIN BEILSTEIN INSTITUTE FOR ORGANIC CHEMISTRY, FRANKFURT-MAIN, DE; BRN 1128908 1972, XP002482956 abstract	1
X	WO 2004/047755 A (TULARIK INC [US]; JAPAN TOBACCO INC [JP]; FOX BRIAN M [US]; FURUKAWA N) 10 June 2004 (2004-06-10) paragraph [0008]; claims 1,27; examples 7-3; tables 7,11	1,70
X	WO 2005/105097 A (GPC BIOTECH AG [DE]; DAUB HENRIK [DE]; WISSING JOSEF [DE]; MISSIO ANDR) 10 November 2005 (2005-11-10) * abstract *claims 1-6	1,70

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/023669

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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

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:

see additional sheet

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.:

1-5, 7-22, 28-70

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.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-5,7-22,28-70

pyranes (f) and (g) fused to a carbonyl substituted pyrimidine (a), (c), (d) or (e)

---

2. claims: 1,2,6,9,11,23-27,32-35,40,57,58,64-70

pyranes (f) and (g) fused to aromatic pyrimidine (b)

---

3. claims: 1,4-5,7-22,32-39,57,64-70

pyridines (h) and (i) fused to a carbonyl substituted pyrimidine (a), (c), (d) or (e)

---

4. claims: 1,6,9-11,32-35,57,64-70

pyridines (h) and (i) fused to aromatic pyrimidine (b)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/023669

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2006124490 A	23-11-2006	AR 053728 A1	16-05-2007
		AU 2006247695 A1	23-11-2006
		CA 2608405 A1	23-11-2006
		EP 1885726 A2	13-02-2008
		KR 20080016567 A	21-02-2008
WO 2007087204 A	02-08-2007	AR 059056 A1	12-03-2008
		AU 2007208478 A1	02-08-2007
		EP 1976854 A2	08-10-2008
		US 2007173495 A1	26-07-2007
WO 2004047755 A	10-06-2004	AU 2003293006 A1	18-06-2004
		BR 0315688 A	06-09-2005
		CA 2514473 A1	10-06-2004
		CN 1753897 A	29-03-2006
		EP 1562956 A2	17-08-2005
		JP 3988830 B2	10-10-2007
		JP 2006509764 T	23-03-2006
		KR 20050090986 A	14-09-2005
		MX PA05005425 A	23-11-2005
		NZ 539952 A	30-05-2008
		ZA 200503823 A	22-02-2006
WO 2005105097 A	10-11-2005	NONE	

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-048050- -00000-0000
Fecha: 2009-05-12 16:23:23 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 614

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [✓] MODELO DE UTILIDAD [ ]

- ◇ Indicación de que se solicita la concesión de una patente [✓]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- ◇ Descripción de la invención [✓]
- ◇ Dibujos de ser estos pertinentes [ ]
- ◇ Comprobante de pago de las tasas establecidas [✓]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- ◇ Indicación de que se solicita el registro de Diseño Industrial [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- ◇ Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- ◇ Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- ◇ Representación gráfica del esquema trazado [ ]
- ◇ Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Claudia M Neiva C
Firma Responsable

Fecha_____

Carrera 13 No. 27-00 Piso 5,7y10´
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

GT

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING - CORPORATION

REFERENCIA	Radicación No.	9 48050
	Solicitud internacional	PCT/US2007/023669
	Fecha inicio fase nacional	15/06/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	Nº 7205

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 03 JUL. 2009
adpa11

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SCHERING - CORPORATION

REFERENCIA	Radicación No.	9 48050
	Solicitud internacional	PCT/US2007/023669
	Fecha inicio fase nacional	15/06/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	7206

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 03 JUL. 2009
adpa11

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