

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-098212- -00000-0000

Fecha: 2007-09-21 14:20:05 Dep. 2020 NUECREACIONE
Tira. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 277

FORMULARIO UNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

24/09/07

SOLICITUD DE:

①

☒ Patente de Invención.

☐ Patente de Modelo de Utilidad.

☒ Capítulo I

☐ Capítulo II

SOLICITANTE (71)

Nombre: **MILLENUM PHARMACEUTICALS, INC**

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Lugar de Constitución: Delaware, Estados Unidos de América

Teléfono: Fax:
E-mail:

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Número Cual

③

REPRESENTANTE
O APODERADO (74)

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⑤

PCT (86)

Solicitud Internacional No. PCT/US2006/006287

Fecha 23/02/2006

Publicación Internacional No. WO 2006/091674 A1

Fecha 31/08/2006

⑥

Título (54)

ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO
DE ENFERMEDADES INFLAMATORIAS

72

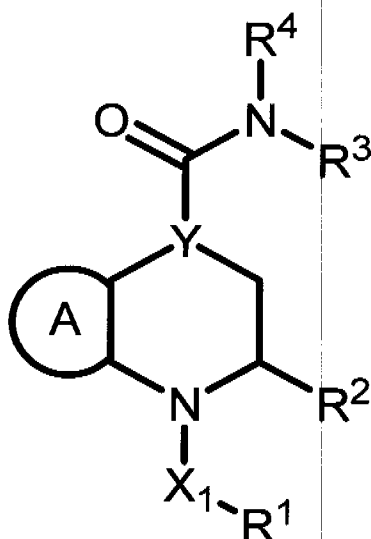
7 Clasificación Internacional (51)		C07D 215/50	
8 Prioridad SI ☒ NO ☐	(33) País de Origen US	(32) Fecha 24/02/2005	(31) Número de Solicitud 60/655,927
9 Comprobante de pago No.		07-75,476	Fecha 18 de septiembre de 2007
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.			

10

Anexos

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

11 FIGURA CARACTERISTICA:



12 Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA: *[Signature]*

C.C. No. 2.930.616 de Bogotá - T.P.A. 2698 CSJ

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-098212- -00000-0000

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 75,476
FECHA : SEPTIEMBRE 18 DE 2007

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
MANUEL MIRANDA	CONSIGNACION	BANCO POPULAR	050-00110-6	67355628	14/09/2007	482,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

G.HOLLMANN RESTREPO
ABOGADOS LTDAG. HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned, acting on behalf of and representing of **MILLENNIUM PHARMACEUTICALS, INC.**, domiciled in Cambridge, Massachussets, Estados Unidos, hereby appoint(s) **LUIS PATIÑO LEYVA** and/or **GUSTAVO HOLLMANN RESTREPO** and/or, domiciled in Bogotá D.C., Republic of Colombia, as our true and legal attorney with the necessary powers:

1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents, utility models, industrial designs and models, commercial ensigns and names, trademarks, slogans, health licenses, copyrights and domain names as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in on this 6th day of December, 2005
Cambridge, MA, U.S.A.

Millennium Pharmaceuticals, Inc.

BY: Ian R. Silverman
Ian R. Silverman, Associate General Counsel

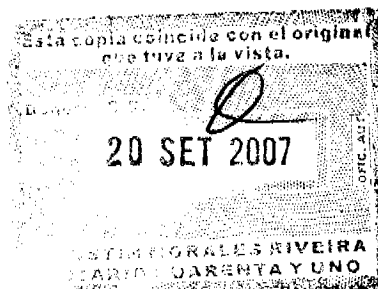
Yo (nosotros), obrando en nombre propio y representación de, con domicilio en nombre(amos) de **LUIS PATIÑO LEYVA y/o GUSTAVO HOLLMANN RESTREPO**, con domicilio en Bogotá D.C., República de Colombia, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus trasposos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

A este efecto, lo facultamos para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la Ley, renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores dando al descargo respectivo, y en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las facultades necesarias, y por este documento desde ahora declaro(amos) válido y bueno todo cuanto los apoderados hicieren en mi (nuestro) beneficio.

Este poder comprende la facultad de ratificar, o confirmar en mi (nuestro) nombre lo actuado, así como la facultad de recibir, desistir, transigir, comprometer, sustituir y revocar sustituciones, recibir notificaciones y nombrar apoderados judiciales o extrajudiciales.

Firmado en el de de



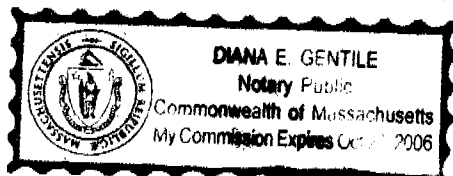
CERTIFICATION
COMPANIES

The undersigned Diana E. Gentile certifies: that the preceding signature(s) reading Ian R. Silva is (are) authentic; that the signer(s) at present fill(s) the position of Associate General Counsel of Millenium Pharmaceuticals, Inc., that he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in Cambridge, MA in accordance with the Laws of Delaware.

All the foregoing facts are known to me due to my having examined the respective documents to which I attest.

Signed in Cambridge, MA on this 6th day of December
of 2005

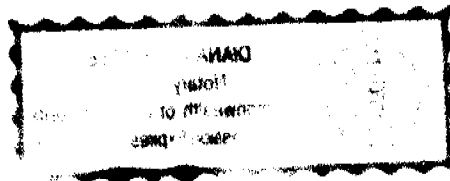
Diana E. Gentile

CERTIFICACIÓN
SOCIEDADES

El(la) infrascrito(a) _____ certifica: que la(s) firma(s) que antecede(n) y dice(n) _____ es (son) auténtica(s), que el (los) signatario(s) desempeña(n) actualmente el cargo(s) de _____ de _____; que tiene(n) facultad para otorgar este poder; y que dicha compañía existe, cumple su objeto social y está organizada en _____ conforme a las Leyes de _____. Todos los hechos anteriores le constan, por haber examinado los documentos respectivos y de todo ello da fe.

Firmado en _____ el _____ de _____ de _____





I HEREBY CERTIFY THAT THIS
IS THE ORIGINAL DOCUMENT

SAMI SWANERK R. 2005

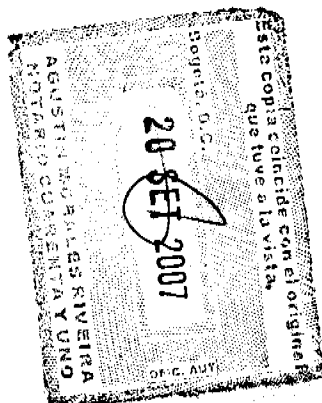
Subscribed and sworn to before me, in my presence, this
8 day of Dec, 2005 a Notary Public

In and for the Washington of DC

Albert L. Themes
Notary Public

My commission expires 6/14, 2009

ALBERT L. THEMES
NOTARY PUBLIC DISTRICT OF COLUMBIA
My Commission Expires 6/14





Apostille

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
United States of America

ALBERT L. THEMES

2. This public document has been signed by _____
NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA
3. acting in the capacity of _____

4. bears the seal/stamp of _____
ALBERT L. THEMES, NOTARY PUBLIC IN AND FOR THE
DISTRICT OF COLUMBIA

CERTIFIED

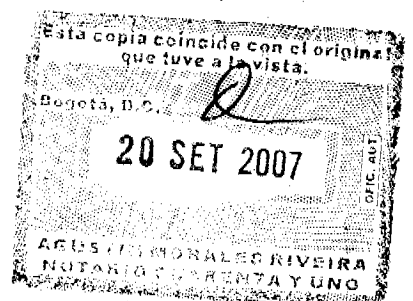
5. at Washington, D.C.
12TH DECEMBER 2005
6. the _____ day of _____
7. by *Secretary of the District of Columbia*
8. No. 149773
9. Seal/Stamp



86-P0138

10. Signature

Patricia Elwood
Patricia Elwood (Interim)



8

Traducción Oficial del Inglés de los sellos, las autenticaciones y la apostilla adjuntas al poder que la compañía MILLENIUM PHARMACEUTICALS INC. domiciliada en Cambridge, Massachussets, Estados Unidos de América, otorga a Luis Patiño Leyva y/o Gustavo Hollmann Restrepo.

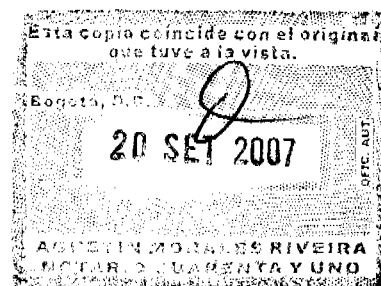
[Sello:] DIANA E. GENTILE
Notaria Pública
Estado de Massachussets
Mi comisión expira Octubre 27/2006

CERTIFICO MEDIANTE LA PRESENTE QUE
ESTE ES EL DOCUMENTO ORIGINAL
SAMI SWANEK 12.8.05

Suscrito y juramentado en mi presencia, el
día de hoy 8 de Diciembre de 2005, un
Notario Público en y para Washington D.C.

ALBERT L. THEMES
NOTARIO PUBLICO DISTRITO DE COLUMBIA
Mi comisión expira 6/14/2009
(Firma y Sello Oficial)

----- (continúa en la 2ª página) -----



APOSTILLA

(Convención de La Haya del 5 de Octubre de 1961)

1. Distrito de Columbia, Estados Unidos de América
Este documento público
2. Ha sido firmado por: ALBERT L. THEMES
3. En su calidad de: NOTARIO PUBLICO EN Y PARA EL
DISTRITO DE COLUMBIA
4. Y lleva el sello oficial: DE NOTARIO PUBLICO EN Y PARA
EL DISTRITO DE COLUMBIA

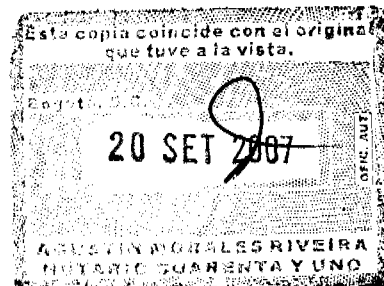
CERTIFICADO

5. En: Washington D.C.
6. El día: 12 DE DICIEMBRE DE 2005
7. Por: El Secretario del Distrito de Columbia
8. Bajo el No. 149773
9. Sello: SECRETARÍA DISTRITO DE COLUMBIA
10. Firma: Patricia Elwood (Interina)

M. Méndez S.
JOSE MIGUEL MENDEZ

Traductor Oficial

Res. 911 de Mayo 1988 MINJUSTICIA

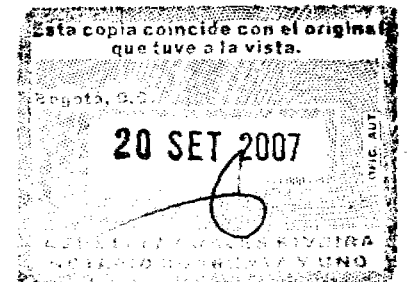


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ESTADO DE GUATEMALA
099257
Jose Mendez

RECORRIDO
DEL 10/09/07

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ESTADO DE GUATEMALA
099257
2007 SET 20 P 12:00
Wuy

MINISTERIO DE
RELACIONES EXTERIORES



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 August 2006 (31.08.2006)

PCT

(10) International Publication Number
WO 2006/091674 A1

(51) International Patent Classification:

C07D 215/50 (2006.01) C07D 495/04 (2006.01)
C07D 401/06 (2006.01) A61K 31/47 (2006.01)
C07D 413/06 (2006.01) A61K 31/506 (2006.01)
C07D 401/12 (2006.01) A61K 31/4375 (2006.01)
C07D 409/06 (2006.01) A61K 31/4365 (2006.01)
C07D 413/12 (2006.01) A61P 19/00 (2006.01)
C07D 471/04 (2006.01) A61P 11/00 (2006.01)

(21) International Application Number:

PCT/US2006/006287

(22) International Filing Date:

23 February 2006 (23.02.2006)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/655,927 24 February 2005 (24.02.2005) US

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(72) Inventors; and

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(74) Agents: SHAIR, Karoline, K., M. et al.; Millennium
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Massachusetts 02139 (US).

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

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
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, 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).

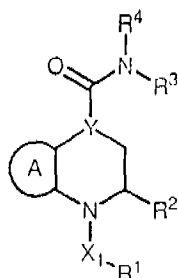
Published:

— 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

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

(54) Title: PGD2 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES

(57) Abstract: Disclosed are CRTH2 inhibitors represented by
Structural Formula (I). The values for the variables of Structural
Formula (I) are provided herein.



(I)

WO 2006/091674 A1

MPI05-005P1RNWOMPGD2 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASESPRIORITY INFORMATION

[0001] The present application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional application number 60/655,927, filed February 24, 2005, entitled "PGD2 Receptor Antagonists for the Treatment of Inflammatory Diseases", the entire contents of which is hereby incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] CRTH2 is a G protein-coupled chemoattractant receptor expressed on Th2 cells (Nagata *et al.*, *J. Immunol.*, 1999, 162, 1278-1286), eosinophils, and basophils (Hirai *et al.*, *J. Exp. Med.*, 2001, 193, 255-261). Prostaglandin D2 (PGD2) is a natural ligand for CRTH2, and is the major inflammatory mediator produced from mast cells. It has been shown that activation of CRTH2 by PGD2 induces migration and activation of Th2 cells (Hirai *et al.*, *J. Exp. Med.* 2001, 193, 255-261; Gervais *et al.*, *J. Allergy Clin. Immunol.* 2001, 108, 982-988) which in turn are involved in the orchestration of an allergic inflammatory response by directly or indirectly inducing migration, activation, priming and prolonged survival of effector cells, such as eosinophils and basophils (Sanz *et al.*, *J. Immunol.* 1998, 160, 5637-5645; Pope *et al.*, *J. Allergy Clin. Immunol.* 2001, 108, 594-601; Teran L. M., *Clin. Exp. Allergy* 1999, 29, 287-290). The role of PGD2 in the initiation and maintenance of allergic inflammation has also been demonstrated in mouse models of asthma by showing that overproduction of PGD2 in vivo by PGD2 synthase exacerbates airway inflammation (Fujitani *et al.*, *J. Immunol.* 2002, 168, 443-449).

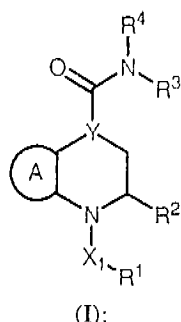
[0003] Accordingly, compounds which are modulators, preferably inhibitors, of the interaction between CRTH2 and PGD2 should be useful for the treatment of diseases and disorders that are mediated by CRTH2, PGD2, Th2 cells, eosinophils, and/or basophils. These diseases include but are not limited to allergic disorders, asthmatic disorders, and inflammatory disorders such as allergic rhinitis, allergic asthma, bronchoconstriction, atopic dermatitis and systemic inflammatory disorders.

[0004] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of the interaction between CRTH2 and its natural ligand PGD2. Thus, compounds of the invention and pharmaceutical compositions thereof are useful for treating inflammatory disorders and/or disorders with an inflammatory component.

DETAILED DESCRIPTION OF THE INVENTION

[0005] This invention provides compounds that are inhibitors of CRTH2, and accordingly are useful for the treatment inflammatory disorders and/or disorders with an inflammatory component. The compounds of this invention are represented by formula I:

12



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted, fused 5-6 membered aryl or heteroaryl ring;

Y is $>C(R^5)-$ or $>N-$;

X_1 is $-C(=O)-$, $-SO_2-$, $-CONR-$, $-C(R)_2-$, or $-CO_2-$,

R^1 is an optionally substituted group selected from an aliphatic, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group.

R^2 is a C_1-C_3 alkyl group, a C_1-C_3 haloalkyl group or C_3-C_6 cycloalkyl group wherein the C_1-C_3 alkyl group represented by R^2 is optionally substituted with R^5 ;

R^3 is hydrogen, C_1-C_6 alkyl optionally substituted by R^6 , C_1-C_6 fluoroalkyl, or an optionally substituted group selected from a C_3-C_6 cycloalkyl, a monocyclic non-aromatic heterocyclic, a monocyclic aryl, or a monocyclic heteroaryl group;

R^4 is $-[C(R^7)_2]_m-B$; or R^3 and R^4 may be taken together with the intervening nitrogen atom to form an optionally substituted monocyclic or bicyclic heteroaryl or non-aromatic heterocyclic group; or

R^5 and R^6 may be taken together with the intervening carbon and nitrogen atoms to form an optionally substituted monocyclic non-aromatic nitrogen-containing heterocyclic group;

R^5 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-COOR'$ or $-N(R')_2$;

R^6 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-N(R')_2$, $-C(O)R'$, $-COOR'$, $C(O)N(R')_2$, or an optionally substituted group selected from a monocyclic cycloalkyl, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic heterocyclic group;

each R^7 is independently hydrogen, fluoro, or C_1-C_3 alkyl;

each R , R' or R'' is independently hydrogen or a C_1-C_4 aliphatic group or $N(R')_2$ is a monocyclic non-aromatic nitrogen-containing heterocyclic group;

m is zero or one; and

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B is $-H$, $-C(R^7)_3$, $-C(R^7)_2-C(R^7)_3$, or an optionally substituted group selected from a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, or a monocyclic or bicyclic non-aromatic heterocyclic group.

[0006] In some embodiments, compounds of the invention include compounds of formula (I) other than compounds where X_1 is $-COO-$ and R^1 is ethyl and ring A is substituted with: a) two occurrences of OMe , b) two occurrences of Me , or c) one occurrence of CF_3 . In some other embodiments, compounds of the invention include those compounds where X_1 is other than $-COO-$

[0007] 2. *Compounds and Definitions:*

[0008] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M. B. and March, J., John Wiley & Sons, New York: 2001.

[0001] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic", "cycloalkyl", or "cycloalkenyl"). For example, suitable aliphatic groups include substituted or unsubstituted linear, branched or cyclic alkyl, alkenyl, alkynyl groups and hybrids thereof, such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl, or (cycloalkyl)alkenyl. Unless otherwise specified, in various embodiments, aliphatic groups have 1-20, 1-15, 1-12, 1-10, 1-8, 1-6, 1-4, or 1-3 carbon atoms.

[0002] The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic", used alone or as part of a larger moiety, refer to a saturated or partially unsaturated cyclic aliphatic ring system having from 3 to about 14 members, wherein the aliphatic ring system is optionally substituted. In some embodiments, the cycloaliphatic group includes saturated ring systems ("cycloalkyl") having from about 3 to about 8 members. Cycloaliphatic groups include, without limitation, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cycloheptenyl, cyclooctyl, cyclooctenyl, and cyclooctadienyl. In some embodiments, the cycloalkyl has 3-6 carbons. The terms "cycloaliphatic", "carbocycle", "carbocyclyl", "carbocyclo", or "carbocyclic" also include aliphatic rings that are fused to one or more aromatic or nonaromatic rings,

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such as decahydronaphthyl or tetrahydronaphthyl, where the radical or point of attachment is on the aliphatic ring.

[0003] The term "alkoxy", or "thioalkyl", as used herein, refers to an alkyl group, as previously defined, attached to the principal carbon chain through an oxygen ("alkoxy") or sulfur ("thioalkyl") atom.

[0004] The terms "haloaliphatic", "haloalkyl", "haloalkenyl" and "haloalkoxy" refer to an aliphatic, alkyl, alkenyl or alkoxy group, as the case may be, substituted with one or more halogen atoms. As used herein, the term "halogen" or "halo" means F, Cl, Br, or I. Unless otherwise indicated, the terms "alkyl", "alkenyl", and "alkoxy" include haloalkyl, haloalkenyl and haloalkoxy groups, including, in particular, those with 1-5 fluorine atoms. By way of example, the terms "C₁₋₃ aliphatic" and "C₁₋₃ alkyl" include within their scope trifluoromethyl and pentafluoroethyl groups.

[0005] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR⁺ (as in N-substituted pyrrolidinyl)).

[0006] The terms "aryl" and "ar-", used alone or as part of a larger moiety, e.g., "aralkyl", "aralkoxy", or "aryloxyalkyl", refer to a C₆ to C₁₄ aromatic moiety comprising one to three aromatic rings, which are optionally substituted. Preferably, the aryl group is a C₆₋₁₀ aryl group. Aryl groups include, without limitation, phenyl, naphthyl, and anthracenyl. The term "aryl", as used herein, also includes groups in which an aromatic ring is fused to one or more heteroaryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the aromatic ring. Nonlimiting examples of such fused ring systems include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, fluorenyl, indanyl, phenanthridinyl, tetrahydronaphthyl, indolinyl, phenoxazinyl, benzodioxanyl, and benzodioxolyl. An aryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "aryl" may be used interchangeably with the terms "aryl group", "aryl ring", and "aromatic ring".

[0007] An "aralkyl" or "arylalkyl" group comprises an aryl group covalently attached to an alkyl group, either of which independently is optionally substituted. Preferably, the aralkyl group is C₆₋₁₀ aryl(C₁₋₆)alkyl, including, without limitation, benzyl, phenethyl, and naphthylmethyl.

[0008] The terms "heteroaryl" and "heteroar-", used alone or as part of a larger moiety, e.g., heteroaralkyl, or "heteroaralkoxy", refer to groups having 5 to 14 ring atoms, preferably 5, 6, 9, or 10 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to four heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and

includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizynyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar-", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*-quinolizynyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, and pyrido[2,3-*b*]-1,4-oxazin-3(4*H*)-one. A heteroaryl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0009] As used herein, unless otherwise indicated, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 3- to 7-membered monocyclic or 7- to 10-membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0-3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or ⁺NR (as in *N*-substituted pyrrolidinyl).

[0010] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, pyrrolidonyl, piperidinyl, pyrrolinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*-indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono-, bi-, tri-, or polycyclic, preferably mono-, bi-, or tricyclic, more preferably mono- or bicyclic. The term "heterocyclylalkyl"

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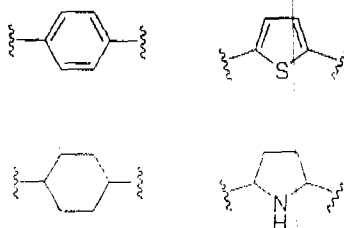
refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0011] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond between ring atoms. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0012] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms is replaced with a substituent. In general, unless otherwise indicated, suitable substituents include those described below for a substituted aliphatic group.

[0013] A methylene unit of the alkylene chain also can be optionally replaced by a functional group. In some embodiments, an internal methylene unit is replaced with the functional group. Examples of suitable functional groups are described in the specification and claims herein.

[0014] The terms "arylene", "heterocyclene" and "carbocyclene"/"cycloalkylene" refer to aryl, heteroaryl, non-aromatic heterocyclic or carbocyclic/cycloalkyl ring(s), respectively, in a molecule that are bonded to two other groups in the molecule through a single covalent from two of its ring atoms. Examples of suitable arylene groups include phenylene, pyrrolylene, thienylene, furanylene, imidazolylene, triazolylene, tetrazolylene, oxazolylene, isoxazolylene, oxadiazolylene, pyrazolylene, pyridinylene, pyrimidinylene, pyrazinylene, thiazolylene; examples of suitable mono-cyclic carbocyclenes include cyclopropylene, cyclopentylene, cyclohexylene and cycloheptylene; and examples of suitable non-aromatic heterocyclenes include piperidinylene, piperazinylene, pyrrolidinylene, pyrazolidinylene, imidazolidinylene, tetrahydrofuranylene, tetrahydrothienylene, isooxazolidinylene, oxazolidinylene, isothiazolidinylene, thiazolidinylene, oxathiolanylene, dioxolanylene, and dithiolanylene. By way of example, the structure of 1,4-phenylene, 2,5-thienylene, 1,4 cyclohexylene and 2,5-pyrrolodinylenes are shown below:



[0015] The term "substituted", as used herein, means that one or more hydrogens of the designated moiety are replaced, provided that the substitution results in a stable or chemically feasible

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compound. A stable compound or chemically feasible compound is one in which the chemical structure is not substantially altered when kept at a temperature from about -80°C to about +40°C, in the absence of moisture or other chemically reactive conditions, for at least a week, or a compound which maintains its integrity long enough to be useful for therapeutic or prophylactic administration to a patient. The phrase "one or more substituents", as used herein, refers to a number of substituents that equals from one to the maximum number of substituents possible based on the number of available bonding sites, provided that the above conditions of stability and chemical feasibility are met.

[0016] Unless otherwise indicated, an aryl (including aralkyl, aralkoxy, aryloxyalkyl and the like) or heteroaryl (including heteroaralkyl and heteroarylalkoxy and the like) group may contain one or more substituents and thus may be "optionally substituted". In addition to the substituents defined above and herein, suitable substituents on the unsaturated carbon atom of an aryl or heteroaryl group also include and are generally selected from halogen; -R°; -OR°; -SR°; -NO₂; -CN; -N(R°)₂; -NR°C(O)R°; -NR°C(S)R°; -NR°C(O)N(R°)₂; -NR°C(S)N(R°)₂; -NR°CO₂R°; -NR°NR°C(O)R°; -NR°NR°C(O)N(R°)₂; -NR°NR°CO₂R°; -C(O)C(O)R°; -C(O)CH₂C(O)R°; -CO₂R°; -C(O)R°; -C(S)R°; -C(O)N(R°)₂; -C(S)N(R°)₂; -OC(O)N(R°)₂; -OC(O)R°; -C(O)N(OR°)R°; -C(NOR°)R°; -S(O)₂R°; -S(O)₂OR°; -SO₂N(R°)₂; -S(O)R°; -NR°SO₂N(R°)₂; -NR°SO₂R°; -N(OR°)R°; -C(=NH)-N(R°)₂; -P(O)₂R°; -PO(R°)₂; or -OPO(R°)₂; wherein each independent occurrence of R° is selected from hydrogen, or an optionally substituted group selected from C₁₋₆ aliphatic, aryl, heteroaryl, heterocyclic, or cycloaliphatic or, notwithstanding the definition above, two independent occurrences of R°, on the same substituent or different substituents, taken together with their intervening atom(s) form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

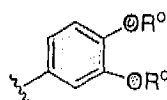
[0017] Unless otherwise indicated, an aliphatic or heteroaliphatic group, or a non-aromatic heterocyclic ring may contain one or more substituents and thus may be "optionally substituted". In addition to the substituents defined above and herein, suitable substituents on the saturated carbon of an aliphatic or heteroaliphatic group, or of a non-aromatic heterocyclic ring are selected from those listed above for the unsaturated carbon of an aryl or heteroaryl group and additionally include the following: =O, =S, =NNHR°, =NN(R°)₂, =NNHC(O)R°, =NNHCO₂(alkyl), =NNHSO₂(alkyl), or =NR°, where each R° is independently selected from hydrogen or an optionally substituted C₁₋₆ aliphatic group.

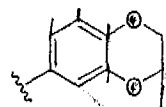
[0018] In addition to the substituents defined above and herein, optional substituents on the nitrogen of a non-aromatic heterocyclic ring also include and are generally selected from -R°, -N(R°)₂, -C(O)R°, -CO₂R°, -C(O)C(O)R°, -C(O)CH₂C(O)R°, -SO₂R°, -SO₂N(R°)₂, -C(=S)N(R°)₂,

$-C(=NH)-N(R^+)_2$, or $-NR^+SO_2R^+$; wherein R^+ is hydrogen, or an optionally substituted group selected from C_{1-6} aliphatic, aryl, heteroaryl, heterocyclic, or cycloaliphatic or, notwithstanding the definition above, two independent occurrences of R^+ , on the same substituent or different substituents, taken together with their intervening atom(s) form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0019] As detailed above, in some embodiments, two independent occurrences of R^0 (or R^+ or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) to form an optionally substituted 3-12 membered saturated, partially unsaturated, or fully unsaturated monocyclic or bicyclic ring having 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0020] Exemplary rings that are formed when two independent occurrences of R^0 (or R^+ , or any other variable similarly defined in the specification and claims herein), are taken together with their intervening atom(s) include, but are not limited to the following: a) two independent occurrences of R^0 (or R^+ , or any other variable similarly defined in the specification or claims herein) that are bound to the same atom and are taken together with that atom to form a ring, for example, $N(R^0)_2$, where both occurrences of R^0 are taken together with the nitrogen atom to form a piperidin-1-yl, piperazin-1-yl, or morpholin-4-yl group; and b) two independent occurrences of R^0 (or R^+ , or any other variable similarly defined in the specification or claims herein) that are bound to different atoms and are taken together with both of those atoms to form a ring, for example where a phenyl group is substituted with

two occurrences of OR^0 , these two occurrences of R^0 are taken together with the oxygen atoms to which they are bound to form a fused 6-membered oxygen containing ring:



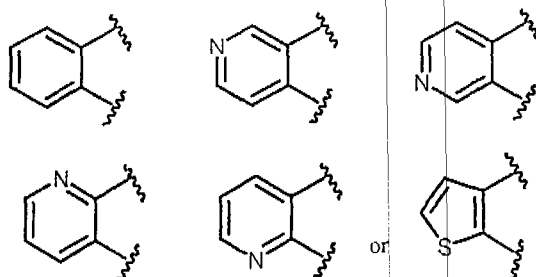
It will be appreciated that a variety of other rings (e.g., also spiro, and bridged rings) can be formed when two independent occurrences of R^0 (or R^+ , or any other variable similarly defined in the specification and claims herein) are taken together with their intervening atom(s) and that the examples detailed above are not intended to be limiting.

[0021] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the *R* and *S* configurations for each asymmetric center, (*Z*) and (*E*) double bond isomers, and (*Z*) and (*E*) conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures

depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[0022] 3. Description of Exemplary Compounds:

[0023] As described generally above for compounds of formula I, ring A is an optionally substituted, fused 5-6-membered aryl or heteroaryl ring. In some embodiments, ring A is an optionally substituted group selected from:



[0024] Preferably, Ring A is an optionally substituted, fused phenyl group. In general, suitable Ring A substituents are as provided in the section describing suitable aryl and heteroaryl group substituents. Preferably, Ring A, as defined generally and in preferred embodiments above, is substituted by n substituents represented by R^8 , wherein n is 0, 1, 2, 3 or 4, preferably 0 or 1. Each R^8 is independently halo, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{R}^9$, $-\text{N}(\text{R}^{10})\text{CO}_2\text{R}^{9a}$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{OC}(\text{O})\text{R}^9$, $-\text{OC}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{SO}_2\text{R}^{9a}$, $-\text{S}(\text{O})\text{R}^{9a}$, $-\text{SO}_2\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{9a}$ or an optionally substituted group selected from C_{1-3} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic heterocyclic group, wherein each R^9 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, each R^{9a} is independently an optionally substituted C_{1-6} aliphatic group; and each R^{10} is independently hydrogen, a C_{1-6} aliphatic group, $-\text{CO}_2\text{R}^{9a}$, $-\text{SO}_2\text{R}^{9a}$, or $-\text{C}(\text{O})\text{R}^9$, or $\text{N}(\text{R}^{10})_2$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group. Preferably, each R^8 is independently halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-\text{NO}_2$, $-\text{CN}$, amine, C_{1-3} alkylamine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl.

[0025] As described generally above for compounds of formula I, Y is $>\text{C}(\text{R}^x)-$ or $>\text{N}-$, wherein R^x is hydrogen or a C_1 - C_4 aliphatic group. Y is preferably $>\text{C}(\text{R}^x)-$. More preferably Y is $>\text{CH}-$.

[0026] As described generally above for compounds of formula I, X_1 is $-\text{C}(=\text{O})-$, $-\text{SO}_2-$, $-\text{CONR}-$, $-\text{C}(\text{R})_2-$, or $-\text{CO}_2-$. Preferably, X_1 is $-\text{C}(=\text{O})-$.

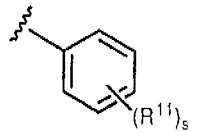
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[0027] As described generally above for compounds of formula I, R^1 is an optionally substituted group selected from an aliphatic, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group. Preferably, R^1 is an optionally substituted monocyclic or bicyclic aryl or heteroaryl group. In other preferred embodiments, R^1 is an optionally substituted group selected from phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl. In yet other preferred embodiments, R^1 is an optionally substituted monocyclic non-aromatic heterocyclic or non-aromatic carbocyclic group. In preferred embodiments, R^1 is an optionally substituted monocyclic non-aromatic heterocyclic or non-aromatic carbocyclic group selected from cyclopropyl, cyclobutyl, azetidiny, cyclopentyl, pyrrolidinyl, cyclohexyl, cycloheptyl, morpholinyl, piperidinyl, piperazinyl, or thiomorpholinyl. In still other preferred embodiments, R^1 is optionally substituted phenyl or pyridyl. In yet other preferred embodiments, R^1 is optionally substituted phenyl.

[0028] In general, suitable substituents for a substitutable aromatic ring carbon or nitrogen atom of an aryl or heteroaryl group represented by R^1 are as provided in the section describing suitable substituents for an aryl or heteroaryl group; suitable substituents for a substitutable ring carbon or nitrogen atom of a non-aromatic heterocyclic ring in the group represented by R^1 are as provided in the section describing suitable substituents for a non-aromatic heterocyclic group; and suitable substituents for an aliphatic group or a substitutable ring carbon of a carbocyclic group represented by R^1 are as provided in the section describing suitable substituents for an aliphatic group.

[0029] In some embodiments, R^1 is substituted with one or more occurrences of R^{11} , wherein each R^{11} is independently halo, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NO_2$, $-N(R^{12}R^{13})$, $-N(R^{13})C(O)R^{12}$, $-N(R^{13})CO_2R^{12a}$, $-N(R^{13})C(O)N(R^{12}R^{13})$, $-C(O)N(R^{12}R^{13})$, $-OC(O)R^{12}$, $-OC(O)N(R^{12}R^{13})$, $-C(O)R^{12}$, $-CO_2R^{12}$, $-SO_2R^{12a}$, $-S(O)R^{12a}$, $-SO_2N(R^{12}R^{13})$, $-N(R^{13})SO_2R^{12a}$, or an optionally substituted group selected from C_{1-8} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic carbocyclic group, wherein each R^{12} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group, each R^{12a} is an optionally substituted C_{1-6} aliphatic group, and each R^{13} is independently hydrogen, a C_{1-6} aliphatic group, $-CO_2R^{12a}$, $-SO_2R^{12a}$, or $-C(O)R^{12}$, or $-N(R^{12}R^{13})$ is an optionally substituted monocyclic heteroaryl or non-aromatic heterocyclic group. Preferably, each R^{11} is independently halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-NO_2$, $-CN$, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl. More preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each optionally substituted at any

one or more substitutable ring carbon atoms with R^{11} . Even more preferably, R^1 is a phenyl group represented by the following structural formula:



s is 0, 1, 2, 3 or 4, preferably 0-2, and more preferably 0 or 1.

[0030] Alternatively, R^1 is substituted with $T_2-V_2-T_3-M-R^Y$, and R^1 is further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} .

[0031] M is absent or an optionally substituted monocyclic arylene, an optionally substituted monocyclic non-aromatic carbocycle or an optionally substituted monocyclic non-aromatic heterocycle. Examples of suitable arylene groups include phenylene, pyrrolylene, thienylene, furanyle, imidazolylen, triazolylen, tetrazolylen, oxazolylen, isoxazolylen, oxadiazolylen, pyrazolylen, pyridinylen, pyrimidylen, pyrazinylen, thiazolylen; examples of suitable monocyclic carbocycles include cyclopropylene, cyclopentylene, cyclohexylene and cycloheptylene; and examples of suitable non-aromatic heterocycles include piperidinylen, piperazinylen, pyrrolidinylen, pyrazolidinylen, imidazolidinylen, tetrahydrofuranyle, tetrahydrothienylene, isooxazolidinylen, oxazolidinylen, isothiazolidinylen, thiazolidinylen, oxathiolanylen, dioxolanylen, and dithiolanylen. Phenylene, [2,5]thienylene and [2,5]furanyle are preferred arylene groups. Suitable substituents for an arylene are as provided in the section describing aryl and heteroaryl group substituents; and suitable substituents for non-aromatic heterocycle and carbocycle are as described in the sections providing suitable substituents for a non-aromatic heterocyclic group and aliphatic group, respectively. Preferred substituents for a substitutable aromatic ring carbon in a group represented by M and a substitutable ring carbon or ring nitrogen atom in a non-aromatic ring represented by M are as described above for an aryl or heteroaryl group.

[0032] V_2 is absent, $-O-$, $-C(O)-$, $-N(R^{19})-$, $-S-$, $-S(O)-$, $-C(O)NR^{19}-$, $-NR^{19}C(O)-$, $-S(O)_2NR^{19}-$, $-NR^{19}S(O)_2-$, or $-S(O)_2-$. Preferably, V_2 is absent or $-O-$.

[0033] R^Y is $-C(O)OR^{18}$, $-C(O)R^{18}$, $-OC(O)R^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2R^{18a}$, $-S(O)_2COR^{18}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}S(O)_2R^{18a}$, $S(O)_2OR^{18}$, $-S(O)OR^{18}$, $-S(O)R^{18a}$, $-SR^{18}$, $-C(O)NR^{19}S(O)_2R^{18a}$, $-CN$, $-NR^{19}C(O)N(R^{19})_2$, $-OC(O)NR^{19}$, $-N(R^{19})_2$, $-OR^{18}$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group. Suitable substituents for the non-aromatic heterocyclic group and the heteroaryl group represented by R^Y are as provided in the section below describing suitable substituents for a heterocyclic group and heteroaryl group, respectively. Preferably, R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-$

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$\text{NR}^{19}\text{C(O)OR}^{18a}$, $-\text{S(O)}_2\text{N(R}^{19})_2$, $-\text{NR}^{19}\text{S(O)}_2\text{R}^{18a}$, $-\text{NR}^{19}\text{C(O)N(R}^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} . More preferably, R^Y is $-\text{C(O)OR}^{18}$, $-\text{C(O)N(R}^{19})_2$, optionally *N*-substituted tetrazolyl or optionally *N*-substituted imidazolyl.

[0034] Each R^{18} is independently hydrogen or C_{1-6} aliphatic group. Preferably, each R^{18} is independently H or $\text{C}_1\text{-C}_3$ alkyl. More preferably, R^{18} is -H, methyl, or ethyl.

[0035] Each R^{18a} is independently C_{1-6} aliphatic group. Preferably, each R^{18a} is independently H or $\text{C}_1\text{-C}_3$ alkyl. More preferably, R^{18a} is -H, methyl, or ethyl.

[0036] Each R^{19} is independently selected from hydrogen, a C_{1-6} aliphatic group, $-\text{CO}_2\text{R}^{18}$, $-\text{SO}_2\text{R}^{18}$, or $-\text{C(O)R}^{18}$, or $-\text{NR}^{19}$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group. Preferably, each R^{19} is H or $\text{C}_1\text{-C}_3$ alkyl or $\text{N(R}^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group. More preferably, R^{19} is -H, methyl, or ethyl.

[0037] R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl. R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl.

[0038] T_2 is absent, or a C_{1-10} straight chain alkylene, and T_3 is a C_{1-10} straight chain alkylene wherein T_2 and T_3 together contain no more than 10 carbon atoms, and provided that T_3 is a C_{2-10} straight chained alkylene when M is absent and V_2 is $-\text{O}-$, $-\text{S}-$, $-\text{N(R}^{19})-$, $-\text{C(O)N(R}^{19})-$ or $-\text{S(O)}_2\text{N(R}^{19})-$ and R^Y is $-\text{NR}^{19}\text{S(O)}_2\text{R}^{18a}$, $-\text{NR}^{19}\text{S(O)}_2\text{R}^{18a}$, $-\text{NR}^{19}\text{C(O)R}^{18}$, $-\text{NR}^{19}\text{C(O)OR}^{18a}$, $-\text{NR}^{19}\text{C(O)N(R}^{19})_2$, $-\text{CN}$, $-\text{OH}$, $-\text{SH}$, $-\text{N(R}^{19})_2$. T_2 and T_3 are optionally and independently substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, alkoxy, haloalkoxy, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine or hydroxyl. T_2 is preferably absent. Preferably, T_3 is a C_{1-6} straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl.

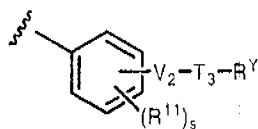
[0039] In some embodiments, R^1 is a monocyclic aryl or heteroaryl group substituted with $-\text{T}_2\text{-V}_2\text{-T}_3\text{-M-R}^Y$ and is further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} .

[0040] Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrolyl, tetrazolyl, indolyl, benzotriazolyl,

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benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholiny or benzpiperaziny, each substituted with $-V_2-T_3-R^Y$, and each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} .

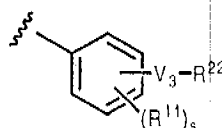
[0041] More preferably, R^1 is a phenyl group represented by the following structural formula:



$-V_2-T_3-R^Y$ is preferably para to the X_1 moiety as referred to in compounds of formula I.

[0042] In another alternative, R^1 is substituted by $-V_3-R^{22}$, and is optionally further substituted at any one or more substitutable carbon atoms with R^{11} . V_3 is a covalent bond, $-O-$, $-C(O)-$, $-N(R^{13})-$, $-S-$, $-S(O)-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-S(O)_2NR^{13}-$, $-NR^{13}S(O)_2-$, or $-S(O)_2-$. Preferably, V_3 is a covalent bond or $-O-$. R^{22} is an optionally substituted monocyclic or bicyclic non-aromatic carbocyclic or an optionally substituted monocyclic or bicyclic non-aromatic heterocyclic group. Preferably, R^{22} is an optionally substituted monocyclic non-aromatic heterocyclic group. More preferably, R^{22} is an optionally substituted cyclohexanyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothienyl, morpholiny, thiomorpholiny, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperaziny, isothiazolidinyl S,S, dioxide, or piperidinyl. Even more preferably, R^{22} is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholiny, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperaziny, or piperidinyl. Suitable substituents for the non-aromatic carbocyclic group and non-aromatic heterocyclic group represented by R^{22} are as defined below for aliphatic and non-aromatic heterocyclic groups, respectively. Preferred substituents at a substitutable ring carbon atom of a non-aromatic carbocyclic ring or a substitutable carbon atom of a non-aromatic heterocyclic group represented by R^{22} are alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$, or $-C(O)NR^{23}_2$. Preferred substituents at a substitutable ring nitrogen atom of a non-aromatic heterocyclic group represented by R^{22} are alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ or $-(CH_2)_qCH(CH_3)CO_2R^{23}$, wherein q is an integer from 1-4, and each R^{23} is independently $-H$, alkyl, haloalkyl, or hydroxyalkyl.

[0043] In some embodiments, R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$, and the monocyclic aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} . Preferably, R^1 is a phenyl group represented by the following structural formula:



$-V_3-R^{22}$ is preferably para to the X_1 moiety as referred to in compounds of formula I.

[0044] In yet another alternative, R^1 is a substituted or unsubstituted aliphatic group. Preferably, R^1 is $-T_2-V_2-T_3-M-R^Y$. More preferably, R^1 is $-V_2-T_3-R^Y$.

[0045] As described generally above, R^2 is a C_1-C_3 alkyl group, a C_1-C_3 haloalkyl group or C_3-C_6 cycloalkyl group. The C_1-C_3 alkyl group represented by R^2 is optionally substituted with R^5 . Preferably, R^2 is C_1-C_2 alkyl or C_3-C_6 cycloalkyl.

[0046] As described generally above, R^3 is hydrogen, C_1-C_6 alkyl optionally substituted by R^6 , C_1-C_6 fluoroalkyl, or an optionally substituted group selected from a C_3-C_8 cycloalkyl, a monocyclic non-aromatic heterocyclic, a monocyclic aryl, or a monocyclic heteroaryl group. Suitable substituents for the monocyclic non-aromatic heterocyclic group and monocyclic aryl or heteroaryl group represented by R^3 are as provided in the section describing suitable substituents for an aryl or heteroaryl group and a non-aromatic heterocyclic group, respectively. Preferably, R^3 is a C_1-C_4 alkyl group.

[0047] As described generally above, R^4 is $-[C(R^7)_2]_m-B$, or R^3 and R^4 may be taken together with the intervening nitrogen atom to form an optionally substituted monocyclic or bicyclic heteroaryl or non-aromatic heterocyclic group, or R^3 and R^4 may be taken together with the intervening carbon and nitrogen atoms to form an optionally substituted monocyclic non-aromatic nitrogen-containing heterocyclic group. In another alternative, R^4 is $-(CH_2)_m-B$.

R^5 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-COOR'$ or $-N(R')_2$.

R^6 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-N(R')_2$, $-C(O)R'$, $-COOR'$, $C(O)N(R')_2$, or an optionally substituted group selected from a monocyclic cycloalkyl, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic heterocyclic group. Suitable substituents for the monocyclic cycloalkyl group, the monocyclic non-aromatic heterocyclic group, the monocyclic aryl group, and the monocyclic heteroaryl group represented by R^6 are as provided in the section describing suitable substituents for an aliphatic group, a non-aromatic heterocyclic group, an aryl group, and a heteroaryl group, respectively.

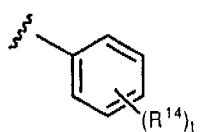
Each R^7 is independently hydrogen, fluoro, or C_1-C_3 alkyl. Preferably, R^7 is hydrogen or methyl, more preferably hydrogen.

Each R , R^X or R' is independently hydrogen or a C_1-C_4 aliphatic group or $N(R')_2$ is a monocyclic non-aromatic nitrogen-containing heterocyclic group.

m is zero or one.

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B is $-H$, $-C(R^7)_3$, $-C(R^7)_2-C(R^7)_3$, an optionally substituted group selected from a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, or a monocyclic or bicyclic non-aromatic heterocyclic group. Suitable substituents for these groups are as provided in the section describing suitable substituents for the monocyclic or bicyclic cycloalkyl group, the monocyclic or bicyclic aryl group, the monocyclic or bicyclic heteroaryl group, and the monocyclic or bicyclic non-aromatic heterocyclic group. Preferred substituents for a substitutable ring carbon atom of a group represented by B is R^{14} . Preferably B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} . More preferably, B is a phenyl group represented by the following structural formula:



t is 0, 1, 2, 3 or 4, preferably 0-2 and more preferably 0-1.

Each R^{14} is independently C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, R^{14a} , R^{14b} , $-T-R^{14a}$, $-T-R^{14b}$, $-V-T_1-R^b$, $-V-T-R^{14a}$, $-V_1-T-R^{14a}$ or $-V_1-T_1-R^{14b}$. Preferably, each R^{14} is independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-NO_2$, $-CN$, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl. R^{14a} are independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-NO_2$, $-CN$, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl.

V is $-O-$, $-N(R)-$, $-C(O)N(R)-$ or $-S(O)_2N(R)-$.

V_1 is $-S(O)_2-$, $-C(O)-$, $-N(R)C(O)-$ or $-N(R)SO_2-$.

T is a C_1 - C_4 optionally substituted alkylene. Examples of suitable substituents for the alkylene group represented by T include halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, alkoxy, haloalkoxy, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine or hydroxyl.

T_1 is a C_2 - C_4 optionally substituted alkylene. Examples of suitable substituents for the alkylene group represented by T_1 include halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, alkoxy, haloalkoxy, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine or hydroxyl.

Each R^{14a} is independently selected from $-OR^{15a}$, $-SR^{15a}$, $-C(O)N(R^{16})_2$, $-C(O)R^{15}$, $-CO_2R^{15}$, $-SO_2R^{15a}$, $-S(O)R^{15a}$, $-SO_2N(R^{16})_2$, an optionally substituted monocyclic aryl or heteroaryl group, or an optionally substituted monocyclic non-aromatic heterocyclic group. Suitable substituents for the monocyclic aryl or heteroaryl group and the monocyclic non-aromatic heterocyclic group represented

by R^{14a} are as provided in the section below describing suitable substituents for an aryl, heteroaryl, and a non-aromatic heterocyclic group, respectively.

Each R^{14b} is independently selected from halo, -OH, -SH, -CN, -NO₂, -N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁵, -N(R¹⁶)CO₂R^{15a}, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)R¹⁵, -OC(O)N(R¹⁶)₂ or -N(R¹⁶)SO₂R^{15a}.

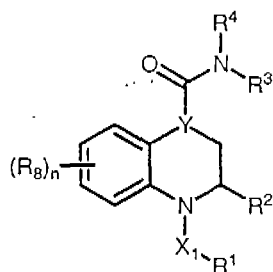
Each R^{15} is independently hydrogen or a C₁₋₆ aliphatic group.

Each R^{15a} is a C₁₋₆ aliphatic group.

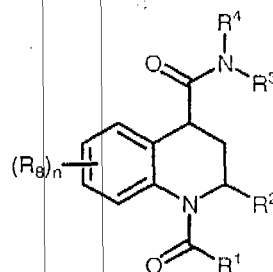
Each R^{16} is independently selected from hydrogen, a C₁₋₆ aliphatic group, -CO₂R^{15a}, -SO₂R^{15a}, or -C(O)R¹⁵, or N(R¹⁶)₂ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

[0048] In a preferred embodiment, for compounds of formula (I), R^1 is an optionally substituted group selected from a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group, and Y is >C(R³)-.

[0049] In another preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III):



(II)



(III)

[0050] The values and preferred values for the variables in Structural Formulas (II) and (III) are as described above for Structural Formula (I). Preferably in Structural Formula (II), R^1 is an optionally substituted group selected from a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group, and Y is >C(R³)-. Preferably in Structural Formula (III), R^1 is an optionally substituted group selected from a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group.

[0051] It will be appreciated that certain other embodiments are of interest:

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[0052] In a first preferred embodiment, a compound of the invention is represented by Structural Formulas (II) and (III), wherein:

R^1 is a monocyclic or bicyclic aryl or heteroaryl group optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ; and

the values and preferred values for R^{11} and the remainder of the variables in Structural Formulas (II) and (III) are as described above for Structural Formula (I).

[0053] In a second preferred embodiment, a compound of the invention is represented by Structural Formulas (II) and (III), wherein:

R^1 is an optionally substituted monocyclic or bicyclic aryl or heteroaryl group optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for R^{11} , R^{14} , and the remainder of the variables in Structural Formulas (II) and (III) are as described above for Structural Formula (I).

[0054] In a third preferred embodiment, a compound of the invention is represented by Structural Formulas (II) and (III), wherein:

R^1 is an optionally substituted monocyclic or bicyclic aryl or heteroaryl group optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for m, R^{11} , R^{14} and the remainder of the variables in Structural Formulas (II) and (III) are as described above for Structural Formula (I).

[0055] In a fourth preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III) wherein:

R^1 is a monocyclic or bicyclic aryl or heteroaryl group substituted with $-T_2-V_2-T_3-M-R^Y$ and further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophienyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each substituted with $-T_2-V_2-T_3-M-R^Y$, and each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ; and

the values and preferred values for R^Y , M, V_2 , T_2 , T_3 , R^{11} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I). M and T_2 are preferably absent.

[0056] In a fifth preferred, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

R^1 is a monocyclic or bicyclic aryl or heteroaryl group substituted with $-T_2-V_2-T_3-M-R^Y$ and further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophienyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each substituted with $-T_2-V_2-T_3-M-R^Y$, and each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for R^Y , M, V_2 , T_2 , T_3 , R^{11} , R^{12} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I). M and T_2 are preferably absent.

[0057] In a sixth preferred, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

R^1 is a monocyclic or bicyclic aryl or heteroaryl group substituted with $-T_2-V_2-T_3-M-R^Y$ and further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} . Preferably, R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrollyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each substituted with $-T_2-V_2-T_3-M-R^Y$, and each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;

R^2 is C_1-C_2 alkyl or C_3-C_6 cycloalkyl;

R^3 is a C_1-C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for m , R^Y , M , V_2 , T_2 , T_3 , R^{11} , R^{14} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I). M and T_2 are preferably absent.

[0058] In a seventh preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$. The aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} ;

the values and preferred values for V_3 , R^{11} , R^{22} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I).

[0059] In an eighth preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$. The aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} ;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for V_3 , R^{11} , R^{14} , R^{22} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I).

[0060] In a ninth preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

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R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$. The aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} ;

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for m , V_3 , R^{11} , R^{14} , R^{22} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I).

[0061] In a tenth preferred embodiment, a compound of the invention is represented by Structural Formula (II) or (III), wherein:

R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$. The aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} ;

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

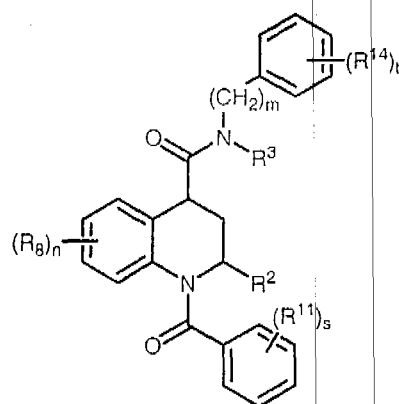
R^{22} is an optionally substituted monocyclic non-aromatic heterocyclic group;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

the values and preferred values for m , V_3 , R^{11} , R^{14} and the remainder of the variables in Structural Formulas (II) and (III) are as described for Structural Formula (I).

[0062] In the first through the tenth preferred embodiments described directly above, Y in Structural Formula (II) is preferably $>C(R^X)-$.

[0063] In yet another preferred embodiment, a compound of the present invention is represented by Structural Formula (IV):



(IV).

[0064] The values and preferred values for the variables in Structural Formula (IV) are as described above for Structural Formula (I).

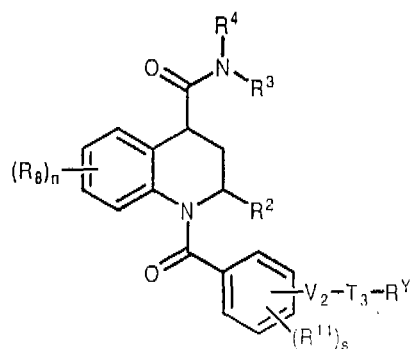
[0065] In an eleventh preferred embodiment, a compound of the present invention is represented by Structural Formula (IV), wherein:

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

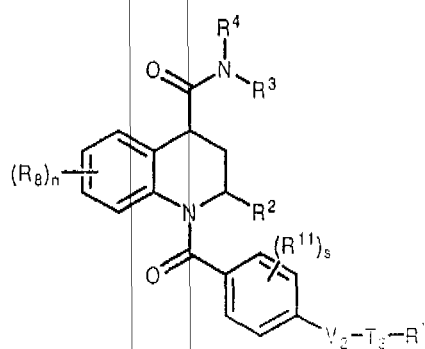
R^3 is a C_1 - C_4 alkyl group; and

the values and preferred values for the remainder of the variables in Structural Formula (IV) are as described above for Structural Formula (I).

[0066] In still another preferred embodiment, a compound of the present invention is represented by Structural Formula (V) or (VI):



(V).



(VI).

[0067] The values and preferred values for the variables in Structural Formulas (V) and (VI) are as described above for Structural Formula (I).

[0068] In a twelfth preferred embodiment, a compound of the present invention is represented by Structural Formula (V) or (VI), wherein R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl; R^3 is a C_1 - C_4 alkyl

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group; R^4 is $-(CH_2)_m-B$; B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and the values and preferred values for m, R^{14} and the remainder of the variables in Structural Formula (V) and (VI) are as described above for Structural Formula (I).

[0069] In a thirteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (V) or (VI), wherein:

R^2 is C_1-C_2 alkyl or C_3-C_6 cycloalkyl;

R^3 is a C_1-C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;

V_2 is a covalent bond or $-O-$;

T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} . Preferably, R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, an optionally *N*-substituted tetrazolyl or an optionally *N*-substituted imidazolyl;

each R^{18} is independently H or C_1-C_3 alkyl. Preferably, each R^{18} is independently $-H$, methyl or ethyl;

each R^{18a} is independently C_1-C_3 alkyl. Preferably, each R^{18a} is independently methyl or ethyl;

each R^{19} is H or alkyl or NR^{19}_2 is a nitrogen-containing non-aromatic heterocyclic group.

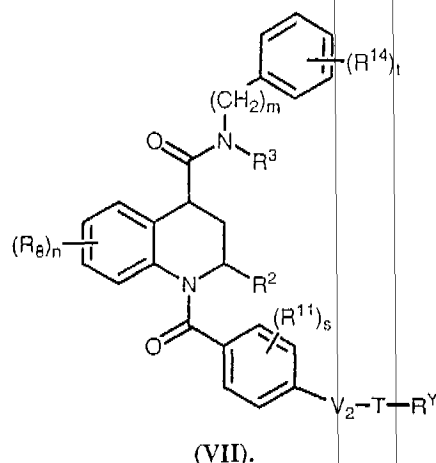
Preferably, each R^{19} is independently $-H$, methyl or ethyl;

R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl;

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl; and

the values and preferred values for m, R^{14} and the remainder of the variables in Structural Formula (V) and (VI) are as described above for Structural Formula (I).

[0070] In still another preferred embodiment, a compound of the present invention is represented by Structural Formula (VII):



[0071] The values and preferred values for the variables in Structural Formula (VII) are as described above for Structural Formula (I).

[0072] In a fourteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (VII):

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

V_2 is a covalent bond or -O-;

T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} . Preferably, R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, an optionally *N*-substituted tetrazolyl or an optionally *N*-substituted imidazolyl;

each R^{18} is independently H or C_1 - C_3 alkyl. Preferably, each R^{18} is independently -H, methyl or ethyl;

each R^{18a} is independently C_1 - C_3 alkyl. Preferably, each R^{18a} is independently methyl or ethyl;

each R^{19} is H or alkyl or $N(R^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group.

Preferably, each R^{19} is independently -H, methyl or ethyl;

R^{20} is an optionally substituted piperidinonyl, oxazolidinonyl, oxazolidinonyl, thiazolidinonyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl,

thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl;

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl; and

the values and preferred values for the remainder of the variables in Structural Formula (V) and (VI) are as described above for Structural Formula (I).

[0073] In a fifteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (VII):

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

V_2 is a covalent bond or -O-;

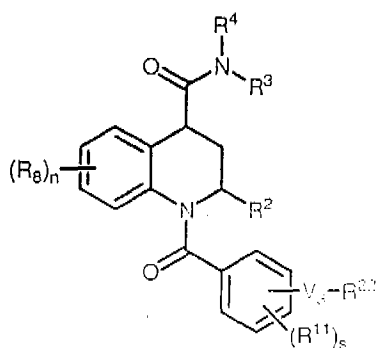
T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is -C(O)OR¹⁸, -C(O)N(R¹⁹)₂, optionally *N*-substituted tetrazolyl or optionally *N*-substituted imidazolyl;

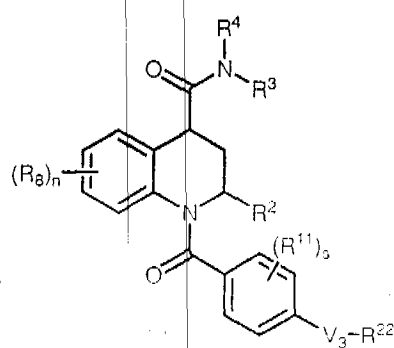
R^{18} and each R^{19} are independently -H, methyl, or ethyl; and

the values and preferred values for the remainder of the variables in Structural Formula (V) and (VI) are as described above for Structural Formula (I).

[0074] In another preferred embodiment, a compound of the present invention is represented by Structural Formula (VIII) or (IX):



(VIII)



(IX)

[0075] The values and preferred values for the variables in Structural Formula (VIII) and (IX) are as described above for Structural Formula (I).

[0076] In a sixteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (VIII) or (IX) wherein: R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl; R^3 is a C_1 - C_4 alkyl group; R^4 is $-(CH_2)_m-B$; R^{22} is an optionally substituted monocyclic non-aromatic heterocyclic group; B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and the values and preferred values for m, R^{14} and the remainder of the variables in Structural Formulas (VIII) and (IX) are as described for Structural Formula (I).

[0077] In a seventeenth preferred embodiment, a compound of the present invention is represented by Structural Formula (VIII) or (IX), wherein:

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;

R^{22} is an optionally substituted cyclohexanyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothienyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, isothiazolidinyl S,S, dioxide, or piperidinyl. Preferably, R^{22} is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$, or $-C(O)N(R^{23})_2$, and each optionally substituted at any substitutable nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_4CO_2H$, $-(CH_2)_4C(O)N(R^{23})_2$, $-(CH_2)_4CH(CH_3)CON(R^{23})_2$; $-(CH_2)_4C(CH_3)_2CON(R^{23})_2$; $-(CH_2)_4C(CH_3)_2CO_2R^{23}$ or $-(CH_2)_4CH(CH_3)CO_2R^{23}$; and

the values and preferred values for m, q, R^{14} , R^{23} and the remainder of the variables in Structural Formulas (VIII) and (IX) are as described for Structural Formula (I).

[0078] In an eighteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (VIII) or (IX), wherein:

V is absent or $-O-$;

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl;

R^3 is a C_1 - C_4 alkyl group;

R^4 is $-(CH_2)_m-B$;

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;

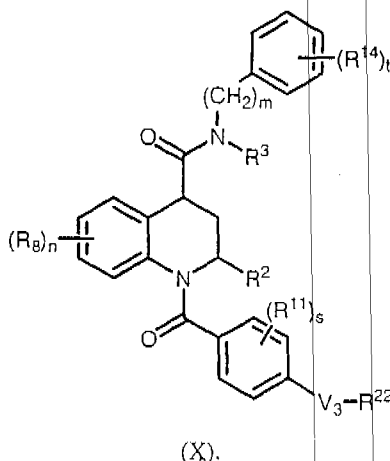
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R^{22} is an optionally substituted cyclohexanyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothienyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, isothiazolidinyl S,S, dioxide, or piperidinyl. Preferably, R^{22} is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$, or $-C(O)N(R^{23})_2$, and each optionally substituted at any substitutable nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ or $-(CH_2)_qCH(CH_3)CO_2R^{23}$; and

the values and preferred values for m , q , R^{14} , R^{23} and the remainder of the variables in Structural Formulas (VIII) and (IX) are as described for Structural Formula (I).

In certain preferred embodiments V_3 is absent.

[0079] In another preferred embodiment, a compound of the present invention is represented by Structural Formula (X):



wherein the values and preferred values for the variables in Structural Formula (X) are as described for Structural Formula (I). In certain preferred embodiments V_3 is absent.

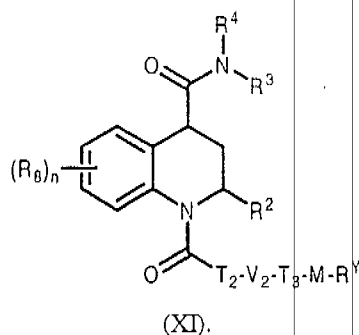
[0080] In a nineteenth preferred embodiment, a compound of the present invention is represented by Structural Formula (X) wherein:

V is absent or $-O-$;

R^2 is C_1 - C_2 alkyl or C_3 - C_6 cycloalkyl; R^3 is a C_1 - C_4 alkyl group; R^{22} is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted at any substitutable carbon

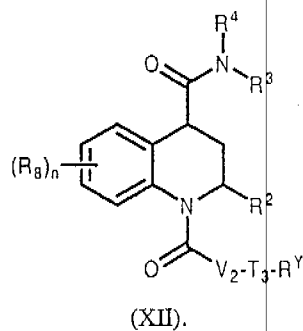
atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-\text{C}(\text{O})\text{OR}^{23}$, $-\text{C}(\text{O})\text{R}^{23}$, $-\text{OC}(\text{O})\text{R}^{23}$, or $-\text{C}(\text{O})\text{N}(\text{R}^{23})_2$, and each optionally substituted at any substitutable nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-\text{C}(\text{O})\text{OR}^{23}$, $-\text{C}(\text{O})\text{R}^{23}$, $-(\text{CH}_2)_q\text{CO}_2\text{H}$, $-(\text{CH}_2)_q\text{C}(\text{O})\text{N}(\text{R}^{23})_2$, $-(\text{CH}_2)_q\text{CH}(\text{CH}_3)\text{CON}(\text{R}^{23})_2$; $-(\text{CH}_2)_q\text{C}(\text{CH}_3)_2\text{CON}(\text{R}^{23})_2$; $-(\text{CH}_2)_q\text{C}(\text{CH}_3)_2\text{CO}_2\text{R}^{23}$ or $-(\text{CH}_2)_q\text{CH}(\text{CH}_3)\text{CO}_2\text{R}^{23}$; and the values and preferred values for m , q , R^{14} , R^{23} and the remainder of the variables in Structural Formulas (X) are as described for Structural Formula (I).

[0081] In still another preferred embodiment, a compound of the present invention is represented by Structural Formula (XI):



wherein the values and preferred values for the variables in Structural Formula (XI) are as described for Structural Formula (I).

[0082] In another preferred embodiment, a compound of the present invention is represented by Structural Formula (XII):



wherein the values and preferred values for the variables in Structural Formula (XII) are as described for Structural Formula (I).

[0083] In a twentieth preferred embodiment, a compound of the present invention is represented by Structural Formula (XII), wherein:

V_2 is a covalent bond or $-\text{O}-$;

T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally N -

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substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} ;

each R^{18} is independently H or C_1 - C_3 alkyl;

each R^{18a} is independently C_1 - C_3 alkyl;

each R^{19} is H or alkyl or $N(R^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group;

R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl;

and the values and preferred values for the remainder of the variables in Structural Formula (XII) are as described for Structural Formula (I).

[0084] In a twenty-first preferred embodiment, a compound of the present invention is represented by Structural Formula (XII), wherein:

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;

V_2 is a covalent bond or $-O-$;

T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} . Preferably, R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, optionally *N*-substituted tetrazolyl or optionally *N*-substituted imidazolyl;

each R^{18} is independently H or C_1 - C_3 alkyl. Preferably, each R^{18} is independently H, methyl, or ethyl;

each R^{18a} is independently C_1 - C_3 alkyl. Preferably, each R^{18a} is independently methyl, or ethyl;

each R^{19} is H or alkyl or $N(R^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group. Preferably, each R^{19} is independently H, methyl, or ethyl;

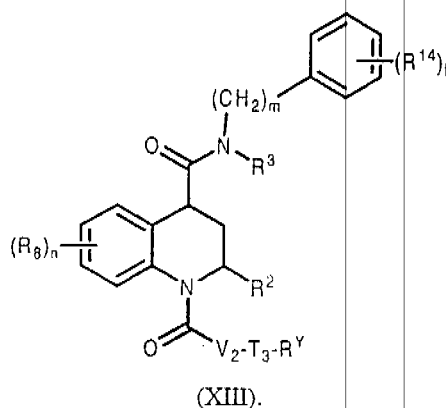
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R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl; and

and the values and preferred values for R^{14} and the remainder of the variables in Structural Formulas (XII) are as described for Structural Formula (I).

[0085] In another preferred embodiment, a compound of the present invention is represented by Structural Formula (XIII):



wherein V_2 , T_3 , R^Y , R^{18} , R^{18a} and R^{19} are as described for Structural Formula (XII). The values and preferred values for the remainder of the variables in Structural Formula (XIII) are as described for Structural Formula (I). Preferably, R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, optionally N -substituted tetrazolyl or optionally N -substituted imidazolyl; and R^{18} and each R^{19} are independently $-H$, methyl, or ethyl.

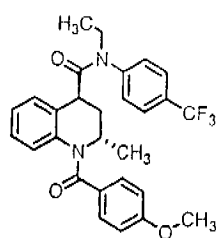
[0086] More preferably in Structural Formulas (I)-(XIII), R^8 , R^{11} and R^{14} are independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, $-NO_2$, $-CN$, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl.

[0087] More preferably in Structural Formulas (III)-(XIII), R^2 and $C(O)NR^3R^4$ are *trans*. In Structural Formulas (I) and (II), R^2 and $C(O)NR^3R^4$ are preferably *trans* when Y is $>C(R^5)-$.

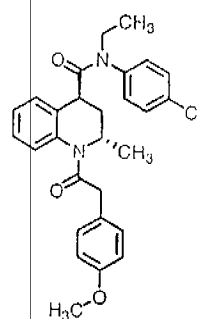
[0088] Table 1 below depicts certain exemplary compounds of formula I.

[0089] Table 1. Examples of formula I compounds

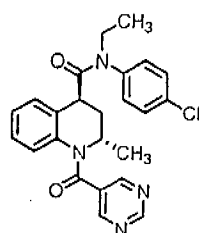
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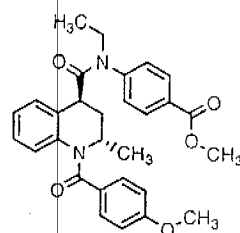
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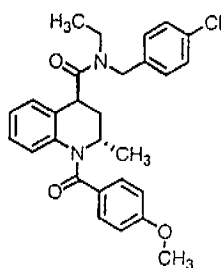
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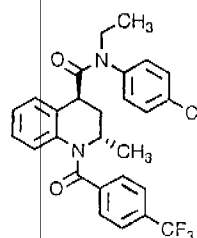
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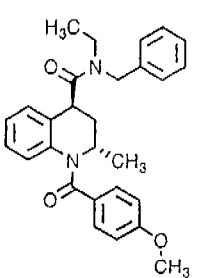
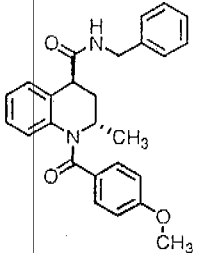
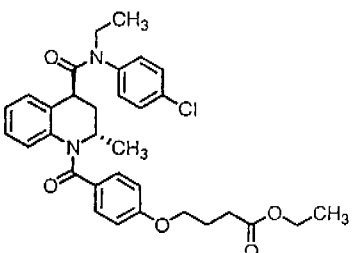
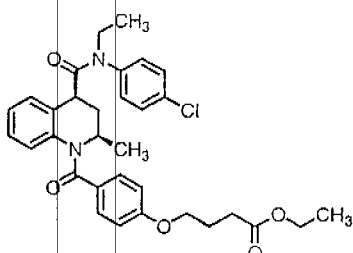
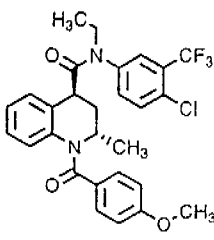
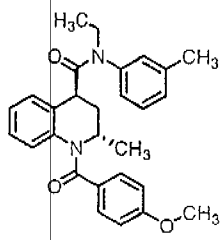
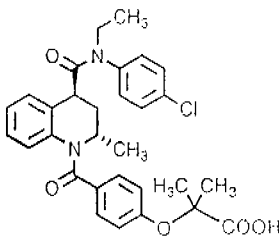
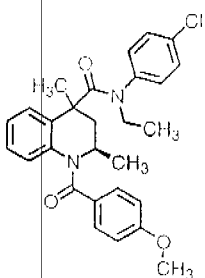


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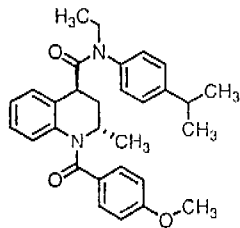
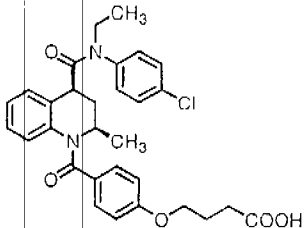
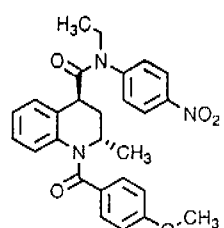
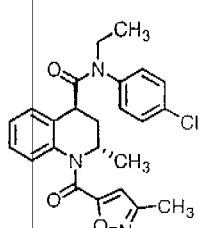
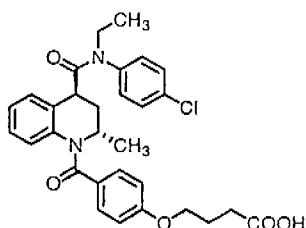
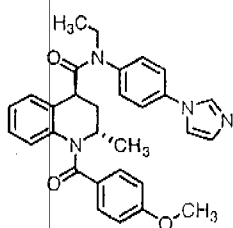


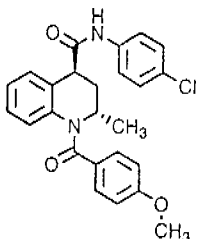
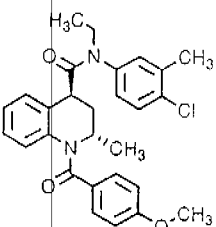
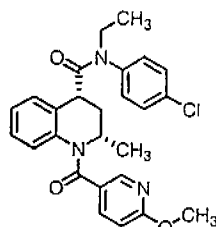
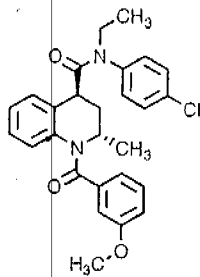
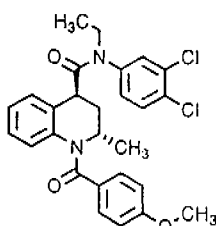
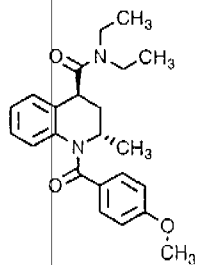
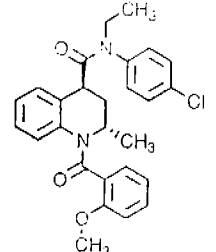
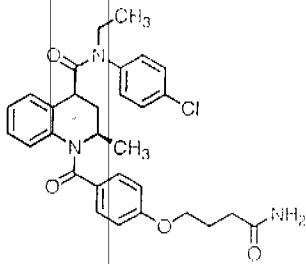
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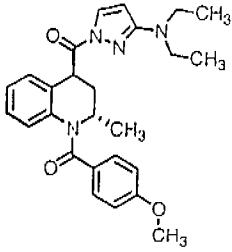
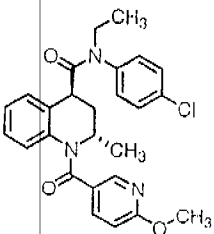
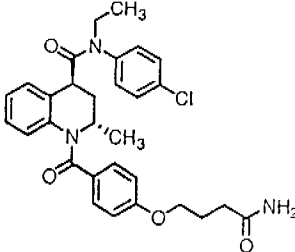
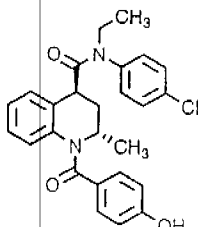
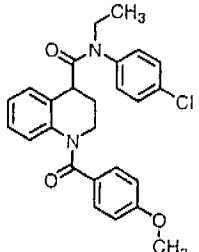
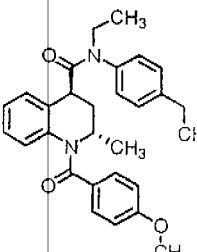
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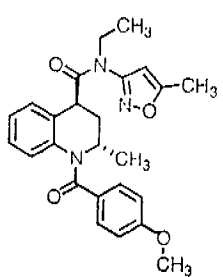
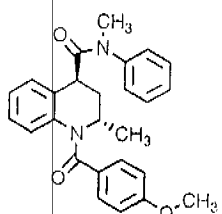
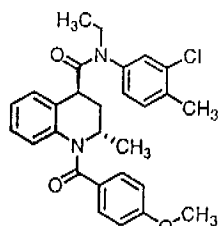
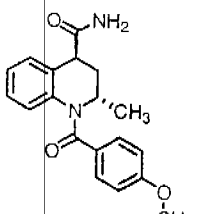
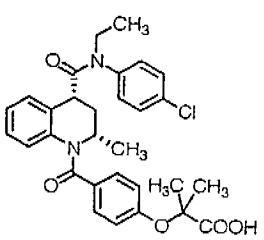
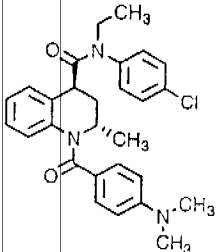
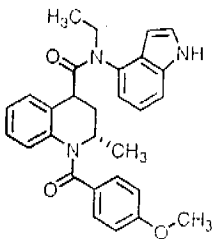
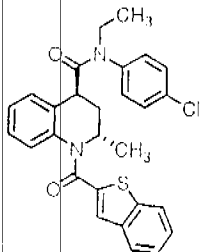
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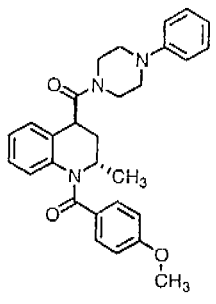
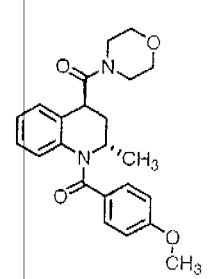
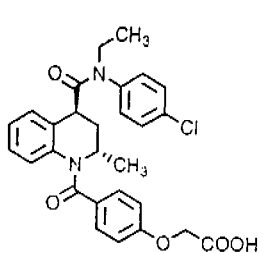
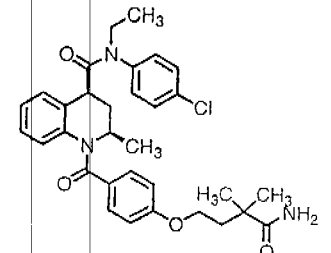
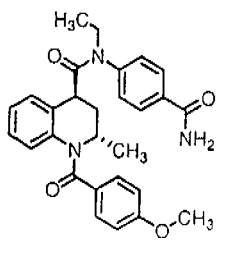
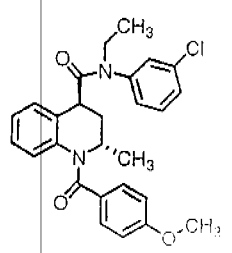
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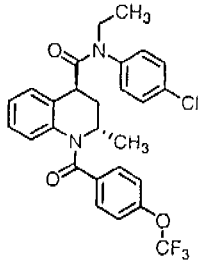
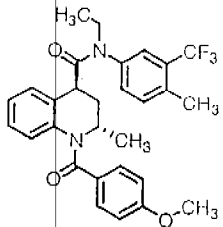
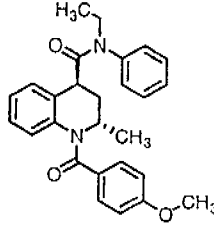
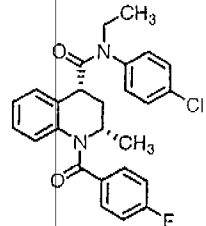
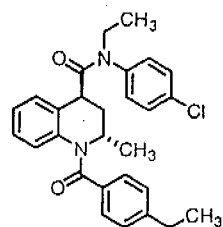
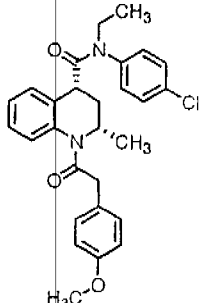
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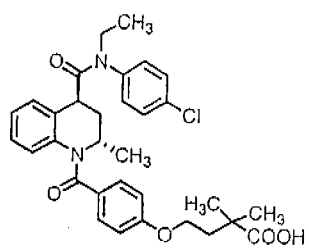
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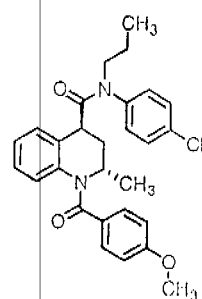
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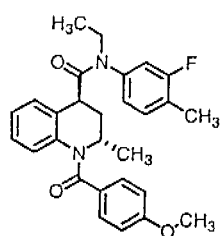
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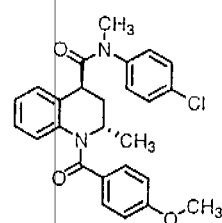
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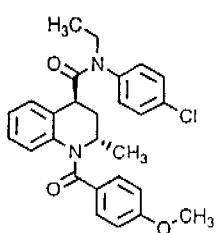
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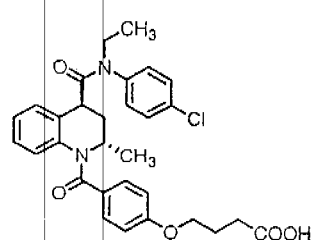
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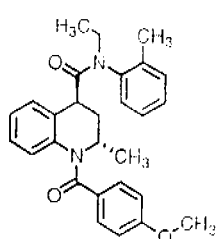
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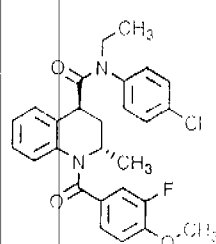
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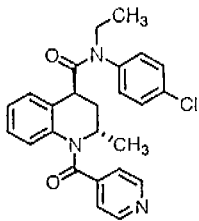
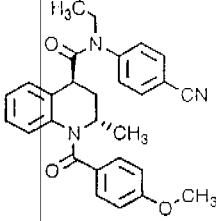
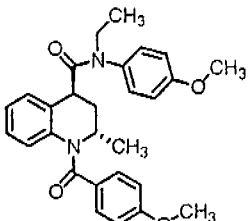
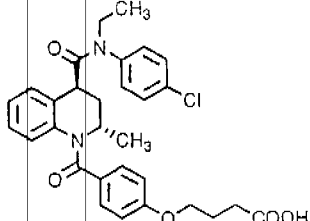
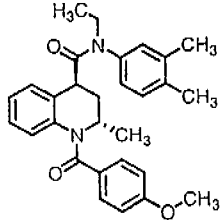
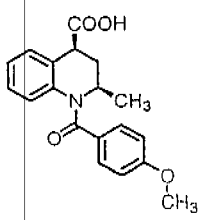
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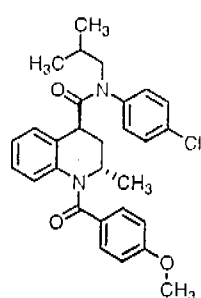
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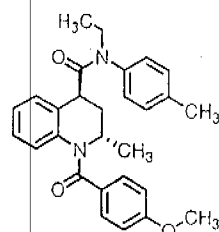
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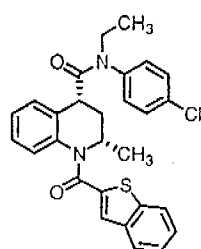
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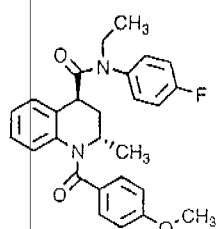
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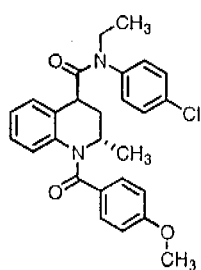
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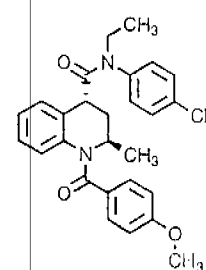
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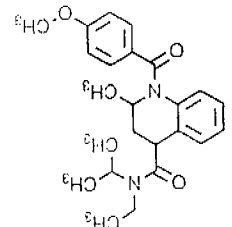
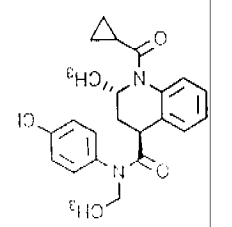
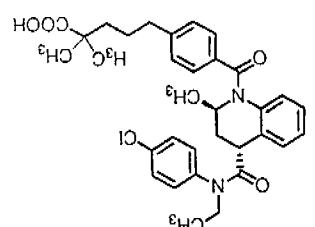
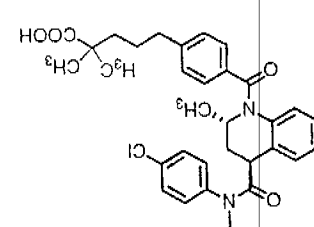
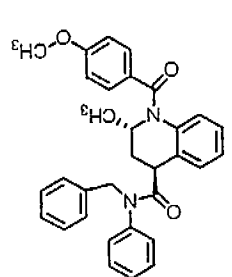
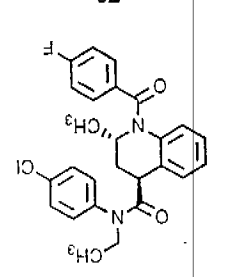
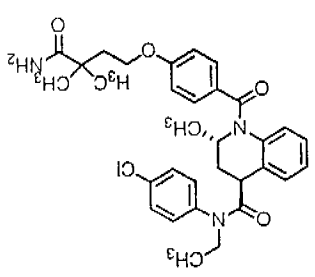
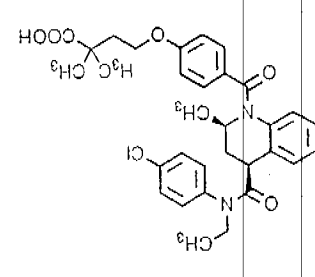
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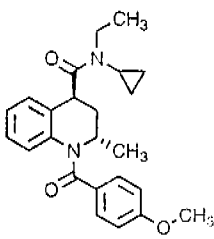
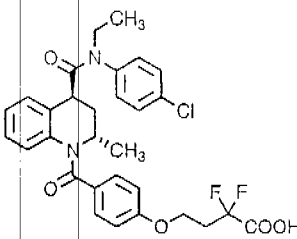
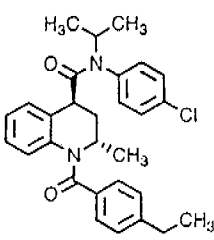
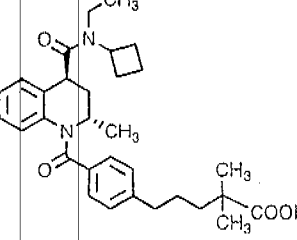
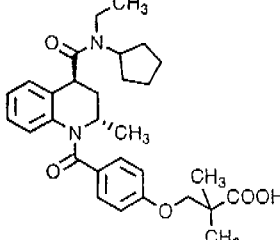
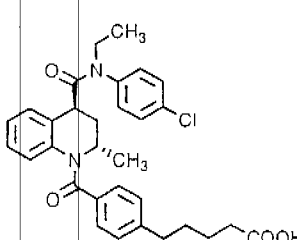


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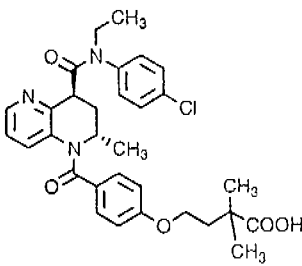
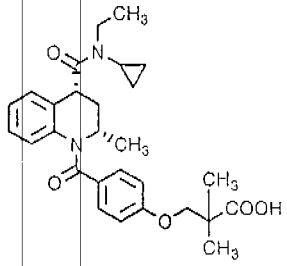
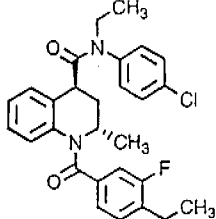
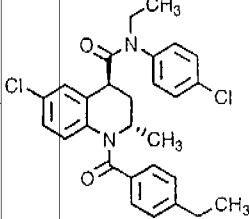
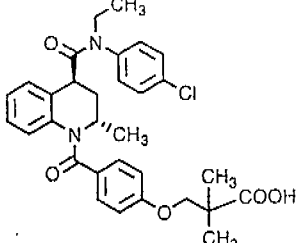
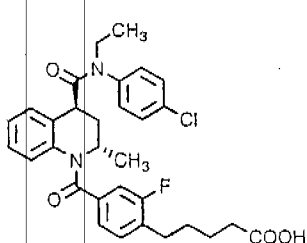
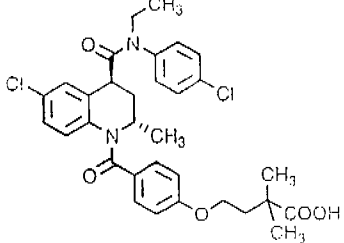
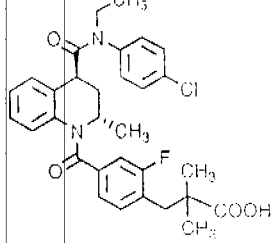
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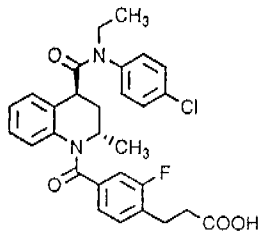
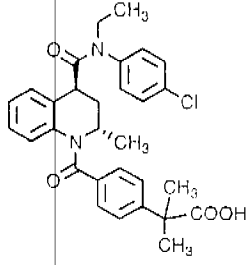
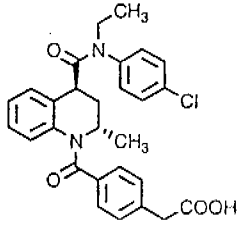
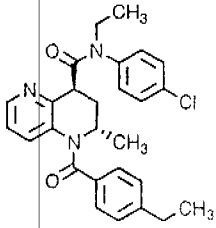
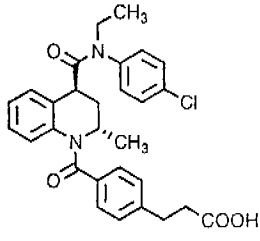
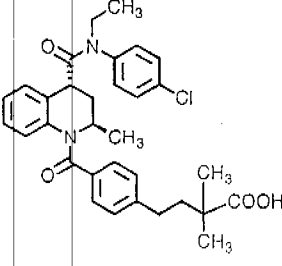
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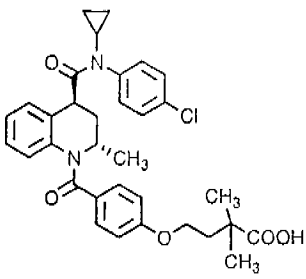
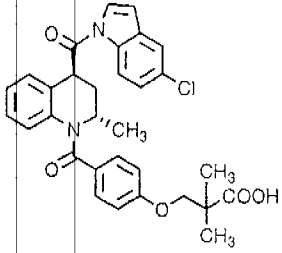
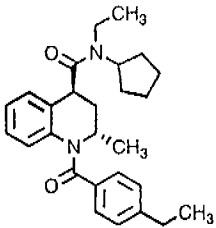
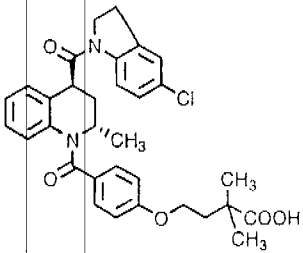
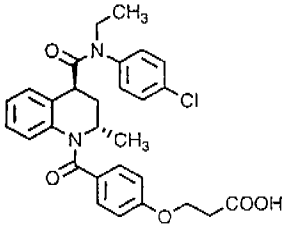
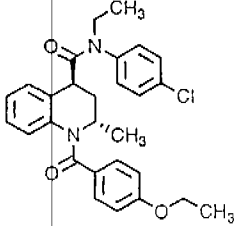
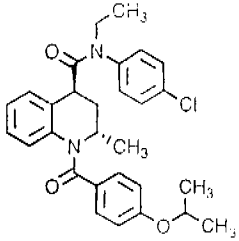
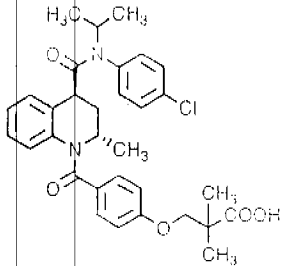
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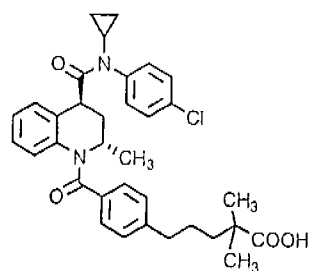
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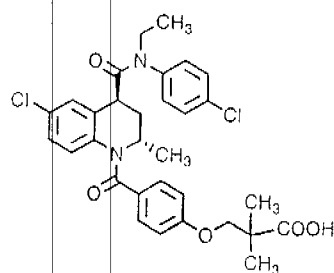
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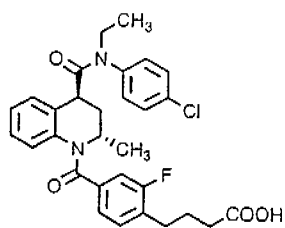
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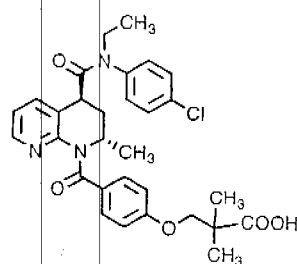
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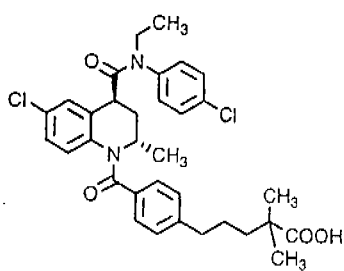
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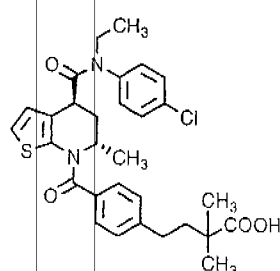
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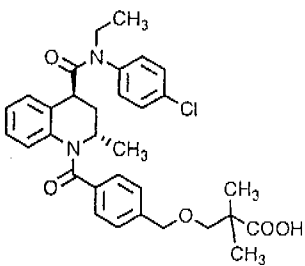
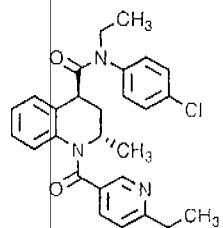
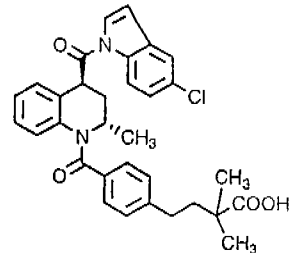
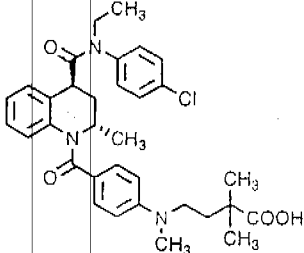
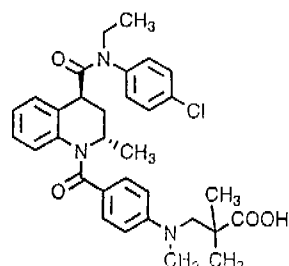
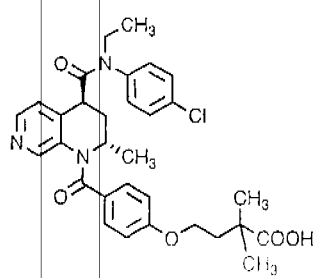
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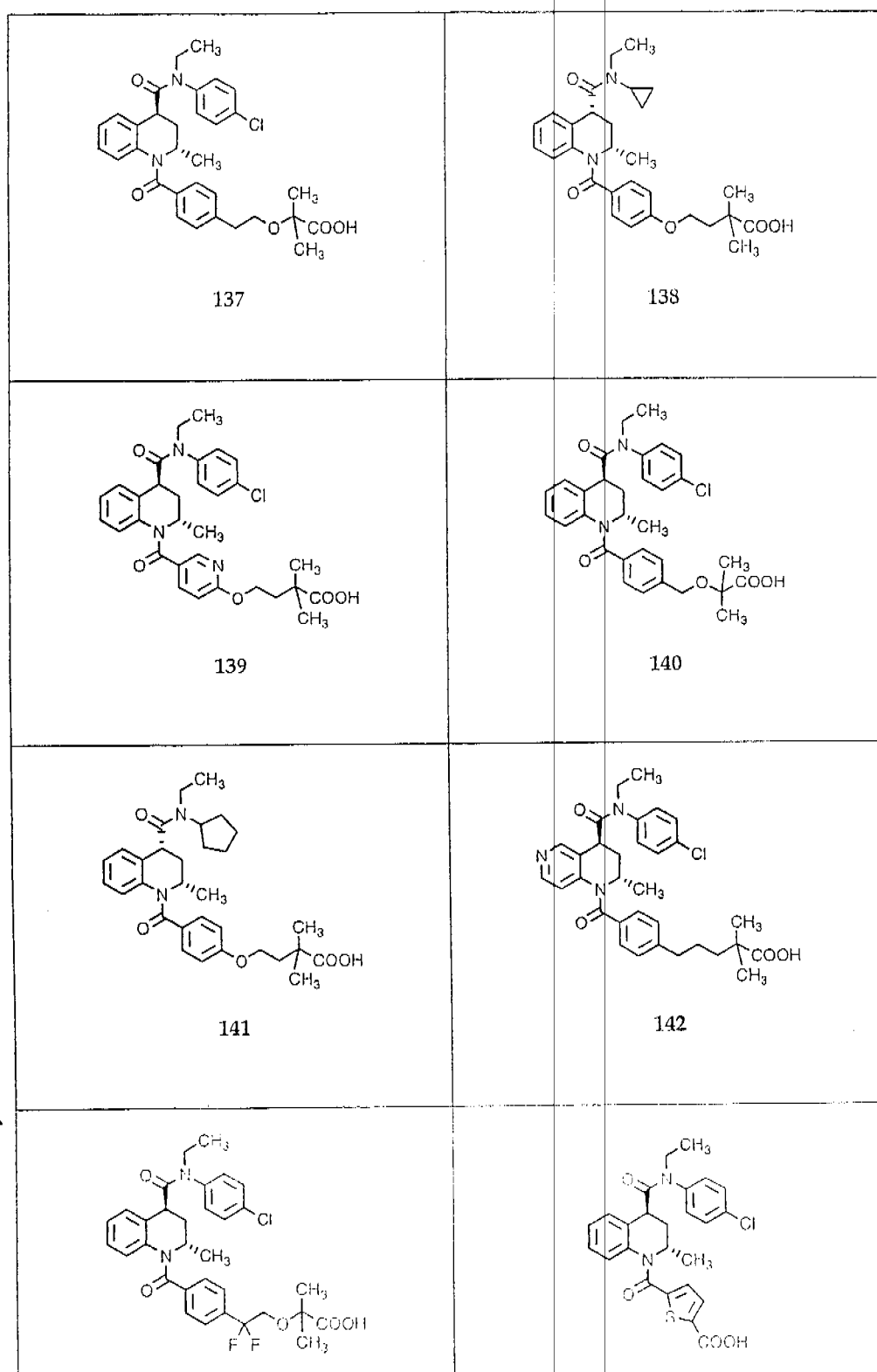
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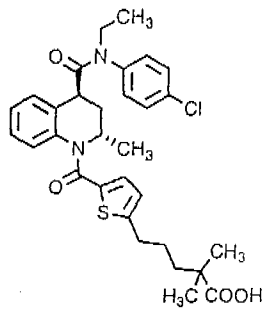
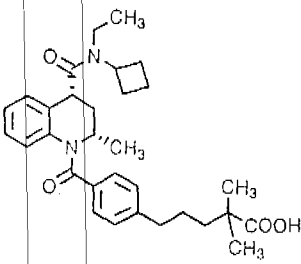
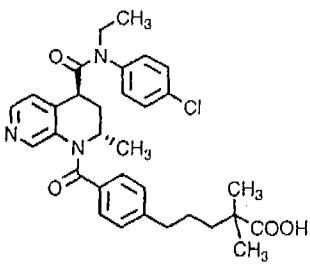
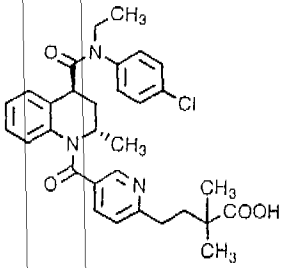
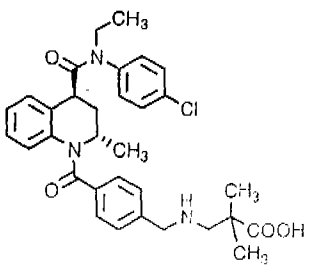
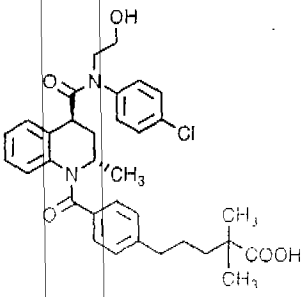
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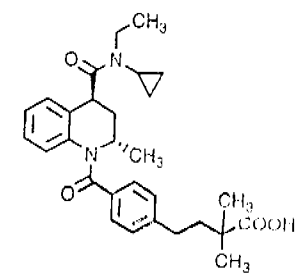
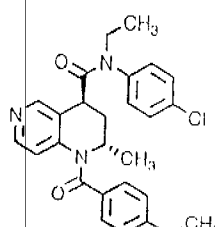
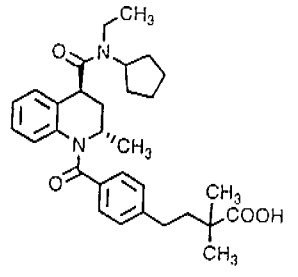
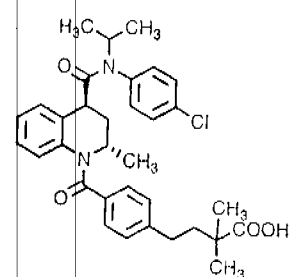
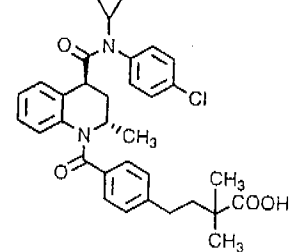
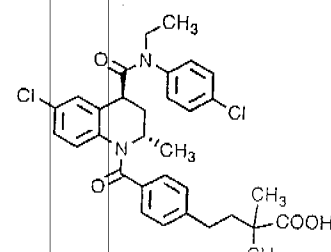
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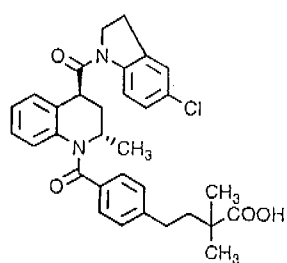


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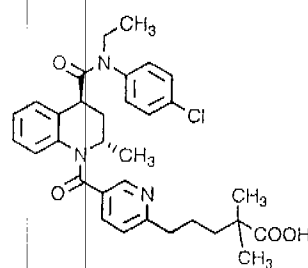
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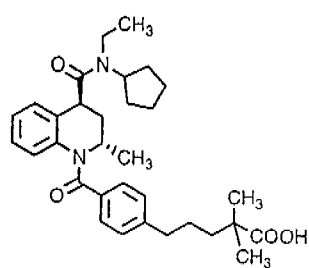
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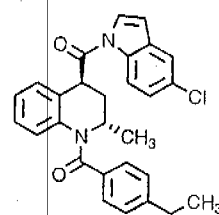
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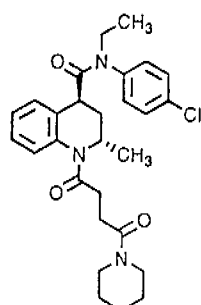
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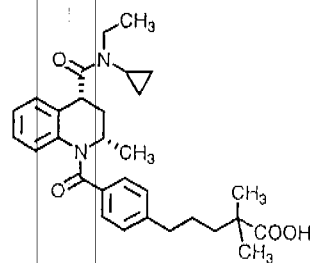
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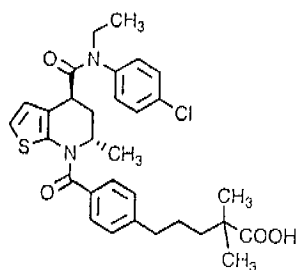
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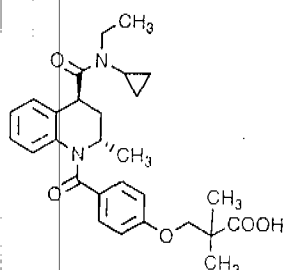
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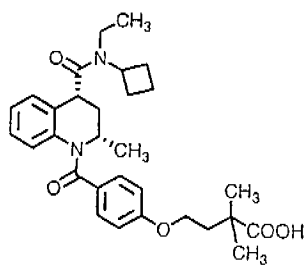
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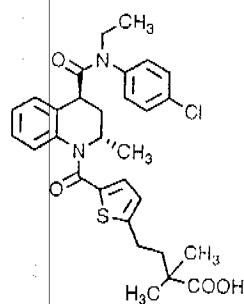
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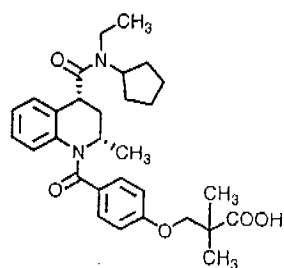
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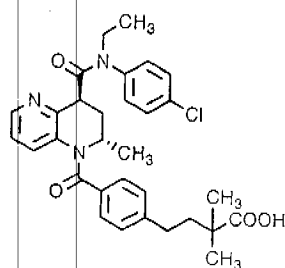
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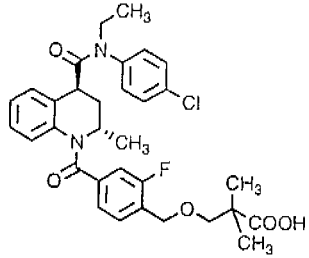
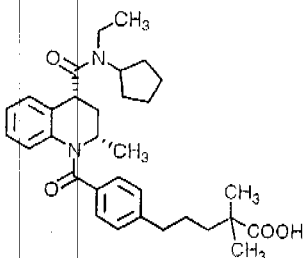
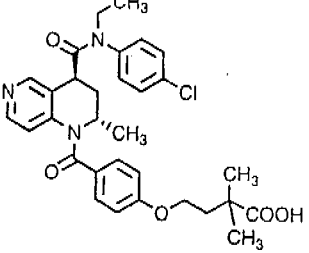
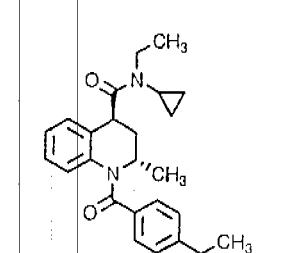
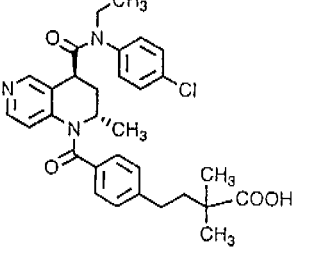
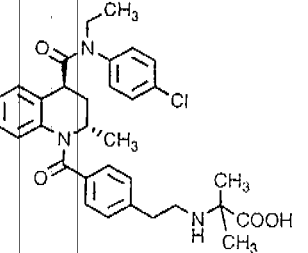
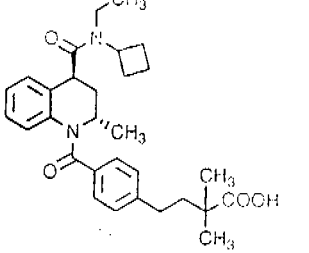
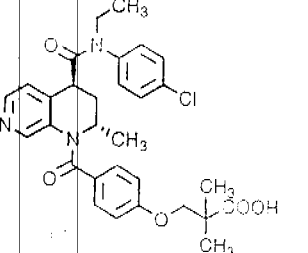


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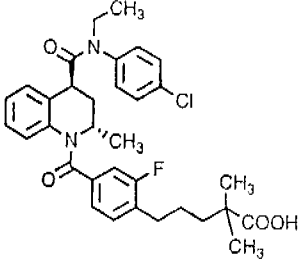
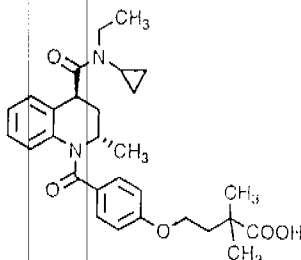
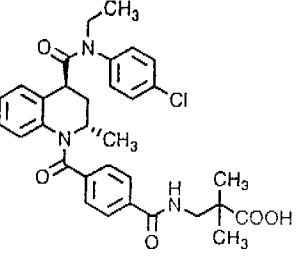
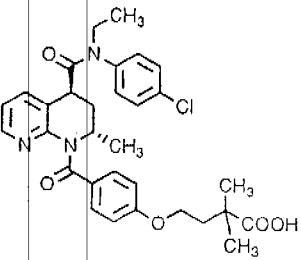
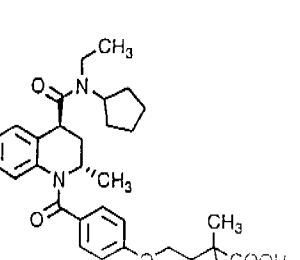
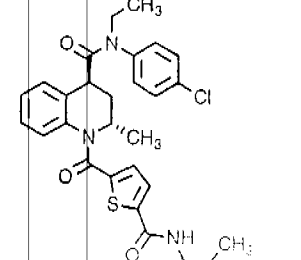


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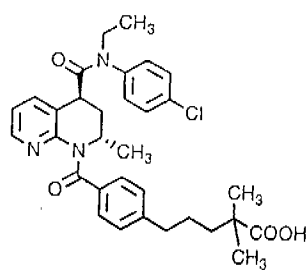
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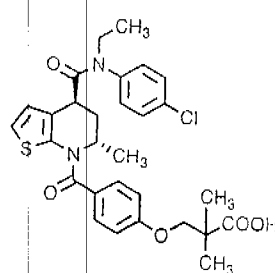
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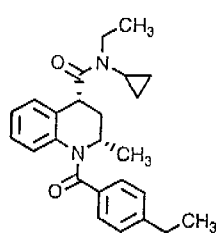
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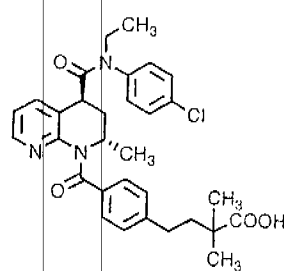
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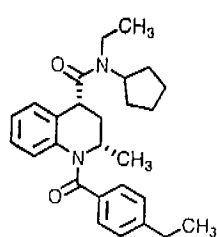
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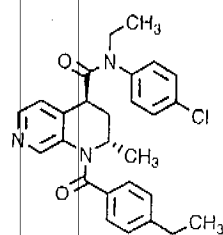
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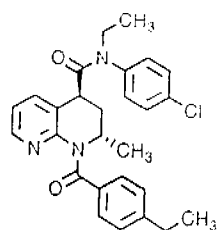
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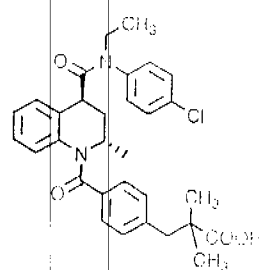
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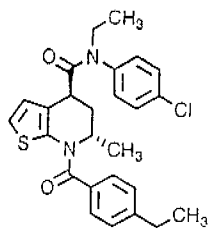
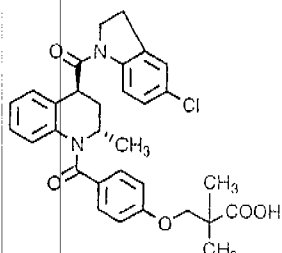
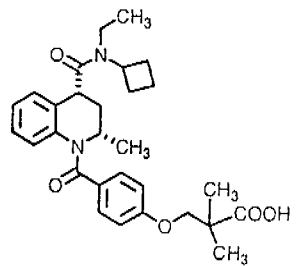
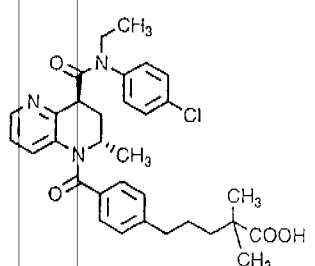
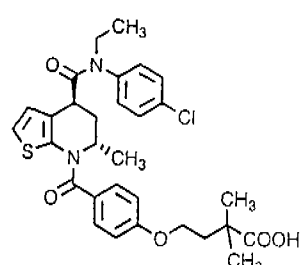
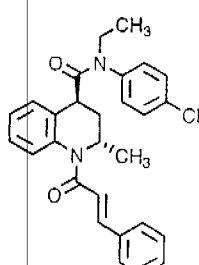
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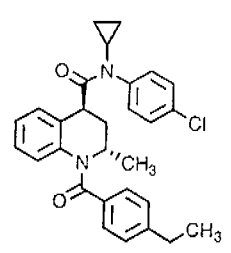
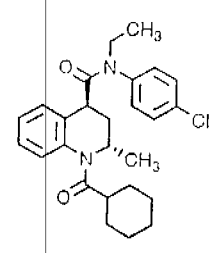
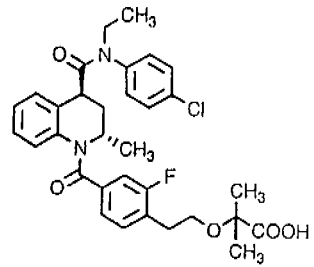
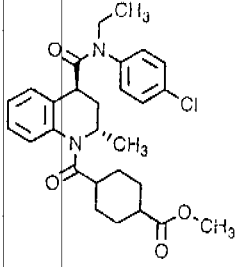
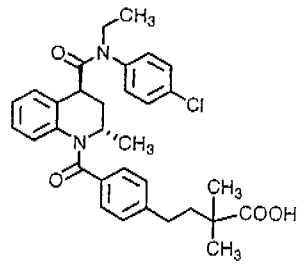
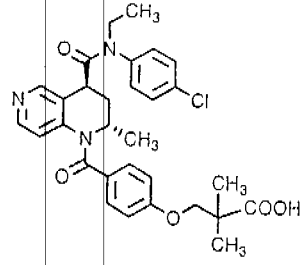
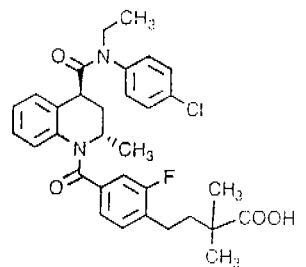
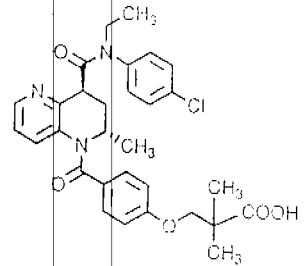
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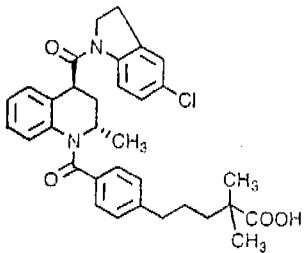
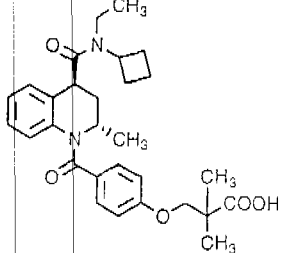
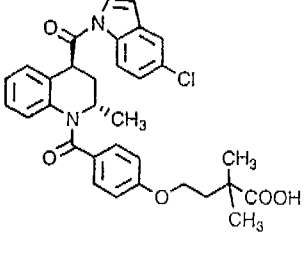


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[0090] 4. Uses, Formulation and Administration

[0091] As discussed above, the present invention provides compounds that are useful as inhibitors of CRTH2, and thus compounds of the invention are useful for treating (therapeutically or prophylactically) disorders with an inflammatory component and allergic conditions. Compounds of the invention can also be used to treat inflammatory disorders and allergic conditions mediated by Th2 cells, eosinophils, and basophils.

[0092] Accordingly, in another aspect of the present invention, pharmaceutically acceptable compositions are provided, wherein these compositions comprise any of the compounds as described herein, and optionally comprise a pharmaceutically acceptable carrier, adjuvant or vehicle. In certain embodiments, these compositions optionally further comprise one or more additional therapeutic agents.

[0093] It will also be appreciated that certain of the compounds of present invention can exist in free form for treatment, or where appropriate, as a pharmaceutically acceptable derivative thereof. According to the present invention, a pharmaceutically acceptable derivative includes, but is not limited to, pharmaceutically acceptable prodrugs, salts, esters, salts of such esters, or any other adduct or derivative which upon administration to a patient in need is capable of providing, directly or indirectly, a compound as otherwise described herein, or a metabolite or residue thereof.

[0094] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describe pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 1977, 66, 1-19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_1-4alkyl)_4$ salts. This invention also envisions the quaternization of any basic nitrogen-containing groups of the compounds disclosed herein. Water or oil-soluble or dispersable products may be obtained by such quaternization. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0095] As described above, the pharmaceutically acceptable compositions of the present invention additionally comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle, which, as used herein, includes any and all solvents, diluents, or other liquid vehicle, dispersion or suspension

aids, surface active agents, isotonic agents, thickening or emulsifying agents, preservatives, solid binders, lubricants and the like, as suited to the particular dosage form desired. Remington's Pharmaceutical Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980) discloses various carriers used in formulating pharmaceutically acceptable compositions and known techniques for the preparation thereof. Except insofar as any conventional carrier medium is incompatible with the compounds of the invention, such as by producing any undesirable biological effect or otherwise interacting in a deleterious manner with any other component(s) of the pharmaceutically acceptable composition, its use is contemplated to be within the scope of this invention. Some examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as lactose, glucose and sucrose; starches such as corn starch and potato starch; cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil; safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols; such as propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate; agar; buffering agents such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and phosphate buffer solutions, as well as other non-toxic compatible lubricants such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the composition, according to the judgment of the formulator.

[0096] In another aspect, a method for the treatment of an inflammatory disease or a disease with an inflammatory component is provided comprising administering an effective amount of a compound, or a pharmaceutical composition thereof to a subject in need thereof. Compounds and compositions of the invention are inhibitors of CRTH2, and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of one or more of CRTH2, PGD2 (including DP activity), Th2 cells, eosinophils, and/or basophils is implicated in the disease, condition, or disorder. When activation of one or more of CRTH2, PGD2 (including DP activity), Th2 cells, eosinophils, and/or basophils is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as a "CRTH2-mediated disease" or disease symptom. Accordingly, in another aspect, the present invention provides a method for treating or

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lessening the severity of a disease, condition, or disorder where activation of one or more of CRTH2, PGD2 (including DP activity), Th2 cells, eosinophils, and/or basophils is implicated in the disease state.

[0097] In certain embodiments of the present invention an "effective amount" of the compound or pharmaceutically acceptable composition is that amount effective for treating an inflammatory disease or disease with an inflammatory component. In other embodiments, an "effective amount" of a compound is an amount which inhibits binding of PGD2 to its receptor CRTH2 and thereby inhibits one or more processes mediated by the binding in a subject, for example, the release of proinflammatory mediators. An "effective amount" of a compound can achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in the prevention of or a decrease in the symptoms associated with an inflammatory disease or a disease mediated by one or more of CRTH2, PGD2 (including DP activity), Th2 cells, eosinophils, and basophils.

[0098] In one embodiment, the inflammatory disease is an allergic condition. Examples of allergic conditions for which the disclosed compounds, pharmaceutical compositions and methods are believed to be particularly effective include atopic dermatitis, allergic rhinitis, rheumatoid arthritis, chronic obstructive pulmonary disorder (COPD), COPD exacerbations, or allergic asthma. Other allergic conditions include systemic anaphylaxis or hypersensitivity responses, drug allergies (e.g., to penicillin, cephalosporins), insect sting allergies and dermatoses such as dermatitis, eczema, atopic dermatitis, allergic contact dermatitis and urticaria.

[0099] Examples of diseases with an inflammatory component for which the disclosed compounds, pharmaceutical composition and methods are believed to be particularly effective include osteoarthritis, inflammatory bowel disease [e.g., such as ulcerative colitis, Crohn's disease, ileitis, Celiac disease, nontropical Sprue, enteritis, enteropathy associated with seronegative arthropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy, and ileoanal anastomosis] and disorders of the skin [e.g., psoriasis, erythema, pruritis, and acne].

[00100] Many autoimmune diseases also have an inflammatory component. Examples include multiple sclerosis, systemic lupus erythematosus, myasthenia gravis, juvenile onset diabetes, glomerulonephritis and other nephritides, autoimmune thyroiditis, Behcet's disease and graft rejection (including allograft rejection or graft-versus-host disease). The inflammatory component of these disorders is believed to be mediated, at least in part, by CRTH2.

[00101] Diseases characterized by reperfusion have an inflammatory component that is believed to be mediated, at least in part by, by CRTH2. Examples include stroke, cardiac ischemia, and the like. The disclosed compounds and compositions also can be used to treat these disorders.

[00102] Other diseases and conditions with an inflammatory component believed to be mediated by CRTH2 include mastitis (mammary gland), vaginitis, cholecystitis, cholangitis or pericholangitis

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(bile duct and surrounding tissue of the liver), chronic bronchitis, chronic sinusitis, chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as interstitial lung diseases (ILD) (e.g., idiopathic pulmonary fibrosis, or ILD associated with rheumatoid arthritis, or other autoimmune conditions), hypersensitivity pneumonitis, collagen diseases and sarcoidosis. Yet other diseases or conditions with inflammatory components which are amenable to treatment according to methods disclosed herein include vasculitis (e.g., necrotizing, cutaneous, and hypersensitivity vasculitis), spondyloarthropathies, scleroderma, atherosclerosis, restenosis and myositis (including polymyositis, dermatomyositis), pancreatitis and insulin-dependent diabetes mellitus.

[00103] In a preferred embodiment, the invention provides a method of treating asthma comprising administering an effective amount of a compound of general formula I (and subsets thereof as described herein) to a subject in need thereof.

[00104] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating an inflammatory disease or allergic condition. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. The compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00105] The pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

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[00106] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00107] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00108] The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00109] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microcapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

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[00110] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00111] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00112] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00113] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such as magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they

release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00114] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00115] It will also be appreciated that the compounds and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the compounds and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an inventive compound may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents which are normally administered to treat or prevent a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated".

[00116] For example, compounds of the invention can also be administered in combination with one or more additional therapeutic agents, such as, theophylline, β -adrenergic bronchodilators, corticosteroids, antihistamines, antiallergic agents, immunosuppressive agents (e.g., cyclosporin A, FK-506, prednisone, methylprednisolone), hormones (e.g., adrenocorticotrophic hormone (ACTH)), cytokines (e.g., interferons (e.g., IFN β -1a, IFN δ -1b)) and the like.

[00117] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

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[00118] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another aspect, includes a composition for coating an implantable device comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device. In still another aspect, the present invention includes an implantable device coated with a composition comprising a compound of the present invention as described generally above, and in classes and subclasses herein, and a carrier suitable for coating said implantable device.

[00119] Another aspect of the invention relates to inhibiting CRTH2 activity in a biological sample or a patient, which method comprises administering to the patient, or contacting said biological sample with a compound of formula I or a composition comprising said compound. The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00120] Inhibition of CRTH2 activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ-transplantation, biological specimen storage, and biological assays.

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EXPERIMENTAL PROCEDURES

[00121] **General.** All reactions involving air-sensitive reagents were performed under a nitrogen atmosphere. Reagents were used as received from commercial suppliers unless otherwise noted. ¹H NMR data were recorded using the Bruker UltraShield 300 MHz/54-mm instrument equipped with Bruker B-ACS60 Auto Sampler or the Varian 300 MHz instrument. Intermediates and final compounds were purified by flash chromatography using one of the following instruments: 1. Biotage 4-channel Quad UV Flash Collector equipped with a Quad 1 Pump Module and the Quad 12/25 Cartridge module. 2. Biotage 12-channel Quad UV Flash Collector equipped with a Quad 3 Pump Module and a Quad 3 Cartridge module. 3. ISCO combi-flash chromatography instrument. LC/MS spectra were obtained using a MicroMass Platform LC (Phenomenx C18 column, 5 micron, 50x4.6 mm) equipped with a Gilson 215 Liquid Handler. Standard LC/MS conditions are as follows:

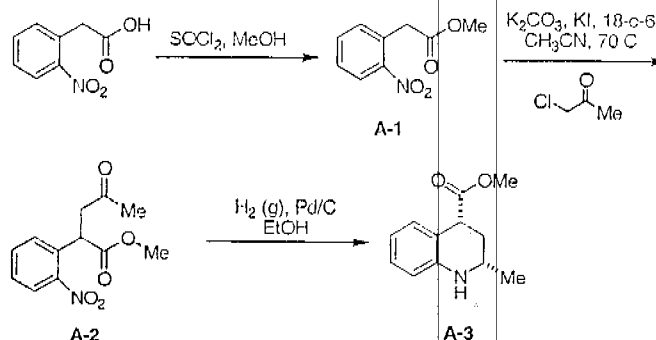
% A (Water)	95.0	HP1100 LC Pump Gradient Timetable						
% B (Acetonitrile)	5.0	The gradient Timetable contains 4 entries which are:						
% Ammonium acetate	0.1							
Flow (ml/min)	2.500	Time	A%	B%	C%	D%	Flow	Pressure
Stop Time (mins)	3.8	0.00	95.0	5.0	0.0	0.0	2.500	400
Min Pressure (bar)	0	2.00	0.0	100.0	0.0	0.0	2.500	400
Max Pressure (bar)	400	3.00	0.0	100.0	0.0	0.0	2.500	400
Oven Temperature Left(°C)	10.0	3.05	95.0	5.0	0.0	0.0	2.000	400
Oven Temperature Right(°C)	10.0							

LC-MS data were acquired using the "Ammonium acetate-standard" method unless otherwise noted.

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[00122] Synthesis of (±)-*cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester

[00123] Scheme 1



[00124] A round bottom flask with magnetic stirrer was charged with (2-nitro-phenyl)-acetic acid (10.0 g, 55.0 mmol) and methanol (70 mL) under an argon atmosphere. To the resulting yellow solution at room temperature was added thionyl chloride (12.1 mL, 166 mmol) dropwise via addition funnel (Note: Reaction is very exothermic). The resulting reaction mixture was stirred at room temperature for 12-18 hours and concentrated *in vacuo* to afford 13.3 g of crude (2-nitro-phenyl)-acetic acid methyl ester as an orange oil. This material was used directly in subsequent reactions.

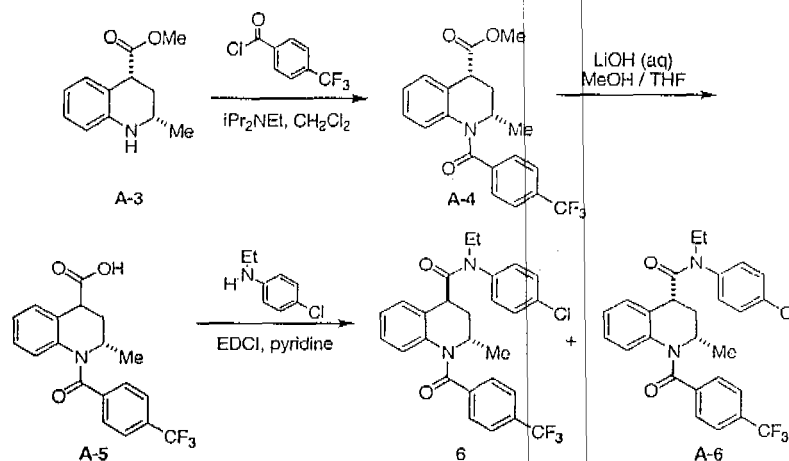
[00125] A three-neck round bottom flask with magnetic stirrer was charged with crude (2-nitro-phenyl)-acetic acid methyl ester (7.23 g, 37.0 mmol), potassium carbonate (46.1 g, 33.3 mmol), 18-crown-6 (0.650 g), and potassium iodide (0.650 g) under an argon atmosphere. To the flask was added acetonitrile (80 mL) and the mixture heated at 70 °C for one hour. To the reaction was added chloroacetone (3.50 mL, 44.0 mmol) and the reaction stirred at 70 °C under argon for 18-20 hours. The reaction was cooled to room temperature and filtered through a pad of celite. The resulting filtrate was concentrated *in vacuo* to afford 9.64 g of crude material. Purification via flash chromatography (0-40% ethyl acetate / hexanes eluent) yielded 4.74 g of 2-(2-nitro-phenyl)-4-oxo-pentanoic acid methyl ester (51%).

[00126] A round bottom flask with magnetic stirrer was charged with 2-(2-nitro-phenyl)-4-oxo-pentanoic acid methyl ester (4.74 g, 19.1 mmol) and anhydrous ethanol (50 mL). To the reaction was added 10% palladium on carbon (0.948 g, 20% by weight) and the reaction stirred at room temperature under a hydrogen gas atmosphere (balloon) for 18-20 hours. The reaction was filtered through a pad of celite and the celite pad washed with warm ethanol. The combined filtrates were concentrated *in vacuo* to afford an off-white colored solid. This material was purified via Isco flash system (0-20% ethyl acetate / hexanes) to yield 2.64 g of *cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester as a white solid (68%). ¹H-NMR (CDCl₃) δ: 1.23 (3H, d), 1.95 (1H, dd),

2.10 - 2.18 (1H, m), 3.34 - 3.46 (1H, m), 3.74 (3H, s), 3.94 (1H, dd), 6.51 (1H, dd), 6.60 - 6.67 (1H, m), 6.94 - 7.03 (2H, m). MS m/z : 206 (M+1).

[00127] General Procedure A

[00128] Scheme 2



[00129] ($\pm$)-*trans*-2-Methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (6)

[00130] A round bottom flask with magnetic stirrer was charged with *cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (556 mg, 2.71 mmol) in methylene chloride (8.00 mL) under an argon atmosphere. Into the reaction was added 4-trifluoromethyl-benzoyl chloride (0.61 mL, 4.07 mmol) and *N,N*-diisopropylethylamine (1.20 mL, 6.89 mmol). The reaction was stirred at room temperature for 18-20 hours. The reaction was transferred to a separatory funnel containing a saturated sodium bicarbonate solution (15 mL), then diluted with methylene chloride (15 mL) and shaken vigorously. The resulting organic layer was separated, washed with brine (1 x 20 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford an orange residue (1.359 g). The residue was purified via flash chromatography (20 % ethyl acetate / hexanes eluent) to yield *cis*-2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester as a tan-colored solid (990 mg, 97%).

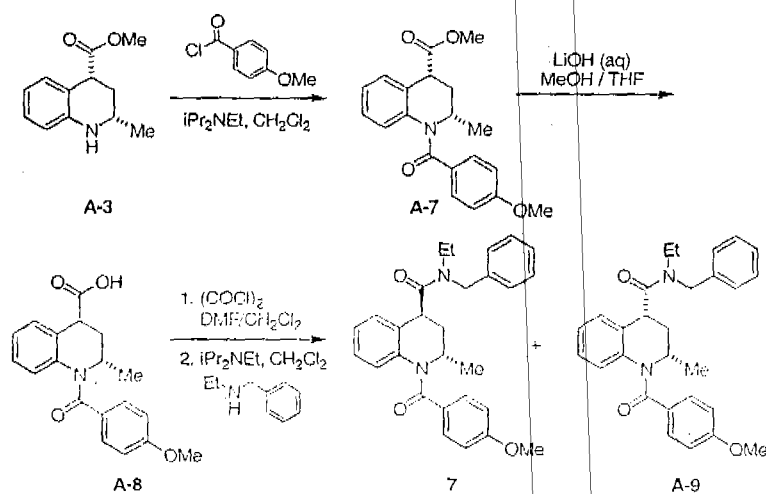
[00131] A round bottom flask with magnetic stirrer was charged with *cis*-2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (980 mg, 2.60 mmol) in tetrahydrofuran (10.0 mL). To the reaction was added a solution of lithium hydroxide (179 mg, 7.47 mmol) in water (10 mL), followed by methanol (10 mL). The reaction was stirred at room temperature for 18-20 hours under an argon atmosphere. The reaction was transferred to a separatory funnel and the pH adjusted to 2 via addition of 1N hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 35 mL) and the combined extractions were washed with brine (1 x 50 mL), dried

over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to yield 2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (mixture of *cis* and *trans* isomers) as an off-white solid (912 mg, 97%). The mixture was used without purification in subsequent reactions.

[00132] A round bottom flask with magnetic stirrer was charged with 2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (886 mg, 2.44 mmol) in anhydrous pyridine (25.0 mL). To the reaction was added *N*-ethyl-*p*-chloroaniline (0.410 mL, 2.95 mmol), followed by EDCI (833 mg, 4.34 mmol). The reaction was stirred at room temperature under an argon atmosphere for 18-20 hours. The reaction was poured into a 1:1 mixture of water/brine (50 mL) and extracted with ethyl acetate (3 x 35 mL). The combined extractions were washed with brine (1 x 50 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a brown residue. The residue was purified via silica gel chromatography (hexanes / ethyl acetate) to yield ($\pm$)-*trans*-2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (39%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.02 (d, 3H), 1.12 (t, 3H), 1.64 - 1.74 (m, 1H), 2.49 - 2.58 (m, 1H), 3.59 - 3.72 (m, 1H), 3.77 - 3.90 (m, 2H), 5.03 - 5.14 (m, 1H), 6.35 - 6.41 (m, 1H), 6.74 - 6.84 (m, 2H), 6.89 - 6.95 (m, 1H), 7.17 - 7.25 (m, 2H), 7.44 - 7.52 (m, 2H), 7.63 - 7.69 (m, 2H). MS m/z : 501 ($M+1$).

[00133] General Procedure B

[00134] Scheme 3



[00135] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-ethyl-amide (7)

[00136] A round bottom flask with magnetic stirrer was charged with *cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (5.42 g, 26 mmol) in dichloromethane (100 mL) under an argon atmosphere at room temperature. To the reaction was added *N,N*-diisopropylethylamine (11.8 mL, 68 mmol), followed by *p*-anisoyl chloride (6.31 g, 37 mmol). The reaction was stirred at room temperature for 18-20 hours and poured into saturated sodium bicarbonate (1000 mL), diluted with dichloromethane (50 mL), and shaken vigorously. The resulting organic layer was separated, washed with brine (1 x 100 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford an oily residue. Diethyl ether (50 mL) was added to the residue and the resulting white solid was collected via suction filtration to afford *cis*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (6.94 g, 78%).

[00137] A round bottom flask with magnetic stirrer was charged with *cis*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (3.00 g, 8.8 mmol) in anhydrous tetrahydrofuran (70 mL). To the reaction was added a solution of lithium hydroxide (423 mg, 18 mmol) in water (24 mL), followed by methanol (24 mL). The reaction was stirred at room temperature for 18-20 hours under an argon atmosphere. The reaction was transferred to a separatory funnel and the pH adjusted to 2 via addition of 1N hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 35 mL) and the combined extractions were washed with brine (1 x 50 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* and diethyl ether (50 mL) added to the resulting residue. The precipitated solid was collected via suction filtration to afford 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid as a mixture of *cis* and *trans*-isomers (2.71 g, 95%). ¹H-NMR (d₆-DMSO) δ : 1.22 (d, 3H), 1.63 (ddd, 1H), 2.94 (ddd, 1H), 3.76 (s, 3H), 3.89 (dd, 1H), 4.83 - 4.91 (m, 1H), 6.51 (d, 1H), 6.72 - 6.76 (m, 2H), 6.95 (ddd, 1H), 7.11 (ddd, 1H), 7.26 - 7.35 (m, 3H). MS m/z = 326 (M+1).

[00138] 1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (2.00 g, 6.15 mmol) was suspended in methylene chloride (50 mL). One drop of dimethylformamide was added, followed by oxalyl chloride (1.56 g, 1.07 mL, 12.3 mmol). The suspension became homogeneous on stirring. After 2 hours, the yellow solution was concentrated under reduced pressure and azeotroped with toluene. To a solution of the resulting acid chloride (120 mg, 349 mmol) in methylene chloride (1 mL) was added diisopropylethylamine (451 μ L, 0.349 mmol), followed by ethyl-benzyl-amine (71 mg, 77 μ L, 0.523 mmol). The mixture was shaken overnight at room temperature. Upon completion, the reaction was diluted with ethyl acetate, washed with saturated sodium bicarbonate (aqueous) and brine, dried over sodium sulfate, filtered and concentrated to afford the crude amide. Purification by silica gel chromatography (elution with a hexane / ethyl acetate

gradient) afforded pure ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-ethyl-amide (53 mg, 34%). ¹H-NMR (CDCl₃) δ : 0.98 (d, 3H), 1.13 (t, 3H), 1.74 (ddd, 1H), 2.52 (ddd, 1H), 3.62 - 3.92 (m, 8H), 5.03 - 5.13 (m, 1H), 6.44 (d, 1H), 6.72 - 6.84 (m, 4H), 6.86 - 6.92 (m, 1H), 7.19 - 7.23 (m, 2H), 7.43 - 7.54 (m, 4H). MS m/z: 443 (M+1).

[00139] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-trifluoromethyl-phenyl)-amide (1)

[00140] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-trifluoromethyl-phenyl)-amide was made following general procedure B, substituting ethyl-(4-trifluoromethyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-trifluoromethyl-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-trifluoromethyl-phenyl)-amide. ¹H-NMR (CDCl₃) δ : 0.99 (d, 3H), 1.15 (t, 3H), 1.71 - 1.79 (m, 1H), 2.53 - 2.62 (m, 1H), 3.69 - 4.00 (m, 6H), 5.06 - 5.12 (m, 1H), 6.47 (d, 1H), 6.74 - 6.91 (m, 5H), 7.41 (d, 2H), 7.51 (d, 2H), 7.77 (d, 2H). MS m/z: 497 (M⁺).

[00141] ($\pm$)-*trans*-1-[2-(4-Methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (2)

[00142] ($\pm$)-*trans*-1-[2-(4-Methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 4-methoxyphenylacetyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-[2-(4-methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification by flash chromatography (dichloromethane / methanol gradient: 99/1 to 98/2) yielded ($\pm$)-*trans*-1-[2-(4-methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (24%). ¹H-NMR (CDCl₃) δ : 0.96 (d, 3H), 1.13 (t, 3H), 1.40 - 1.50 (m, 1H), 2.45 - 2.56 (m, 1H), 3.60 - 3.70 (m, 1H), 3.75 (q, 2H), 3.80 (s, 2H), 3.82 (s, 3H), 4.98 - 5.10 (m, 1H), 6.70 (d, 1H), 6.90 (d, 2H), 7.00 - 7.23 (m, 5H), 7.30 (m, 2H), 7.45 (d, 2H). MS m/z: 477/479 (M+1).

[00143] ($\pm$)-*trans*-2-Methyl-1-(pyrimidine-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (3)

[00144] ($\pm$)-*trans*-2-Methyl-1-(pyrimidine-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting pyrimidine-5-carbonyl chloride for 4-trifluoromethyl-benzoyl chloride. Pyrimidine-5-carbonyl chloride was prepared by reaction of pyrimidine-5-carboxylic acid with oxalyl chloride and dimethylformamide in methylene chloride. The crude 2-methyl-1-(pyrimidine-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification by silica gel chromatography (2% methanol / methylene chloride)

yielded (±)-*trans*-2-methyl-1-(pyrimidine-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (44%). ¹H-NMR (CDCl₃) δ: 1.02 - 1.18 (m, 6H), 1.65 - 1.75 (m, 1H), 2.50 - 2.60 (m, 1H), 3.60 - 3.70 (m, 1H), 3.80 (q, 2H), 4.98 - 5.10 (m, 1H), 6.40 (d, 1H), 6.70 (d, 1H), 6.90 - 7.00 (m, 2H), 7.20 (d, 2H), 7.50 (d, 2H), 8.85 (s, 2H), 9.15 (s, 1H). MS m/z: 435/437 (M+1).

[00145] (±)-*trans*-4-[Ethyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carbonyl]-amino]-benzoic acid methyl ester (4)

[00146] (±)-*trans*-4-[Ethyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carbonyl]-amino]-benzoic acid methyl ester was made following general procedure B, substituting 4-ethylamino-benzoic acid methyl ester for ethyl-benzyl-amine. The crude 4-[ethyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carbonyl]-amino]-benzoic acid methyl ester was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-4-[ethyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carbonyl]-amino]-benzoic acid methyl ester. ¹H-NMR (CDCl₃) δ: 0.97 (d, 3H), 1.19 (t, 3H), 1.72 - 1.81 (m, 1H), 2.52 - 2.61 (m, 1H), 3.71 - 3.78 (m, 4H), 3.89 - 3.93 (m, 2H), 3.97 (s, 3H), 5.06 - 5.12 (m, 1H), 6.60 (d, 1H), 6.75 - 6.90 (m, 5H), 7.36 (d, 2H), 7.51 (d, 2H), 7.87 (d, 2H). MS m/z: 487 (M⁺), 459.

[00147] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-benzyl)-ethyl-amide (5)

[00148] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-benzyl)-ethyl-amide was made following general procedure B, substituting *N*-ethyl-4-chlorobenzylamine for ethyl-benzyl-amine. ¹H-NMR (CDCl₃, mixture of rotamers) δ: 1.07 - 1.28 (m, 6H), 1.83 (ddd, 0.4H), 2.03 (ddd, 0.6H), 2.42 - 2.64 (m, 1H), 3.39 - 3.52 (m, 2H), 3.75 (s, 3H), 4.07 - 4.28 (m, 1H), 4.50 - 4.72 (m, 2H), 4.99 - 5.20 (m, 1H), 6.49 - 7.53 (m, 12H). MS m/z: 381 (M+1).

[00149] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzylamide (8)

[00150] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzylamide was made following general procedure B, substituting benzylamine for ethyl-benzyl-amine. The crude product was isolated as a mixture of *cis* and *trans* isomers. Purification by HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzylamide. ¹H-NMR (CDCl₃) δ: 1.20 (d, 3H), 1.81 (ddd, 1H), 2.75 - 2.86 (m, 1H), 3.70 - 3.78 (m, 4H), 4.34 - 4.40 (m, 2H), 4.79 - 4.88 (m, 1H), 5.85 - 5.94 (m, 1H), 6.61 - 6.67 (m, 2H), 6.75 (d, 1H), 6.97 - 7.16 (m, 5H), 7.18 - 7.24 (m, 5H). MS m/z = 415 (M+1).

[00151] (±)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (9) and (±)-*cis*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (10)

[00152] ($\pm$)-*trans*-1-(4-Hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (585 mg, 1.30 mmol) was dissolved in dimethylformamide (20 mL). Potassium carbonate (1.5 g) was added, followed by ethyl-4-bromobutyrate (2.53 g, 1.9 mL, 13 mmol). The reaction was warmed to 90 °C and stirred under nitrogen overnight. Upon completion, the reaction was cooled to room temperature. The solvent layer was decanted and concentrated. The residue was dissolved in ethyl acetate. The residual solids in the reaction flask were washed with ethyl acetate and the washings combined with the filtrate ethyl acetate solution. The combined ethyl acetate layers were washed with water (3x) and brine, dried over sodium sulfate, filtered, and concentrated to afford the crude product. The crude material was a mixture of *cis* and *trans* isomers due to racemization under the alkylation conditions. The mixture was purified by silica gel chromatography (ethyl acetate / hexanes gradient) to afford pure ($\pm$)-*trans*-4-(4-((4-chloro-phenyl)-ethyl-carbamoyl)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-phenoxy)-butyric acid ethyl ester as a foam (88%) and pure ($\pm$)-*cis*-4-(4-((4-Chloro-phenyl)-ethyl-carbamoyl)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-phenoxy)-butyric acid ethyl ester. Data for the *trans* isomer: ¹H-NMR (CDCl₃) δ : 0.97 (d, 3H), 1.13 (t, 3H), 1.24 (t, 3H), 1.73 (ddd, 1H), 2.01 - 2.14 (m, 2H), 2.41 - 2.59 (m, 3H), 3.61 - 4.00 (m, 5H), 4.06 - 4.18 (m, 2H), 5.01 - 5.14 (m, 1H), 6.44 (d, 1H), 6.68 - 6.84 (m, 4H), 6.89 (dd, 1H), 7.16 - 7.27 (m, 2H), 7.42 - 7.51 (m, 4H). MS *m/z*: 563 (M+1).

[00153] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-ethyl-amide (11)

[00154] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(4-chloro-3-trifluoromethyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-trifluoromethyl-phenyl)-ethyl-amide. ¹H-NMR (CDCl₃) δ : 1.02 (d, 3H), 1.13 (t, 3H), 1.64 - 1.72 (m, 1H), 2.58 - 2.67 (m, 1H), 3.59 - 3.69 (m, 1H), 3.76 (s, 3H), 3.85 - 3.97 (m, 2H), 5.02 - 5.12 (m, 1H), 6.49 (d, 1H), 6.60 - 6.62 (m, 1H), 6.75 (d, 2H), 6.80 - 6.89 (m, 2H), 7.39 (dd, 1H), 7.46 - 7.51 (m, 3H), 7.64 (d, 1H). MS *m/z*: 531 (M+1), 533 (M+2).

[00155] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*m*-tolyl-amide (12)

[00156] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*m*-tolyl-amide was made following general procedure B, substituting ethyl-*m*-tolyl-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*m*-tolyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-

carboxylic acid ethyl-*m*-tolyl-amide. ¹H-NMR (CDCl₃) δ: 0.96 (d, 3H), 1.15 (t, 3H), 1.74 - 1.82 (m, 1H), 2.53 (s, 3H), 2.50 - 2.59 (m, 1H), 3.68 - 3.77 (m, 4H), 3.85 - 3.91 (m, 2H), 5.07 - 5.13 (m, 1H), 6.44 (d, 1H), 6.78 - 6.93 (m, 5H), 7.08 (bs, 2H), 7.22 (d, 2H), 7.51 - 7.54 (m, 2H). MS m/z: 444 (M+1).

[00157] (±)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-acetic acid (13) and (±)-*cis*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-acetic acid (39)

[00158] (±)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-acetic acid was made following the procedures for the synthesis of (±)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid from (±)-*trans*-1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Ethyl-2-bromoisobutyrate was substituted for ethyl-4-bromobutyrate. ¹H-NMR (CDCl₃) δ: 0.97 (d, 3H), 1.12 (t, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 1.67 - 1.75 (m, 1H), 2.47 - 2.58 (m, 1H), 3.57 - 3.73 (m, 1H), 3.76 - 3.90 (m, 2H), 5.06 - 5.11 (m, 1H), 6.42 (d, 1H), 6.73 - 6.92 (m, 5H), 7.19 - 7.28 (m, 2H), 7.46 (d, 4H). *Cis*: ¹H-NMR (CDCl₃) δ: 1.15 (d, 3 H), 1.24 (t, 3 H), 1.53 (s, 3 H), 1.55 (s, 3 H), 1.63 - 1.76 (m, 1 H), 2.47 - 2.58 (m, 1 H), 3.29 - 3.34 (m, 1 H), 3.74 - 3.87 (m, 1 H), 3.97 - 4.14 (m, 1 H), 6.38 (d, 1 H), 6.56 - 6.61 (m, 2 H), 6.85 - 6.96 (t, 1 H), 7.07 - 7.21 (m, 5 H), 7.32 (d, 3 H). MS m/z: 536 (M+1).

[00159] (±)-*cis* and (±)-*trans*-1-(4-Methoxy-benzoyl)-2,4-dimethyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (14)

[00160] A round bottom flask was charged with 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide in anhydrous THF (10.0 mL) under an argon atmosphere. Into the reaction was added lithium hexamethyldisilazide (2.10 mL of a 1M THF solution) via syringe. The reaction was stirred at room temperature for 30 minutes. Next, methyl iodide (0.44 mL, 7.1 mmol) was added and the reaction stirred at room temperature for an additional 18 hours. The reaction mixture was diluted with water (10 mL), transferred to a separatory funnel, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (1 x 70 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a mixture of (±)-*cis* and (±)-*trans*-1-(4-methoxy-benzoyl)-2,4-dimethyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide as a yellow solid (309 mg) containing 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. MS m/z: 477 (M+1).

[00161] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-isopropyl-phenyl)-amide (15)

[00162] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-isopropyl-phenyl)-amide was made following general procedure B, substituting ethyl-(4-isopropyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-isopropyl-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-isopropyl-phenyl)-amide. ¹H-NMR (CDCl₃) δ : 0.96 (d, 3H), 1.15 (t, 3H), 1.28 (d, 6H), 1.72 - 1.81 (m, 1H), 2.50 - 2.59 (m, 1H), 2.92 - 3.01 (m, 1H), 3.64 - 3.73 (m, 1H), 3.75 (s, 3H), 3.81 - 3.93 (m, 2H), 5.04 - 5.14 (m, 1H), 6.43 (d, 1H), 6.69 - 6.91 (m, 5H), 7.17 (d, 2H), 7.32 (d, 2H), 7.52 (d, 2H). MS *m/z*: 471 (M⁺), 472 (M+1).

[00163] ($\pm$)-*cis*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (16) and ($\pm$)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (19)

[00164] ($\pm$)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (520 mg, 0.923 mmol) was dissolved in tetrahydrofuran (15 mL). A solution of lithium hydroxide (77 mg, 1.8 mmol) in water (5 mL) was added. Ethanol was added until the reaction was homogeneous. The resulting solution was allowed to stir at room temperature overnight. The solution was concentrated to remove ethanol and tetrahydrofuran. The resulting aqueous mixture was acidified with concentrated hydrochloric acid until pH = 1 - 2. The heterogeneous mixture was immediately extracted with ethyl acetate (2 x 75 mL). The extracts were combined, washed with brine, dried over sodium sulfate, filtered, and concentrated. The residue was a mixture of *cis* and *trans* isomers. A portion of the crude residue was purified by HPLC to afford pure ($\pm$)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid and pure ($\pm$)-*cis*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid. The remainder of the mixture was used without further purification in subsequent reactions. Data for the *trans* isomer: ¹H-NMR (CD₃OD) δ : 0.97 (d, 3H), 1.12 (t, 3H), 4.73 (ddd, 1H), 2.00 - 2.13 (m, 2H), 2.47 - 2.58 (m, 3H), 3.61 - 3.99 (m, 5H), 5.02 - 5.12 (m, 1H), 6.44 (d, 1H), 6.68 - 6.74 (m, 2H), 6.75 - 6.83 (m, 2H), 6.85 - 6.92 (m, 1H), 7.17 - 7.25 (m, 3H), 7.42 - 7.51 (m, 4H). MS *m/z*: 535 (M+1).

[00165] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-nitro-phenyl)-amide (17)

[00166] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-nitro-phenyl)-amide was made following general procedure B, substituting ethyl-(4-nitro-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-nitro-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-

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tetrahydro-quinoline-4-carboxylic acid ethyl-(4-nitro-phenyl)-amide. ¹H-NMR (CDCl₃) δ: 0.96 (d, 3H), 1.15 (t, 3H), 1.75 - 1.83 (m, 1H), 2.48 - 2.57 (m, 1H), 3.65 - 3.77 (m, 4H), 3.83 - 3.90 (m, 2H), 5.05 - 5.15 (m, 1H), 6.43 (d, 1H), 6.74 - 6.81 (m, 3H), 6.88 - 6.91 (m, 2H), 7.15 (d, 2H), 7.26 - 7.29 (m, 2H), 7.52 - 7.55 (m, 2H). MS m/z: 474 (M+1).

[00167] (±)-*trans*-2-Methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (18)

[00168] To a 0.5 M methanolic solution of sodium methoxide (48 mL, 24 mmol) was added a solution of nitroethane (1.7 mL, 24 mmol) in dimethylacetamide (18 mL) under a nitrogen atmosphere. After the mixture was cooled down to 5 °C, acetyl chloride (1.7 mL, 24 mmol) and ethyl propionate (2.4 mL, 24 mmol) were added and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and partitioned between water and ethyl acetate. The organic layer was separated and washed with brine, dried over magnesium sulfate, and concentrated *in vacuo* to yield an orange oil (3.7 g). The crude material was purified by flash chromatography (10% ethyl acetate / hexanes) to provide 3-methyl-isoxazole-5-carboxylic acid ethyl ester as white crystals (900 mg, 24%).

[00169] A round bottom flask with magnetic stirrer was charged with 3-methyl-isoxazole-5-carboxylic acid ethyl ester (900 mg, 5.8 mmol) in tetrahydrofuran (2.0 mL). To the reaction was added a solution of sodium hydroxide (465 mg, 11.6 mmol) in water (2 mL), followed by methanol (4 mL). The reaction was stirred at room temperature for 18 - 20 hours under an argon atmosphere. The reaction was transferred to a separatory funnel and the pH adjusted to 2 via addition of 1N hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 35 mL) and the combined extractions were washed with brine (1 x 50 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to yield 3-methyl-isoxazole-5-carboxylic acid as a white solid (660 mg, 90%). The solid was used without purification in the next reaction.

[00170] (±)-*trans*-2-Methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 3-methyl-isoxazole-5-carbonyl chloride for 4-trifluoromethyl-benzoyl chloride. 3-Methyl-isoxazole-5-carbonyl chloride was prepared by reaction of the preformed 3-methyl-isoxazole-5-carboxylic acid with oxalyl chloride and dimethylformamide in methylene chloride. In addition, only 1.2 equivalents of lithium hydroxide were used in the ester hydrolysis step. The crude 2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification by silica gel chromatography (dichloromethane / methanol gradient: 99.5/0.5 -> 99/1) yielded (±)-*trans*-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (24%). ¹H-NMR (CDCl₃) δ: 1.02 (t, 3H), 1.13 (d, 3H), 1.40 - 1.50 (m, 1H), 2.25 (s, 3H), 2.70 - 2.80

(m, 1H), 3.40 - 3.52 (m, 1H), 3.80 (q, 2H), 4.95 - 5.10 (m, 1H), 6.35 (d, 1H), 6.42 (s, 1H), 6.70 (d, 1H), 6.90 (t, 1H), 7.00 (t, 1H), 7.10 (d, 2H), 7.40 (d, 2H). MS m/z: 438/440 (M+1).

[00171] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-imidazol-1-yl-phenyl)-amide (20)

[00172] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-imidazol-1-yl-phenyl)-amide was made following general procedure B, substituting ethyl-(4-imidazol-1-yl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-imidazol-1-yl-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-imidazol-1-yl-phenyl)-amide. ¹H-NMR (CDCl₃) δ : 0.98 (d, 3H), 1.15 (t, 3H), 1.73 - 1.84 (m, 1H), 2.48 - 2.64 (m, 1H), 3.75 (bs, 4H), 3.84 - 3.98 (m, 2H), 5.00 - 5.15 (m, 1H), 6.45 (d, 1H), 6.73 - 6.89 (m, 5H), 7.24 (bs, 1H), 7.32 - 7.40 (m, 3H), 7.51 (bs, 4H), 7.91 (bs, 1H). MS m/z: 495 (M⁺).

[00173] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-amide (21)

[00174] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-amide was prepared following general procedure B, substituting 4-chloroaniline for ethyl-benzyl-amine. ¹H-NMR (CDCl₃) δ : 1.18 (d, 3H), 1.74 - 1.85 (m, 1H), 2.87 (ddd, 1H), 3.73 (s, 3H), 3.82 (dd, 1H), 4.83 - 4.95 (m, 1H), 6.61 - 6.67 (m, 2H), 6.76 (d, 1H), 6.99 - 7.13 (m, 2H), 7.14 - 7.21 (m, 2H), 7.25 - 7.31 (m, 3H), 7.36 - 7.43 (m, 2H), 7.87 (s, 1H). MS m/z: 435 (M+1).

[00175] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-methyl-phenyl)-ethyl-amide (22)

[00176] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-methyl-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(4-chloro-3-methyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-methyl-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-3-methyl-phenyl)-ethyl-amide. ¹H-NMR (CDCl₃) δ : 0.99 (d, 3H), 1.14 (t, 3H), 1.72 - 1.80 (m, 1H), 2.44 (s, 3H), 2.50 - 2.59 (m, 1H), 3.62 - 3.73 (m, 1H), 3.77 (s, 3H), 3.79 - 3.92 (m, 2H), 5.07 - 5.13 (m, 1H), 6.45 (d, 1H), 6.74 - 6.83 (m, 4H), 6.88 - 6.93 (m, 1H), 7.04 - 7.06 (m, 1H), 7.13 (bs, 1H), 7.45 (d, 1H), 7.52 (d, 2H). MS m/z: 477 (M⁺).

[00177] ($\pm$)-*cis*-1-(6-Methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (23)

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[00178] Same procedure as for the preparation of ($\pm$)-*trans*-1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Purification via HPLC afforded ($\pm$)-*cis*-1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (4%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.10 (d, 3H), 1.25 (t, 3H), 1.70 - 1.80 (m, 1H), 2.45 - 2.55 (m, 1H), 3.30 - 3.40 (dd, 1H), 3.75 - 3.85 (m, 1H), 3.90 (s, 3H), 4.05 - 4.15 (m, 1H), 4.55 - 4.65 (m, 1H), 6.40 (d, 1H), 6.50 (d, 1H), 6.80 (d, 1H), 7.00 (t, 1H), 7.10 - 7.20 (m, 4H), 7.35 (d, 2H), 7.70 (s, 1H). MS m/z : 464/466 ($M+1$).

[00179] ($\pm$)-*trans*-1-(3-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (24)

[00180] ($\pm$)-*trans*-1-(3-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 3-methoxy-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (24%). $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (d, 3H), 1.13 (t, 3H), 1.71 - 1.80 (m, 1H), 2.45 - 2.56 (m, 1H), 3.58 - 3.65 (m, 1H), 3.67 (s, 3H), 3.77 - 3.93 (m, 2H), 4.98 - 5.10 (m, 1H), 6.44 - 6.52 (d, 1H), 6.70 - 6.74 (d, 1H), 6.76 - 6.91 (m, 3H), 7.06 - 7.15 (m, 4H), 7.21 (s, 1H), 7.41 - 7.49 (d, 2H). MS m/z : 463 ($M+1$).

[00181] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dichloro-phenyl)-ethyl-amide (25)

[00182] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dichloro-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(3,4-dichloro-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dichloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dichloro-phenyl)-ethyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 1.01 (d, 3H), 1.13 (t, 3H), 1.70 - 1.79 (m, 1H), 2.51 - 2.61 (m, 1H), 3.59 - 3.70 (m, 1H), 3.76 (s, 3H), 3.79 - 3.92 (m, 2H), 5.06 - 5.13 (m, 1H), 6.47 (d, 1H), 6.74 - 6.92 (m, 5H), 7.13 (dd, 1H), 7.37 (d, 1H), 7.49 (d, 2H), 7.56 (d, 1H). MS m/z : 497 ($M+1$), 499 ($M+3$).

[00183] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid diethylamide (26)

[00184] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid diethylamide was made following general procedure B substituting diethylamine for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 1.10 - 1.29 (m, 9H), 1.97 (ddd, 1H), 2.51 (ddd, 1H), 3.38 - 3.53

(m, 4H), 4.15 (dd, 1H), 5.06 - 5.17 (m, 1H), 6.49 (d, 1H), 6.70 - 6.75 (m, 2H), 6.82 (ddd, 1H), 6.90 - 7.03 (m, 2H), 7.45 - 7.50 (m, 2H). MS m/z: 381 (M+1).

[00185] (±)-*trans*-1-(2-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (27)

[00186] (±)-*trans*-1-(2-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 2-methoxy-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(2-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(2-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (12%). MS m/z: 463 (M+1).

[00187] (±)-*cis*-1-[4-(3-Carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (28) and (±)-*trans*-1-[4-(3-carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (31)

[00188] A mixture of (±)-*cis* and *trans*-4-(4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-phenoxy)-butyric acid (293 mg, 0.548 mmol) was dissolved in dimethylformamide (5 mL). Hydroxybenzotriazole (111 mg, 0.82 mmol) and diisopropylethylamine (283 mg, 382 µL, 2.19 mmol) were added. To the resulting reaction was added *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (313 mg, 0.82 mmol). The reaction was allowed to stir at room temperature for 5 minutes and ammonium chloride (60 mg, 1.07 mmol) was added. The reaction was stirred at room temperature overnight. Upon completion, the mixture was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed twice with water. The extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfate, filtered, and concentrated. The crude residue was a mixture of *cis* and *trans* isomers. Purification via silica gel chromatography (methylene chloride / methanol gradient) afforded pure (±)-*trans*-1-[4-(3-carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (86%) as well as pure (±)-*cis*-1-[4-(3-carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Data for the *trans* isomer: ¹H-NMR (CDCl₃) δ: 0.97 (d, 3H), 1.11 (t, 3H), 1.72 (ddd, 1H), 2.03 - 2.13 (m, 2H), 2.34 - 2.41 (m, 2H), 2.52 (ddd, 1H), 3.59 - 3.73 (m, 1H), 3.77 - 3.89 (m, 2H), 3.91 - 3.97 (m, 2H), 5.00 - 5.10 (m, 1H), 5.47 (br s, 1H), 5.72 (br s, 1H), 6.44 (d, 1H), 6.68 - 6.82 (m, 4H), 6.88 (dd, 1H), 7.16 - 7.22 (m, 2H), 7.43 - 7.50 (m, 4H). MS m/z: 534 (M+1).

[00189] (±)-*trans*-(3-Diethylamino-pyrazol-1-yl)-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-methanone (29)

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[00190] (±)-*trans*-(3-Diethylamino-pyrazol-1-yl)-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-methanone was prepared following general procedure B, substituting *N,N*-diethyl-1*H*-pyrazol-3-amine for ethyl-benzyl-amine. Purification by HPLC yielded pure (±)-*trans*-(3-diethylamino-pyrazol-1-yl)-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-methanone. ¹H-NMR (CDCl₃) δ: 1.15 - 1.31 (m, 9H), 2.06 (ddd, 1H), 2.75 - 2.86 (m, 1H), 3.33 - 3.43 (m, 4H), 3.74 (s, 3H), 5.00 - 5.13 (m, 2H), 5.96 (d, 1H), 6.50 - 6.56 (m, 1H), 6.67 - 6.73 (m, 2H), 6.87 (ddd, 1H), 6.97 (ddd, 1H), 7.28 (dd, 1H), 7.37 - 7.44 (m, 2H), 8.05 (d, 1H). MS *m/z* = 447 (M+1).

[00191] (±)-*trans*-1-(6-Methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (30)

[00192] A round bottom flask with magnetic stirrer was charged with *cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (400 mg, 1.95 mmol) in methylene chloride (4.00 mL) under a nitrogen atmosphere. Into the reaction was added 6-chloronicotinoyl chloride (480 mg, 2.73 mmol) and *N,N*-diisopropylethylamine (0.95 mL, 5.46 mmol) via syringe. The reaction was stirred at room temperature for 18 - 20 hours. The reaction was transferred to a separatory funnel containing a saturated sodium bicarbonate solution (15 mL), then diluted with methylene chloride (15 mL) and shaken vigorously. The resulting organic layer was separated, washed with brine (1 x 20 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford an orange residue (800 mg). The residue was purified via flash chromatography (1 % methanol / methylene chloride) to yield *cis*-1-(6-chloro-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester as a yellow solid (630 mg, 94%).

[00193] To a solution of *cis*-1-(6-chloro-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (620 mg, 1.8 mmol) in ethylene glycol dimethyl ether (6.00 mL) was added at 0 °C a 5M solution of sodium methoxide in methanol (3.3 mL, 16.2 mmol). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was acidified to pH 1 by addition of aqueous 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to yield 1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (190 mg, 32%).

[00194] A round bottom flask with magnetic stirrer was charged with 1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (190 mg, 0.58 mmol) in anhydrous pyridine (1.5 mL). To the reaction was added *N*-ethyl-*p*-chloroaniline (185 mg, 1.19 mmol), followed by EDCI (156 mg, 0.82 mmol). The reaction was stirred at room temperature under an argon atmosphere for 18 - 20 hours. The reaction was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a yellow oil (350 mg). The crude material was purified via silica gel

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chromatography (1 % methanol / methylene chloride) followed by HPLC to yield ($\pm$)-*trans*-1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (14%). ¹H-NMR (CDCl₃) δ : 1.05 (d, 3H), 1.13 (t, 3H), 1.65 - 1.75 (m, 1H), 2.50 - 2.60 (m, 1H), 3.60 - 3.70 (m, 1H), 3.80 (q, 2H), 3.95 (s, 3H), 5.02 - 5.10 (m, 1H), 6.50 (d, 1H), 6.60 (d, 1H), 6.75 (d, 1H), 6.85 - 7.00 (m, 2H), 7.20 (m, 2H), 7.50 (d, 2H), 7.75 (d, 1H), 8.40 (s, 1H). MS m/z : 464/466 (M+1).

[00195] ($\pm$)-*trans*-1-(4-Hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (32)

[00196] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (1.067 g, 2.30 mmol) was dissolved in methylene chloride (20 mL). The solution was cooled to 0 °C. Boron tribromide (1.15 g, 0.436 mL, 4.61 mmol) was added via syringe. The reaction was warmed to room temperature and stirred. Two additional aliquots of boron tribromide (0.220 uL each) were added at one hour and two hours. The reaction was stirred for one hour after the second additional aliquot of boron tribromide was added. Upon completion, the reaction was slowly dripped into an aqueous sodium hydroxide solution (50 mL of 6M). The resulting emulsion was extracted with ethyl acetate (2 x 100 mL). The extracts were combined, washed with water and brine, dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate/hexanes gradient) to afford pure ($\pm$)-*trans*-1-(4-hydroxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (91 %). ¹H-NMR (CDCl₃) δ : 0.97 (d, 3H), 1.13 (t, 3H), 1.74 (ddd, 1H), 2.51 (ddd, 1H), 3.64 - 3.90 (m, 3H), 5.02 - 5.13 (m, 1H), 6.43 (d, 1H), 6.55 - 6.61 (m, 2H), 6.77 - 6.84 (m, 2H), 6.85 - 6.93 (m, 1H), 7.17 - 7.22 (m, 2H), 7.33 - 7.39 (m, 2H), 7.43 - 7.49 (m, 2H). MS m/z : 477 (M+1).

[00197] ($\pm$)-1-(4-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (33)

[00198] Step 1. ($\pm$)-1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid.

[00199] Quinoline-4-carboxylic acid (580 mg, 3.35 mmol) was dissolved in an aqueous potassium hydroxide solution (1 M, 10 mL). Nickel/aluminum amalgam (3 g) was added in portions over 1.5 hours. The heterogeneous mixture was stirred at room temperature for 48 hours. Upon completion, the reaction was filtered through Celite® and washed with ethyl acetate. The pH of the aqueous layer was adjusted with concentrated hydrochloric acid to 4-5. Solid sodium chloride was added until the aqueous layer was saturated. The ethyl acetate layer was separated. The aqueous phase was extracted with ethyl acetate. The extracts were combined, washed with minimal brine, dried over sodium sulfate, filtered, and concentrated. 1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid was used without further purification (389 mg, 66%). ¹H-NMR (CDCl₃) δ : 1.95 - 2.08 (m, 1H), 2.22 - 2.37 (m, 1H), 3.23 - 3.34 (m, 1H), 3.39 - 3.49 (m, 1H), 3.79 (dd, 1H), 6.56 (d, 1H), 6.69 (dd, 1H), 7.07 (dd, 1H), 7.17 (d, 1H). MS m/z : 178 (M+1).

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[00200] Step 2. ($\pm$)-1-(4-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid.

[00201] 1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid (305 mg, 1.89 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL). Anisoyl chloride (644 mg, 3.78 mmol) was added followed by diisopropylethylamine (733 mg, 1.01 mL, 15.67 mmol). The reaction was stirred at room temperature for 7 days. The mixture was concentrated and partitioned between chloroform and sodium hydroxide (1 M, aqueous). The chloroform extract was set aside. The aqueous phase was acidified with concentrated hydrochloric acid (pH = 3-4). The aqueous phase was then extracted with ethyl acetate (three times). The combined extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude product was used without further purification. MS m/z : 312 (M+1).

[00202] Step 3. ($\pm$)-1-(4-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide.

[00203] 1-(4-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (approx. 1.47 mmol) was suspended in methylene chloride (10 mL) to which one drop of dimethylformamide was added. Oxalyl chloride (375 mg, 275 μ L, 2.95 mmol) was added. Vigorous bubbling ensued, followed by dissolution of the starting material. After stirring for 4 hours at room temperature, the yellow solution was concentrated and azeotroped with toluene to remove excess oxalyl chloride. The resulting acid chloride solution was dissolved in methylene chloride (10 mL). Diisopropylethylamine (569 mg, 768 μ L, 4.41 mmol) was added, followed by 4-chloro-*N*-ethylaniline (457 mg, 2.93 mmol). The mixture was stirred at room temperature overnight. The reaction was poured into ethyl acetate and washed with water and brine. The combined organics were dried over sodium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate / hexanes gradient) to afford ($\pm$)-1-(4-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (193 mg) as a foam. $^1\text{H-NMR}$ (CDCl_3) δ : 1.17 (t, 3H), 2.06 - 2.26 (m, 2H), 3.57 - 3.70 (m, 2H), 3.73 - 3.87 (m, 5H), 4.02 (dd, 1H), 6.52 (d, 1H), 6.66 - 6.74 (m, 2H), 6.84 (ddd, 1H), 6.93 - 7.06 (m, 2H), 7.17 - 7.24 (m, 2H), 7.37 - 7.43 (m, 2H). MS m/z : 449 (M+1).

[00204] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-ethyl-phenyl)-amide (34)

[00205] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-ethyl-phenyl)-amide was prepared following general procedure B, substituting ethyl-(4-ethyl-phenyl)-amine for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 0.95 (d, 3H), 1.13 (t, 3H), 1.26 (t, 3H), 1.76 (ddd, 1H), 2.52 (ddd, 1H), 2.69 (q, 2H), 3.63 - 3.77 (m, 4H), 3.80 - 3.92 (m, 2H), 5.02 - 5.13 (m, 1H), 6.42 (d, 1H), 6.70 - 6.91 (m, 5H), 7.13 - 7.19 (m, 2H), 7.25 - 7.32 (m, 2H), 7.47 - 7.55 (m, 2H). MS m/z : 457 (M+1).

[00206] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(5-methyl-isoxazol-3-yl)-amide (35)

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[00207] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(5-methyl-isoxazol-3-yl)-amide was prepared following general procedure B, substituting *N*-ethyl-5-methylisoxazol-3-amine for ethyl-benzyl-amine. The crude product was isolated as a mixture of *cis* and *trans* isomers. Purification by HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(5-methyl-isoxazol-3-yl)-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 1.04 - 1.30 (m, 6H), 1.84 - 1.98 (m, 1H), 2.45 (br s, 3H), 2.54 - 2.65 (m, 1H), 3.64 - 3.85 (m, 5H), 4.30 (dd, 1H), 4.99 - 5.13 (m, 1H), 5.96 (br s, 1H), 6.49 (d, 1H), 6.70 - 6.77 (m, 2H), 6.83 (br dd, 1H), 6.87 - 7.03 (m, 2H), 7.42 - 7.50 (m, 2H). MS m/z = 434 ($M+1$).

[00208] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl-phenyl-amide (36)

[00209] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl-phenyl-amide was made following general procedure B, substituting *N*-methyl-aniline for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl-phenyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl-phenyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (d, 3H), 1.75 - 1.83 (m, 1H), 2.51 - 2.60 (m, 1H), 3.34 (s, 3H), 3.77 (s, 3H), 3.92 - 3.98 (m, 1H), 5.07 - 5.12 (m, 1H), 6.44 (d, 1H), 6.75 - 6.92 (m, 5H), 7.29 - 7.39 (m, 2H), 7.38 - 7.54 (m, 5H). MS m/z : 415 (M^+).

[00210] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-4-methyl-phenyl)-ethyl-amide (37)

[00211] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-4-methyl-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(3-chloro-4-methyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-4-methyl-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-4-methyl-phenyl)-ethyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (d, 3H), 1.14 (t, 3H), 1.74 - 1.82 (m, 1H), 2.44 (s, 3H), 2.49 - 2.59 (m, 1H), 3.65 - 3.72 (m, 1H), 3.77 (s, 3H), 3.80 - 3.92 (m, 2H), 5.00 - 5.15 (m, 1H), 6.45 (d, 1H), 6.75 - 6.84 (m, 4H), 6.89 - 6.94 (m, 1H), 7.07 (dd, 1H), 7.26 - 7.36 (m, 2H), 7.53 (d, 2H). MS m/z : 477 (M^+).

[00212] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid amide (38)

[00213] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid amide was prepared following general procedure B, substituting ammonia in dioxane for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CD_3OD) δ : 1.20 (d, 3H), 1.81 (ddd, 1H), 2.78 (ddd, 1H), 3.77 (s, 3H), 3.87

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(dd, 1H), 4.90 - 4.98 (m, 1H), 6.55 (d, 1H), 6.74 - 6.83 (m, 2H), 6.94 (ddd, 1H), 7.09 (ddd, 1H), 7.33 (d, 1H), 7.36 - 7.41 (m, 2H). MS m/z = 325 (M+1).

[00214] ($\pm$)-*trans*-1-(4-Dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (40)

[00215] ($\pm$)-*trans*-1-(4-Dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 4-dimethylamino-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (54%). $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (d, 3H), 1.13 (t, 3H), 1.71 - 1.80 (m, 1H), 2.45 - 2.56 (1H, m), 2.93 (s, 6H), 3.64 - 3.93 (m, 3H), 4.98 - 5.10 (m, 1H), 6.50 - 6.59 (m, 3H), 6.78 - 6.90 (m, 3H), 7.19 - 7.23 (m, 2H), 7.41 - 7.49 (m, 4H). MS m/z : 476 (M+1).

[00216] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(1H-indol-4-yl)-amide (41)

[00217] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(1H-indol-4-yl)-amide was prepared following general procedure B, substituting *N*-ethyl-1H-indol-4-amine for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (d, 3H), 1.17 (t, 3H), 1.50 - 1.60 (m, 1H), 2.50 - 2.59 (m, 1H), 3.60 - 3.70 (m, 1H), 3.74 (s, 3H), 3.78 - 3.92 (m, 2H), 5.00 - 5.14 (m, 1H), 6.40 - 6.50 (m, 1H), 6.59 - 6.63 (m, 1H), 6.70 - 7.10 (m, 6H), 7.20 - 7.30 (m, 2H), 7.40 - 7.46 (m, 1H), 7.52 - 7.61 (m, 2H), 9.12 (br s, 1H). MS m/z : 468 (M+1), 469 (M+2)

[00218] ($\pm$)-*trans*-1-(Benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (42)

[00219] ($\pm$)-*trans*-1-(Benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting benzo[b]thiophene-2-carbonyl chloride for 4-trifluoromethyl-benzoyl chloride. Benzo[b]thiophene-2-carbonyl chloride was prepared by reaction of thianaphthene-2-carboxylic acid with oxalyl chloride and dimethylformamide in methylene chloride. The crude 1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification by silica gel chromatography (1% methanol / methylene chloride) followed by purification via HPLC yielded ($\pm$)-*trans*-2-methyl-1-(pyrimidine-5-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (34%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.02 - 1.18 (m, 6H), 1.65 - 1.75 (m, 1H), 2.55 - 2.65 (m, 1H), 3.60 - 3.70 (m, 1H), 3.80 (q, 2H), 5.05 - 5.15 (m, 1H), 6.70 (d, 1H), 6.80 - 7.00 (m, 3H), 7.20 - 7.40 (m, 4H), 7.45 (s, 1H), 7.50 (d, 2H), 7.70 (d, 1H), 7.80 (d, 1H). MS m/z : 489/491 (M+1).

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[00220] ($\pm$)-*trans*-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-(4-phenyl-piperazin-1-yl)-methanone (43)

[00221] ($\pm$)-*trans*-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-(4-phenyl-piperazin-1-yl)-methanone was prepared following general procedure B, substituting 1-phenyl-piperazine for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (d, 3H), 1.95 (ddd, 1H), 2.52 (ddd, 2H), 3.12 - 3.17 (m, 4H), 3.69 - 3.84 (m, 7H), 4.21 (dd, 1H), 5.00 - 5.11 (m, 1H), 6.56 (d, 1H), 6.69 - 6.73 (m, 2H), 6.82 - 7.03 (m, 5H), 7.05 - 7.17 (m, 1H), 7.22 - 7.28 (m, 2H), 7.45 - 7.50 (m, 2H). MS m/z : 470 ($M+1$).

[00222] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl-morpholin-4-yl-methanone (44)

[00223] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl-morpholin-4-yl-methanone was made following general procedure B, substituting morpholine for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 1.21 (d, 3H), 1.96 (ddd, 1H), 2.49 (ddd, 1H), 3.56 - 3.79 (m, 11H), 4.16 (t, 1H), 5.02 - 5.11 (m, 1H), 6.57 (d, 1H), 6.71 - 6.77 (m, 2H), 6.89 (ddd, 1H), 6.96 - 7.08 (m, 2H), 7.45 - 7.51 (m, 2H). MS m/z : 395 ($M+1$).

[00224] ($\pm$)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid (45)

[00225] ($\pm$)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid was made following the procedures for the synthesis of ($\pm$)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid from ($\pm$)-*trans*-1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Methyl chloroacetate was substituted for ethyl-4-bromobutyrate. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (d, 3H), 1.05 (t, 3H), 1.63 (m, 1H), 2.40 (m, 1H), 3.46 - 3.64 (m, 1H), 3.74 - 3.81 (m, 2H), 4.28 (s, 2H), 4.98 (m, 1H), 6.44 (d, 1H), 6.69 - 6.89 (m, 5H), 7.18 - 7.28 (m, 2H), 7.40 (d, 2H), 7.46 (d, 2H). MS m/z : 507 ($M+1$).

[00226] ($\pm$)-*cis*-1-[4-(3-Carbamoyl-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (46) and ($\pm$)-*trans*-1-[4-(3-carbamoyl-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (75)

[00227] ($\pm$)-*cis*-1-[4-(3-Carbamoyl-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide and ($\pm$)-*trans*-1-[4-(3-carbamoyl-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide were made following the procedure detailing the synthesis of ($\pm$)-*cis*-1-[4-(3-carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide and ($\pm$)-*trans*-1-[4-(3-carbamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-

carboxylic acid (4-chloro-phenyl)-ethyl-amide. A mixture of ($\pm$)-*cis* and *trans*-4-(4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-phenoxy)-2,2-dimethyl-butyric acid was substituted for a mixture of ($\pm$)-*cis* and *trans*-4-(4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-phenoxy)-butyric acid. Data for the *trans* isomer: $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (d, 3H), 1.11 (t, 3H), 1.24 (s, 6H), 1.71 (ddd, 1H), 1.96 - 2.01 (m, 2H), 2.48 - 2.59 (m, 1H), 3.59 - 3.73 (m, 1H), 3.74 - 3.90 (m, 2H), 3.93 - 4.01 (m, 2H), 5.00 - 5.12 (m, 1H), 5.39 - 5.85 (br m, 2H), 6.34 (d, 1H), 6.67 - 6.92 (m, 5H), 7.16 - 7.22 (m, 2H), 7.41 - 7.51 (m, 4H). MS m/z : 562 ($M+1$).

[00228] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-carbamoyl-phenyl)-ethyl-amide (47)

[00229] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-carbamoyl-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(4-carbamoyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-carbamoyl-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-carbamoyl-phenyl)-ethyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (d, 3H), 1.14 (t, 3H), 1.71 - 1.79 (m, 1H), 2.49 - 2.59 (m, 1H), 3.66 - 3.76 (m, 4H), 3.82 - 3.96 (m, 2H), 5.03 - 5.08 (m, 1H), 6.04 - 6.12 (bs, 2H), 6.49 (d, 1H), 6.74 - 6.93 (m, 5H), 7.34 (d, 2H), 7.49 (d, 2H), 7.97 (d, 2H). MS m/z : 472 (M^+).

[00230] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-phenyl)-ethyl-amide (48)

[00231] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(3-chloro-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3-chloro-phenyl)-ethyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (d, 3H), 1.15 (t, 3H), 1.72 - 1.79 (m, 1H), 2.51 - 2.61 (m, 1H), 3.64 - 3.73 (m, 1H), 3.77 (s, 3H), 3.81 - 3.94 (m, 2H), 5.07 - 5.12 (m, 1H), 6.46 (d, 1H), 6.75 - 6.93 (m, 5H), 7.16 - 7.19 (m, 1H), 7.27 - 7.28 (m, 1H), 7.42 - 7.44 (m, 2H), 7.51 (d, 2H). MS m/z : 463 (M^+), 465 ($M+2$).

[00232] ($\pm$)-*trans*-2-Methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (49)

[00233] ($\pm$)-*trans*-2-Methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 4-trifluoromethoxy-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 2-methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-

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amide was isolated as a mixture of *cis* and *trans* isomers. Purification via silica gel column (hexanes / ethyl acetate) provided ($\pm$)-*trans*-2-methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (56%). $^1\text{H-NMR}$ (CDCl_3) δ : 1.01 (d, 3H), 1.12 (t, 3H), 1.66 - 1.77 (m, 1H), 2.46 - 2.58 (m, 1H), 3.60 - 3.74 (m, 1H), 3.77 - 3.90 (m, 2H), 5.02 - 5.15 (m, 1H), 6.37 - 6.42 (m, 1H), 6.78 - 6.85 (m, 2H), 6.90 - 6.97 (m, 1H), 7.05 - 7.10 (m, 2H), 7.18 - 7.26 (m, 2H), 7.44 - 7.50 (m, 2H), 7.58 - 7.63 (m, 2H). MS m/z : 517 ($M+1$).

[00234] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methyl-3-trifluoromethyl-phenyl)-amide (50)

[00235] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methyl-3-trifluoromethyl-phenyl)-amide was made following general procedure B, substituting ethyl-(4-methyl-3-trifluoromethyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methyl-3-trifluoromethyl-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methyl-3-trifluoromethyl-phenyl)-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (d, 3H), 1.15 (t, 3H), 1.68 - 1.76 (m, 1H), 2.56 - 2.64 (m, 4H), 3.62 - 3.71 (m, 1H), 3.78 (s, 3H), 3.81 - 3.96 (m, 2H), 5.05 - 5.15 (m, 1H), 6.46 (d, 1H), 6.69 - 6.91 (m, 6H), 7.32 - 7.52 (m, 4H). MS m/z : 511 (M^+), 512 ($M+1$).

[00236] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-phenyl-amide (51)

[00237] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-phenyl-amide was made following general procedure B, substituting *N*-ethylaniline for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-phenyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-phenyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.96 (d, 3H), 1.17 (t, 3H), 1.75 - 1.83 (m, 1H), 2.48 - 2.57 (m, 1H), 3.68 - 3.74 (m, 1H), 3.77 (s, 3H), 3.84 - 3.90 (m, 2H), 5.07 - 5.13 (m, 1H), 6.43 (d, 1H), 6.74 - 6.82 (m, 3H), 6.86 - 6.94 (m, 2H), 7.16 (d, 2H), 7.28 (d, 2H), 7.52 - 7.55 (m, 2H). MS m/z : 430 ($M+1$).

[00238] ($\pm$)-*cis*-1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (52)

[00239] ($\pm$)-*cis*-1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 4-fluoro-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*cis*-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-

tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (13%). ¹H-NMR (CDCl₃) δ: 1.15 (d, 3H), 1.24 (t, 3H), 1.65 - 1.77 (sextuplet, 1H), 2.48 - 2.56 (m, 1H), 3.28 - 3.34 (dd, 1H), 3.73 - 3.85 (sextuplet, 1H), 3.95 - 4.07 (sextuplet, 1H), 4.57 - 4.69 (m, 1H), 6.35 - 6.43 (d, 1H), 6.66 - 6.71 (m, 2H), 6.76 - 6.82 (t, 2H), 6.85 - 6.95 (t, 1H), 7.10 - 7.24 (m, 4H), 7.27 - 7.37 (d, 2H). MS m/z: 451 (M+1).

[00240] *rel*-(2*S*,4*S*)-1-(4-Ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (53)

[00241] (±)-*trans*-1-(4-Ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was prepared following general procedure A, substituting 4-ethyl-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(4-ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC provided (±)-*trans*-1-(4-ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide.

[00242] *rel*-(2*S*,4*S*)-1-(4-Ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated from (±)-*trans*-1-(4-ethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide by preparative chiral HPLC. Analytical data for the enantiomer was identical to the racemate. ¹H-NMR (CDCl₃) δ: 0.98 (d, 3H), 1.13 (t, 3H), 1.17 (t, 3H), 1.67 - 1.77 (m, 1H), 2.59 (q, 2H), 2.49 - 2.61 (m, 1H), 3.61 - 3.75 (m, 1H), 3.78 - 3.93 (m, 2H), 5.04 - 5.14 (m, 1H), 6.44 - 6.50 (m, 1H), 6.73 - 6.83 (m, 2H), 6.85 - 6.92 (m, 1H), 7.04 - 7.10 (m, 2H), 7.17 - 7.21 (m, 2H), 7.41 - 7.48 (m, 4H). MS m/z: 461 (M+1).

[00243] (±)-*cis*-1-[2-(4-Methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (54)

[00244] Same procedure as for the preparation of (±)-*trans*-1-[2-(4-methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Further purification by HPLC afforded (±)-*cis*-1-[2-(4-methoxy-phenyl)-acetyl]-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (13%). ¹H-NMR (CDCl₃) δ: 1.05 (d, 3H), 1.20 (t, 3H), 1.60 (m, 1H), 2.25 - 2.35 (d, 1H), 3.05 - 3.15 (m, 1H), 3.40 (s, 2H), 3.65 - 3.75 (m, 1H), 3.80 (s, 3H), 4.00 - 4.10 (m, 1H), 4.55 - 4.65 (m, 1H), 6.80 (m, 4H), 7.10 (d, 2H), 7.30 (m, 4H), 7.35 (d, 2H). MS m/z: 477/479 (M+1).

[00245] (±)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (55) and (±)-*cis*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (76)

[00246] (±)-*trans*-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid was made following the procedures for

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making ($\pm$)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid from ($\pm$)-*trans*-1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. 5-Bromo-2,2-dimethyl-pentanoic acid ethyl ester was substituted for ethyl-4-bromobutyrate. The crude product was obtained as a mixture of *cis* and *trans* isomers. The *trans* isomer was obtained and characterized. $^1\text{H-NMR}$ (CDCl_3) δ : 0.97 (d, 3H), 1.12 (t, 3H), 1.26 (s, 6H), 1.73 (ddd, 1H), 2.00 - 2.08 (m, 2H), 2.47 - 2.58 (m, 1H), 3.57 - 3.73 (m, 2H), 3.76 - 3.90 (m, 2H), 3.95 - 4.03 (m, 2H), 5.02 - 5.11 (m, 1H), 6.44 (d, 1H), 6.67 - 6.74 (m, 2H), 6.75 - 6.83 (m, 2H), 6.84 - 6.92 (dd, 1H), 7.17 - 7.23 (m, 2H), 7.41 - 7.51 (m, 4H). MS m/z : 563 ($M+1$).

[00247] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-propyl-amide (56)

[00248] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-propyl-amide was made following general procedure B, substituting *N*-propyl-4-chloroaniline for ethyl-benzyl-amine. $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (t, 3H), 0.97 (d, 3H), 1.46 - 1.62 (m, 2H), 1.75 (ddd, 1H), 2.52 (ddd, 1H), 3.53 - 3.66 (m, 1H), 3.69 - 3.88 (m, 5H), 5.02 - 5.12 (m, 1H), 6.44 (m, 1H), 6.69 - 6.94 (m, 5H), 7.17 - 7.23 (m, 2H), 7.42 - 7.53 (m, 4H). MS m/z : 477 ($M+1$).

[00249] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(3-fluoro-4-methyl-phenyl)-amide (57)

[00250] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(3-fluoro-4-methyl-phenyl)-amide was made following general procedure B, substituting ethyl-(3-fluoro-4-methyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(3-fluoro-4-methyl-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(3-fluoro-4-methyl-phenyl)-amide. $^1\text{H-NMR}$ (CDCl_3) δ : 0.99 (d, 3H), 1.15 (t, 3H), 1.76 - 1.84 (m, 1H), 2.34 (bs, 3H), 2.49 - 2.58 (m, 1H), 3.63 - 3.78 (m, 4H), 3.83 - 3.92 (m, 2H), 5.08 - 5.13 (m, 1H), 6.45 (d, 1H), 6.75 - 6.99 (m, 6H), 7.27 - 7.33 (m, 2H), 7.53 (d, 2H). MS m/z : 461 (M^+).

[00251] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-methyl-amide (58)

[00252] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-methyl-amide was made following general procedure B, substituting *N*-methyl-*p*-chloro-aniline for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-methyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-methyl-amide. $^1\text{H-NMR}$ (CDCl_3) δ :

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1.00 (d, 3H), 1.73 - 1.81 (m, 1H), 2.51 - 2.60 (m, 1H), 3.31 (s, 3H), 3.78 (s, 3H), 3.90 - 3.95 (m, 1H), 5.07 - 5.15 (m, 1H), 6.47 (d, 1H), 6.75 - 6.93 (m, 5H), 7.24 - 7.27 (m, 2H), 7.46 - 7.54 (m, 4H). MS m/z : 449 (M^+).

[00253] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (59)

[00254] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was prepared following general procedure A, substituting 4-methoxy-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC provided ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. ^1H -NMR (CDCl_3) δ : 0.98 (d, 3H), 1.12 (t, 3H), 1.67 - 1.79 (m, 1H), 2.45 - 2.59 (m, 1H), 3.60 - 3.73 (m, 1H), 3.76 (s, 3H), 3.77 - 3.91 (m, 2H), 5.01 - 5.15 (m, 1H), 6.41 - 6.47 (m, 1H), 6.71 - 6.84 (m, 4H), 6.85 - 6.93 (m, 1H), 7.18 - 7.25 (m, 2H), 7.43 - 7.54 (m, 4H). MS m/z : 463 ($M+1$).

[00255] *rel*-(2*S*,4*S*)-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (60) and *rel*-(2*R*,4*R*)-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (66)

[00256] *rel*-(2*S*,4*S*)-4-(4-{4-[(4-Chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid and *rel*-(2*R*,4*R*)-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid were isolated from ($\pm$)-*trans*-4-(4-{4-[(4-chloro-phenyl)-ethyl-carbamoyl]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid by preparative chiral HPLC. Data for single enantiomer (identical to enantiomer and to racemate), absolute stereochemistry unknown: ^1H -NMR (CD_3OD) δ : 0.97 (d, 3H), 1.12 (t, 3H), 4.73 (ddd, 1H), 2.00 - 2.13 (m, 2H), 2.47 - 2.58 (m, 3H), 3.61 - 3.99 (m, 5H), 5.02 - 5.12 (m, 1H), 6.44 (d, 1H), 6.68 - 6.74 (m, 2H), 6.75 - 6.83 (m, 2H), 6.85 - 6.92 (m, 1H), 7.17 - 7.25 (m, 3H), 7.42 - 7.51 (m, 4H). MS m/z : 535 ($M+1$).

[00257] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*o*-tolyl-amide (61)

[00258] ($\pm$)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*o*-tolyl-amide was made following general procedure B, substituting ethyl-*o*-tolyl-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*o*-tolyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*o*-tolyl-amide. ^1H -NMR (CDCl_3) δ : 0.96 (d, 3H), 1.14 (t, 3H), 1.75-1.78 (m, 1H), 2.31 (s, 3H), 2.47 - 2.56 (m, 1H), 3.74 - 3.77 (m, 4H), 4.19 - 4.28 (m, 2H), 5.10 - 5.05 (m, 1H), 6.45 (d, 1H), 6.68 - 6.92 (m, 5H), 7.26 - 7.40 (m, 4H), 7.49 - 7.55 (m, 2H). MS m/z : 444 ($M+1$).

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[00259] (±)-*trans*-1-(3-Fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (62)

[00260] (±)-*trans*-1-(3-Fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 3-fluoro-4-methoxy-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(3-fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(3-fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (24%). ¹H-NMR (CDCl₃) δ: 0.99 (d, 3H), 1.13 (t, 3H), 1.65 - 1.71 (m, 1H), 2.53 - 2.62 (m, 1H), 3.57 - 3.68 (m, 1H), 3.79 - 3.90 (m, 2H), 3.84 (s, 3H), 4.98 - 5.10 (m, 1H), 6.42 - 6.45 (d, 1H), 6.66 - 6.69 (d, 1H), 6.77 - 6.91 (m, 3H), 7.17 - 7.28 (m, 3H), 7.35 (d, 1H), 7.44 - 7.47 (d, 2H). MS m/z: 481 (M+1).

[00261] (±)-*trans*-2-Methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (63)

[00262] A round bottom flask with magnetic stirrer was charged with *cis*-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (300 mg, 1.46 mmol) in methylene chloride (3.00 mL) under a nitrogen atmosphere. Into the reaction was added isonicotinoyl chloride hydrochloride (338 mg, 1.90 mmol) and *N,N*-diisopropylethylamine (1.02 mL, 5.84 mmol) via syringe. The reaction was stirred at room temperature for 18 - 20 hours. The reaction was transferred to a separatory funnel containing a saturated sodium bicarbonate solution (15 mL), then diluted with ethyl acetate (15 mL) and shaken vigorously. The resulting organic layer was separated, washed with brine (1 x 20 mL), dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford a yellow residue (530 mg). The residue was purified via flash chromatography (2 % methanol / methylene chloride) to yield *cis*-2-methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester as a white solid (420 mg, 93%).

[00263] To a solution of *N*-ethyl-4-chloroaniline (650 mg, 4.18 mmol) in anhydrous toluene at 10 °C was slowly added a 2M solution of trimethylaluminum in hexanes (2.1 mL, 4.18 mmol). The reaction mixture was stirred at room temperature until gas evolution stopped. A second round bottom flask was charged with *cis*-2-methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid methyl ester (370 mg, 1.19 mmol) and the preformed aluminum amide was added. The resulting reaction mixture was refluxed for 20 hours. The reaction was concentrated, quenched with 1M aqueous hydrochloric acid at 0 °C (exothermic!), basified with 1M aqueous sodium hydroxide, and extracted with ethyl acetate. The resulting organic layer was separated, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated *in vacuo* to afford an orange oil which was purified via flash chromatography (1% methanol / methylene chloride) followed by HPLC to provide (±)-*trans*-2-methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinoline-4-

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carboxylic acid (4-chloro-phenyl)-ethyl-amide (11%). ¹H-NMR (CDCl₃) δ: 1.02 - 1.18 (m, 6H), 1.60 - 1.70 (m, 1H), 2.45 - 2.55 (m, 1H), 3.60 - 3.70 (m, 1H), 3.80 (q, 2H), 4.98 - 5.10 (m, 1H), 6.40 (d, 1H), 6.90 (m, 2H), 7.00 (t, 1H), 7.30 (m, 2H), 7.50 (d, 2H), 7.60 (d, 2H), 8.55 (d, 2H). MS m/z: 434/436 (M+1).

[00264] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-cyano-phenyl)-ethyl-amide (64)

[00265] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-cyano-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(4-cyano-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-cyano-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-cyano-phenyl)-ethyl-amide. ¹H-NMR (CDCl₃) δ: 1.00 (d, 3H), 1.14 (t, 3H), 1.72 - 1.82 (m, 1H), 2.54 - 2.62 (m, 1H), 3.66 - 3.77 (m, 4H), 3.81 - 3.97 (m, 2H), 5.03 - 5.13 (m, 1H), 6.48 (d, 1H), 6.74 - 6.92 (m, 5H), 7.39 (d, 2H), 7.49 (d, 2H), 7.80 (d, 2H). MS m/z: 454 (M⁺).

[00266] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methoxy-phenyl)-amide (65)

[00267] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methoxy-phenyl)-amide was made following general procedure B, substituting ethyl-(4-methoxy-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methoxy-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-methoxy-phenyl)-amide. ¹H-NMR (CDCl₃) δ: 0.97 (d, 3H), 1.13 (t, 3H), 1.73 - 1.81 (m, 1H), 2.47 - 2.56 (m, 1H), 3.63 - 3.89 (m, 9H), 5.05 - 5.14 (m, 1H), 6.43 (d, 1H), 6.74 - 6.92 (m, 5H), 6.98 (d, 2H), 7.18 (d, 2H), 7.52 (d, 2H). MS m/z: 459 (M⁺).

[00268] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dimethyl-phenyl)-ethyl-amide (67)

[00269] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dimethyl-phenyl)-ethyl-amide was made following general procedure B, substituting ethyl-(3,4-dimethyl-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dimethyl-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (3,4-dimethyl-phenyl)-ethyl amide. ¹H-NMR (CDCl₃) δ: 0.97 (d, 3H), 1.15 (t, 3H), 1.94 - 2.05 (m, 1H), 2.32 (s, 6H), 2.49 - 2.58 (m, 1H), 3.66 -

3.77 (m, 4H), 3.84 - 3.92 (m, 2H), 4.95 - 5.11 (m, 1H), 6.43 (d, 1H), 6.74 - 7.13 (m, 6H), 7.43 - 7.51 (m, 4H). MS m/z: 457 (M⁺).

[00270] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-isobutyl-amide (69)

[00271] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-isobutyl-amide was made following general procedure B, substituting (4-chloro-phenyl)-isobutyl-amine for ethyl-benzyl-amine. ¹H-NMR (CDCl₃) δ: 0.90 (d, 6H), 0.96 (d, 3H), 1.69 - 1.84 (m, 2H), 2.50 (ddd, 1H), 3.51 (dd, 1H), 3.66 (dd, 1H), 3.75 (s, 3H), 3.85 (dd, 1H), 5.02 - 5.14 (m, 1H), 6.43 (d, 1H), 6.70 - 6.93 (m, 5H), 7.21 - 7.26 (m, 2H), 7.42 - 7.53 (m, 4H). MS m/z = 491 (M+1).

[00272] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*p*-tolyl-amide (70)

[00273] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-*p*-tolyl-amide was made following general procedure B, substituting ethyl-*p*-tolyl-amine for ethyl-benzyl-amine. ¹H-NMR (CDCl₃) δ: 0.95 (d, 3H), 1.13 (t, 3H), 1.77 (ddd, 1H), 2.40 (s, 3H), 2.51 (ddd, 1H), 3.70 (dd, 1H), 3.75 (s, 3H), 3.81 - 3.91 (m, 2H), 5.03 - 5.15 (m, 1H), 6.41 (d, 1H), 6.72 - 6.83 (m, 3H), 6.83 - 6.93 (m, 2H), 7.11 - 7.18 (m, 2H), 7.24 - 7.31 (m, 2H), 7.49 - 7.56 (m, 2H). MS m/z = 443 (M+1).

[00274] (±)-*cis*-1-(Benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (71)

[00275] Same procedure as for the preparation of (±)-*trans*-1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide. Purification via HPLC gave (±)-*cis*-1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (20%). ¹H-NMR (CDCl₃) δ: 1.18 (d, 3H), 1.25 (t, 3H), 1.70 - 1.80 (m, 1H), 2.55 - 2.65 (m, 1H), 3.35 - 3.45 (dd, 1H), 3.75 - 3.85 (m, 1H), 4.00 - 4.15 (m, 1H), 4.60 - 4.75 (m, 1H), 6.80 - 6.90 (m, 2H), 7.00 (t, 1H), 7.20 - 7.30 (m, 3H), 7.30 - 7.40 (m, 5H), 7.65 (dd, 1H), 7.70 (dd, 1H). MS m/z: 489/491 (M+1).

[00276] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-fluoro-phenyl)-amide (72)

[00277] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-fluoro-phenyl)-amide was made following general procedure B, substituting ethyl-(4-fluoro-phenyl)-amine for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-fluoro-phenyl)-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid ethyl-(4-fluoro-phenyl)-amide. ¹H-NMR (CDCl₃) δ: 0.96 (d,

3H), 1.13 (t, 3H), 1.69 - 1.78 (m, 1H), 2.48 - 2.57 (m, 1H), 3.58 - 3.72 (m, 1H), 3.75 (s, 3H), 3.78 - 3.89 (m, 2H), 5.03 - 5.13 (m, 1H), 6.44 (d, 1H), 6.73 - 6.81 (m, 4H), 6.86 - 6.91 (m, 1H), 7.14 - 7.27 (m, 4H), 7.49 (d, 2H). MS m/z: 447 (M⁺).

[00278] *rel*-(2*S*,4*S*)-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (73) and *rel*-(2*R*,4*R*)-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (74)

[00279] *rel*-(2*S*,4*S*)- and *rel*-(2*R*,4*R*)-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide were isolated from (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide by preparative chiral HPLC. Analytical data for the individual enantiomers was identical to the racemate given above.

[00280] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-phenyl-amide (77)

[00281] (±)-*trans*-1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-phenyl-amide was made following general procedure B, substituting *N*-benzyl-aniline for ethyl-benzyl-amine. The crude 1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-phenyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid benzyl-phenyl-amide. ¹H-NMR (CDCl₃) δ: 0.96 (d, 3H), 1.76 - 1.84 (m, 1H), 2.54 - 2.63 (m, 1H), 3.77 (s, 3H), 3.88 - 3.93 (m, 1H), 4.95 (dd, 2H), 5.09 - 5.17 (m, 1H), 6.47 (d, 1H), 6.76 - 6.95 (m, 5H), 7.06 - 7.09 (m, 2H), 7.18 - 7.27 (m, 5H), 7.36 - 7.39 (m, 3H), 7.54 - 7.56 (m, 2H). MS m/z: 491 (M⁺).

[00282] (±)-*trans*-1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (78)

[00283] (±)-*trans*-1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was made following general procedure A, substituting 4-fluoro-benzoyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude 1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded (±)-*trans*-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (28%). ¹H-NMR (CDCl₃) δ: 0.96 (d, 3H), 1.13 (t, 3H), 1.71 - 1.80 (m, 1H), 2.45 - 2.56 (m, 1H), 3.65 (m, 1H), 3.79 - 3.90 (m, 2H), 4.98 - 5.10 (m, 1H), 6.37 - 6.40 (d, 1H), 6.78 - 6.83 (t, 2H), 6.68 - 6.94 (t, 3H), 7.19 - 7.23 (t, 2H), 7.41 - 7.49 (d, 2H), 7.53 - 7.57 (m, 2H). MS m/z: 451 (M+1).

[00284] (±)-*trans*-4-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl)carbonyl]phenoxy)-2,2-difluorobutanoic acid (84)

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[00285] **Step 1.** ($\pm$)-*trans*-Ethyl 4-(4-([4-([4-(4-chlorophenyl)(ethyl)amino]carbonyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenoxy)-2,2-difluorobutanoate. Ethyl 2,2-difluoro 4-hydroxybutanoate (US Patent #4421690, 20 Dec 1983) (314 mg, 1.9 mmol) and triphenylphosphine (262 mg, 1.9 mmol) were dissolved in toluene (10 mL) at room temperature. ($\pm$)-*trans*-1-(4-Hydroxybenzoyl)-1,2,3,4-tetrahydro-quinoline-4-carboxylic acid (4-chloro-phenyl)-ethyl-amide (119 mg, 0.27 mmol) was added to the resulting mixture, followed by diethyl azodicarboxylate (323 mg, 1.9 mmol). The reaction mixture was stirred for 18 hours at room temperature and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (ethyl acetate/dichloromethane gradient) to afford crude ($\pm$)-*trans*-ethyl 4-(4-([4-([4-(4-chlorophenyl)(ethyl)amino]carbonyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenoxy)-2,2-difluorobutanoate as yellow solid (190 mg). The crude material was used directly in the next step. MS *m/z*: 599 (*M*+1).

[00286] **Step 2.** ($\pm$)-*trans*-4-(4-([4-([4-(4-Chlorophenyl)(ethyl)amino]carbonyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenoxy)-2,2-difluorobutanoic acid.

[00287] To a solution of ($\pm$)-*trans*-ethyl 4-(4-([4-([4-(4-chlorophenyl)(ethyl)amino]carbonyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenoxy)-2,2-difluorobutanoate (190 mg, 0.32 mmol) in THF (4.4 mL) was added a solution of lithium hydroxide (15.2 mg, 0.63 mmol) in water (2 mL). To the resulting mixture was added methanol (2 mL) and the reaction stirred 18 hours at room temperature. The reaction mixture pH was adjusted to 2 via addition of 1N hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to yield ($\pm$)-*trans*-4-(4-([4-([4-(4-chlorophenyl)(ethyl)amino]carbonyl)-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenoxy)-2,2-difluorobutanoic acid. ¹H-NMR (CDCl₃) δ : 0.96 (d, 3H), 1.08 (t, 3H), 1.61 - 1.74 (m, 1H), 2.34 - 2.56 (m, 3H), 3.52 - 3.68 (m, 1H), 3.72 - 3.88 (m, 2H), 4.00 - 4.14 (m, 2H), 4.93 - 5.11 (m, 1H), 6.42 - 6.51 (m, 1H), 6.65 - 6.82 (m, 4H), 6.83 - 6.92 (m, 1H), 7.16 - 7.29 (m, 2H), 7.37 - 7.50 (m, 4H). MS *m/z*: 571 (*M*+1).

[00288] ($\pm$)-*trans*-*N*-Cyclopropyl-*N*-ethyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide (83)

[00289] ($\pm$)-*trans*-*N*-Cyclopropyl-*N*-ethyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide was made following general procedure A, substituting 4-methoxybenzoyl chloride for 4-trifluoromethyl-benzoyl chloride and *N*-ethylcyclopropanamine for *N*-ethyl-*p*-chloroaniline. *N*-Ethylcyclopropanamine was prepared by the reductive amination of cyclopropylamine using acetaldehyde and sodium triacetoxyborohydride in dichloromethane. The crude *N*-cyclopropyl-*N*-ethyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-*N*-cyclopropyl-*N*-ethyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide. ¹H-NMR (CDCl₃) δ : 0.81 - 0.95 (m, 2H), 0.96 - 1.07 (m, 2H), 1.17 (t, 3H), 1.21 (d,

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3H), 1.95 - 2.07 (m, 1H), 2.41 - 2.55 (m, 1H), 2.80 - 2.92 (m, 1H), 3.38 - 3.64 (m, 2H), 3.75 (s, 3H), 4.68 - 4.82 (m, 1H), 5.08 - 5.23 (m, 1H), 6.44 - 6.53 (m, 1H), 6.70 - 6.84 (m, 3H), 6.88 - 7.01 (m, 2H), 7.45 - 7.55 (m, 2H). MS m/z: 393 (M+1).

[00290] ($\pm$)-*trans*-N-(4-Chlorophenyl)-1-(cyclopropylcarbonyl)-N-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide (82)

[00291] ($\pm$)-*trans*-N-(4-Chlorophenyl)-1-(cyclopropylcarbonyl)-N-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide was made following general procedure A, substituting cyclopropanecarbonyl chloride for 4-trifluoromethyl-benzoyl chloride. The crude N-(4-chlorophenyl)-1-(cyclopropylcarbonyl)-N-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide was isolated as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-N-(4-chlorophenyl)-1-(cyclopropylcarbonyl)-N-ethyl-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide. ¹H-NMR (CDCl₃) δ : 0.63 - 0.74 (m, 1H), 0.79 - 1.00 (m, 2H), 0.90 (d, 3H), 1.07 (t, 3H), 1.21 - 1.31 (m, 1H), 1.46 - 1.56 (m, 1H), 1.85 - 1.98 (m, 1H), 2.43 - 2.58 (m, 1H), 3.55 - 3.86 (m, 3H), 4.97 - 5.09 (m, 1H), 6.64 - 6.69 (m, 1H), 6.93 - 7.01 (m, 1H), 7.03 - 7.08 (m, 2H), 7.09 - 7.16 (m, 1H), 7.24 - 7.29 (m, 1H), 7.34 - 7.39 (m, 2H). MS m/z: 397 (M+1).

[00292] N-Ethyl-N-isopropyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide (81)

[00293] N-Ethyl-N-isopropyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide was made following general procedure B, substituting N-ethylpropan-2-amine for ethylbenzyl-amine. Purification via HPLC yielded N-ethyl-N-isopropyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinoline-4-carboxamide as a mixture of *cis* and *trans* isomers. MS m/z: 395 (M+1).

[00294] *rel*-(2*S*,4*S*)-5-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenyl)-2,2-dimethylpentanoic acid (80) and *rel*-(2*R*,4*R*)-5-(4-([4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl)phenyl)-2,2-dimethylpentanoic acid (79)

[00295] Step 1. Methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate.

[00296] 2,2-Dimethyl-4-pentanoic acid (2 g, 15.6 mmol, 1.0 eq.) was dissolved in anhydrous methanol (40 ml). The solution was cooled down to 0°C; a 2 M solution of trimethylsilyl diazomethane in hexanes (11 ml, 21.8 mmol, 1.4 eq.) was added slowly until the reaction mixture turned slight yellow indicating the reaction was complete. Reaction mixture was concentrated down to give methyl-2,2-dimethyl-4-pentanoate as a colorless oil (2 g, 91 %).

[00297] Methyl-2,2-dimethyl-4-pentanoate (1.0 g, 7.0 mmol, 1 eq.) was dissolved in anhydrous dimethylformamide. The solution was purged with nitrogen, and 4-iodobenzoic acid (1.7 g, 7.0 mmol, 1 eq.), triethylamine (1.1 ml, 7.7 mmol, 1.1 eq.) and palladium acetate (79 mg, 0.35 mmol, 0.05 eq.) were sequentially added. Reaction was then heated to 80°C under nitrogen for 18 h. Reaction mixture

was concentrated under vacuo to leave a black oil which was partitioned between water and ethyl acetate and extracted. The aqueous layer was separated and the organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give a dark brown solid. The crude product was purified by silica gel chromatography (methylene chloride/methanol: 98/2 → 96/4 gradient) to provide 4-(4-methoxycarbonyl-4-methyl-pent-1-enyl)-benzoic acid as a light brown solid (915 mg, 50 %).

[00298] 4-(4-Methoxycarbonyl-4-methyl-pent-1-enyl)-benzoic acid (900 mg, 3.4 mmol, 1 eq.) was dissolved in ethanol (13 ml) and triethylamine (568 µl, 4.1 mmol, 1.2 eq.) and palladium on carbon (90 mg, 10 % Pd/C) were then added. The mixture was stirred under hydrogen atmosphere for 20 h. Reaction mixture was filtered over celite and washed with ethanol. The filtrate was evaporated to yield a yellow oil. This oil was dissolved in ethyl acetate and washed with a 1N aqueous hydrochloric acid solution. The aqueous layer was removed and the organic layer was washed with water, and brine, then dried over magnesium sulfate, filtered and concentrated to give 4-(4-methoxycarbonyl-4-methyl-pentyl)-benzoic acid (763 mg, 85 %).

[00299] 4-(4-Methoxycarbonyl-4-methyl-pentyl)-benzoic acid (763 mg, 2.9 mmol, 1 eq.) was dissolved in methylene chloride (9 ml) and the solution was cooled down to 0°C. A 2 M solution of oxalyl chloride in methylene chloride (2.9 ml, 5.8 mmol, 2.0 eq.) was added followed by a catalytic amount of dimethylformamide. The reaction mixture was stirred at rt for 1 h, then concentrated to give the acid chloride as an oil. Methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate was used without further purification in subsequent steps.

[00300] Step 2. (±)-*trans*-Methyl 5-(4-{[4-{{(4-chlorophenyl)(ethyl)amino}carbonyl}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate.

[00301] (±)-*trans*-Methyl 5-(4-{[4-{{(4-chlorophenyl)(ethyl)amino}carbonyl}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate was made following general procedure A, substituting methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate for 4-trifluoromethyl-benzoyl chloride. Purification via silica gel chromatography (0-40% ethyl acetate / hexane gradient) yielded (±)-*trans*-methyl 5-(4-{[4-{{(4-chlorophenyl)(ethyl)amino}carbonyl}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate. MS *m/z*: 575 (M+1).

[00302] Step 3. (±)-*trans*-5-(4-{[4-{{(4-Chlorophenyl)(ethyl)amino}carbonyl}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid.

[00303] To a solution of (±)-*trans*-methyl 5-(4-{[4-{{(4-chlorophenyl)(ethyl)amino}carbonyl}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate (500 mg, 0.87 mmol) in 1:1 THF / methanol (5.0 mL) was added a solution of sodium hydroxide (69.5 mg, 1.74 mmol) in water (1.0 mL). The resulting mixture was heated at 60 °C for 18-20 hours and concentrated. The resulting residue was dissolved in water (~ 50 mL), cooled to 0 °C, and the solution acidified using

3N hydrochloric acid. The resulting precipitated material was collected via suction filtration, washed with 1N hydrochloric acid (3 x 25 mL), and dried to afford crude 5-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid as a mixture of *cis* and *trans* isomers. Purification via HPLC yielded ($\pm$)-*trans*-5-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid (23%).

[00304] Step 4. *rel*-(2*S*,4*S*)-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid and *rel*-(2*R*,4*R*)-(4-([4-((4-chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid.

[00305] *rel*-(2*S*,4*S*)-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid and *rel*-(2*R*,4*R*)-(4-([4-((4-chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid were isolated from ($\pm$)-*trans*-5-(4-([4-((4-Chlorophenyl)(ethyl)amino)carbonyl]-2-methyl-3,4-dihydroquinolin-1(2H)-yl)carbonyl)phenyl)-2,2-dimethylpentanoic acid by preparative chiral HPLC. Data for single enantiomer (identical to enantiomer and to racemate), absolute stereochemistry unknown: $^1\text{H-NMR}$ (CD_3Cl) δ : 0.95 (d, 3H), 1.12 (t, 3H), 1.14 (s, 6H), 1.30 - 1.43 (m, 1H), 1.45 - 1.59 (m, 4H), 1.67 - 1.77 (m, 1H), 2.47 - 2.63 (m, 2H), 3.58 - 3.74 (m, 1H), 3.76 - 3.92 (m, 2H), 5.01 - 5.16 (m, 1H), 6.40 - 6.50 (m, 1H), 6.70 - 6.81 (m, 2H), 6.84 - 6.94 (m, 1H), 6.99 - 7.08 (m, 2H), 7.17 - 7.21 (m, 2H), 7.40 - 7.52 (m, 4H). MS m/z : 561 (M+1).

[00306] Compounds 85-207, as shown in Table 1, can be prepared by the schemes set forth in Schemes 1-3 and by the general procedures A and B and others described herein. Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

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[00307] Biological Testing

[00308] This radioligand membrane binding assay evaluates the ability of compounds to inhibit [³H] Prostaglandin D₂ (PGD₂) binding to the cloned human CRTH2 receptor stably expressed in HEK-293 cells (expressing human CRTh2 receptor and α subunit of the heterotrimeric G protein 16 were prepared by Biosignal Company) using Scintillation Proximity Assay.

[00309] A binding buffer containing 50mM Tris-HCl (pH 7.5), 5mM MgCl₂ and 1mM EDTA is prepared immediately prior to performing the assay. A bead/membrane solution at twice the final assay concentration comprising membranes (membranes bought from Biosignal) from the HEK-293 cells cloned to express CRTH2 receptor bound to and [³H] PGD₂ at two times the final assay concentration are prepared and stored on ice before adding to wells. Cold PGD₂ at twenty times the final assay concentration is prepared and stored on ice before adding to wells defining non-specific binding (NSB) coming plates #3653 are used for this assay.

[00310] 10 mM stock concentrations of compounds in 100% DMSO are prepared and stored at room temperature. A 10 point concentration response curve is then constructed for each compound, starting at 10 μ M (final assay concentration). The compounds are prepared at 40 times final assay concentrations with nine consequent-3-fold dilutions.

[00311] 0.1 μ l of each concentration of compound are added to the appropriate well of the 384 plate and 2 μ l of cold PGD₂ is added into the wells defining NSB. 20 μ l of [³H] PGD₂ and then 20 μ l of 2x of bead/membrane solution are then added to each well.

[00312] The plates are allowed to incubate at room temperature for approximately 2 hours and then counted on Packard Topcount using SPA tritium protocol for 1 minute / well.

[00313] The percent inhibition of PGD₂ binding (PGD₂ used at the K_D value or lower) to the HEK-293 cell membranes is determined, the assay is always run as duplicate for n=1 for a total of n=2 and shown below.

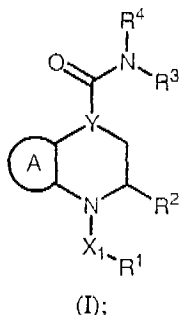
[00314] Compounds 1, 3, 6, 7, 9, 12, 13, 17-20, 22, 24-27, 30-32, 34, 36, 37, 40, 42, 45, 47, 48, 51, 55, 56, 58, 62-65, 67, 70, 72, 75, 77-78, 81-84 have K_i <1 μ M.

[00315] Compounds 2, 5, 11, 15, 33, 35, 50, 57, 61, 76 have K_i <10 μ M.

[00316] While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

1. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted, fused 5-6 membered aryl or heteroaryl ring;

Y is $>C(R^5)-$ or $>N-$;

X_1 is $-C(=O)-$, $-SO_2-$, $-CONR-$, $-C(R)_2-$, or $-CO_2-$,

R^1 is an optionally substituted group selected from an aliphatic, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group.

R^2 is a C_1-C_3 alkyl group, a C_1-C_3 haloalkyl group or C_3-C_6 cycloalkyl group wherein the C_1-C_3 alkyl group represented by R^2 is optionally substituted with R^5 ;

R^3 is hydrogen, C_1-C_6 alkyl optionally substituted by R^6 , C_1-C_6 fluoroalkyl, or an optionally substituted group selected from a C_3-C_8 cycloalkyl, a monocyclic non-aromatic heterocyclic, a monocyclic aryl, or a monocyclic heteroaryl group;

R^4 is $-[C(R^7)_2]_m-B$; or R^3 and R^4 may be taken together with the intervening nitrogen atom to form an optionally substituted monocyclic or bicyclic heteroaryl or non-aromatic heterocyclic group; or

R^4 and R^4 may be taken together with the intervening carbon and nitrogen atoms to form an optionally substituted monocyclic non-aromatic nitrogen-containing heterocyclic group;

R^5 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-COOR'$ or $-N(R')_2$;

R^6 is $-OH$, $-O(C_{1-4} \text{ aliphatic})$, $-N(R')_2$, $-C(O)R'$, $-COOR'$, $C(O)N(R')_2$, or an optionally substituted group selected from a monocyclic cycloalkyl, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic heterocyclic group;

each R^7 is independently hydrogen, fluoro, or C_1-C_3 alkyl;

each R , R^3 or R^4 is independently hydrogen or a C_1-C_4 aliphatic group or $N(R')_2$ is a monocyclic non-aromatic nitrogen-containing heterocyclic group;

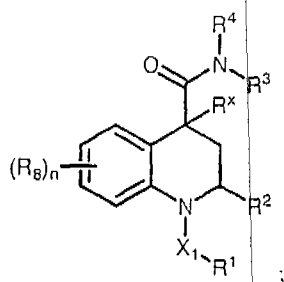
m is zero or one; and

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B is $-\text{H}$, $-\text{C}(\text{R}^7)_3$, $-\text{C}(\text{R}^7)_2-\text{C}(\text{R}^7)_3$, or an optionally substituted group selected from a monocyclic or bicyclic cycloalkyl, a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, or a monocyclic or bicyclic non-aromatic heterocyclic group,

provided that compounds of formula (I) are other than those compounds where X_1 is $-\text{COO}-$ and R^1 is ethyl and ring A is substituted with: a) two occurrences of OMe, b) two occurrences of Me, or c) one occurrence of CF_3 .

2. The compound of Claim 1 wherein R^1 is an optionally substituted group selected from a monocyclic or bicyclic aryl, a monocyclic or bicyclic heteroaryl, a monocyclic or bicyclic non-aromatic heterocyclic, or a monocyclic or bicyclic non-aromatic carbocyclic group.
3. The compound of Claim 2 wherein Y is $>\text{C}(\text{R}^5)-$.
4. The compound of Claim 3 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

n is 0 or an integer from 1-4;

each R^8 is independently halo, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{R}^9$, $-\text{N}(\text{R}^{10})\text{CO}_2\text{R}^{9a}$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{OC}(\text{O})\text{R}^9$, $-\text{OC}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{SO}_2\text{R}^{9a}$, $-\text{S}(\text{O})\text{R}^{9a}$, $-\text{SO}_2\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{9a}$ or an optionally substituted group selected from a C_{1-8} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic heterocyclic group;

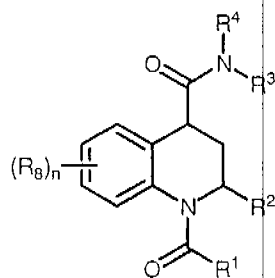
each R^9 is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each R^{9a} is independently an optionally substituted C_{1-6} aliphatic group; and

each R^{10} is independently hydrogen, a C_{1-6} aliphatic group, $-\text{CO}_2\text{R}^{9a}$, $-\text{SO}_2\text{R}^{9a}$, or $-\text{C}(\text{O})\text{R}^9$, or $\text{N}(\text{R}^{10})_2$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

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5. The compound of Claim 4 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 5 wherein:

R^1 is an optionally substituted monocyclic or bicyclic aryl or heteroaryl group optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;

each R^{11} is independently halo, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NO_2$, $-N(R^{12}R^{13})$, $-N(R^{13})C(O)R^{12}$, $-N(R^{13})CO_2R^{12a}$, $-N(R^{13})C(O)N(R^{12}R^{13})$, $-C(O)N(R^{12}R^{13})$, $-OC(O)R^{12}$, $-OC(O)N(R^{12}R^{13})$, $-C(O)R^{12}$, $-CO_2R^{12}$, $-SO_2R^{12a}$, $-S(O)R^{12a}$, $-SO_2N(R^{12}R^{13})$, $-N(R^{13})SO_2R^{12a}$, an optionally substituted group selected from a C_{1-8} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic group;

each R^{12} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each R^{12a} is an optionally substituted C_{1-6} aliphatic group; and

each R^{13} is independently hydrogen, a C_{1-6} aliphatic group, $-CO_2R^{12a}$, $-SO_2R^{12a}$, or $-C(O)R^{12}$, or $-N(R^{12}R^{13})$ is a monocyclic heteroaryl or non-aromatic heterocyclic group.

7. The compound of Claim 6 wherein:

B is a monocyclic aryl or heteroaryl group, or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ; and

each R^{14} is independently C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, R^{14a} , R^{14b} , $-T-R^{14a}$, $-T-R^{14b}$, $-V-T_1-R^b$, $-V-T-R^{14a}$, $-V_1-T-R^{14a}$ or $-V_1-T_1-R^{14b}$;

V is $-O-$, $-N(R)-$, $-C(O)N(R)-$ or $-S(O)_2N(R)-$;

V_1 is $-S(O)_2-$, $-C(O)-$, $-N(R)C(O)-$ or $-N(R)SO_2-$;

T is a C_1 - C_2 optionally substituted alkylene;

T_1 is a C_2 - C_4 optionally substituted alkylene;

each R^{14a} is independently selected from $-OR^{15a}$, $-SR^{15a}$, $-C(O)N(R^{15})_2$, $-C(O)R^{15}$, $-CO_2R^{15}$, $-SO_2R^{15a}$, $-S(O)R^{15a}$, $-SO_2N(R^{16})$, an optionally substituted monocyclic aryl or heteroaryl group or an optionally substituted monocyclic non-aromatic heterocyclic group;

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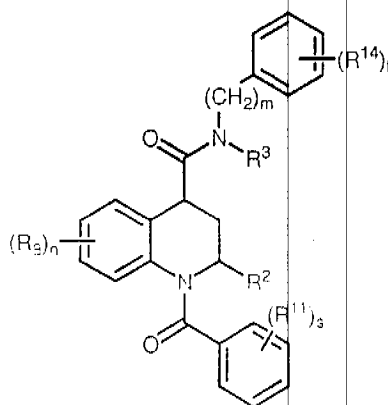
each R^{14b} is independently selected from halo, -OH, -SH, -CN, -NO₂, -N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁵, -N(R¹⁶)CO₂R^{15a}, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)R¹⁵, -OC(O)N(R¹⁶)₂ or -N(R¹⁶)SO₂R^{15a},

each R^{15} is independently hydrogen or a C₁₋₆ aliphatic group;

each R^{15a} is a C₁₋₆ aliphatic group; and

each R^{16} is independently selected from hydrogen, a C₁₋₆ aliphatic group, -CO₂R^{15a}, -SO₂R^{15a}, or -C(O)R¹⁵, or N(R¹⁶)₂ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

8. The compound of Claim 7 wherein
 R^2 is C₁-C₂ alkyl or C₃-C₆ cycloalkyl ;
 R^3 is a C₁-C₄ alkyl group, and
 R^4 is -(CH₂)_m-B.
9. The compound of Claim 8 wherein R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrolyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each optionally substituted at any one or more substitutable ring carbon atoms with R¹¹.
10. The compound of Claim 9 wherein -C(O)NR³R⁴ and -R² are *trans* relative to one another.
11. The compound of Claim 10 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein s and t are independently 0, 1, 2, 3 or 4.

12. The compound of Claim 11 wherein R^8 , R^{11} and R^{14} , when present, are independently, halo, CO_2R^{12} , $CONR^{12}R^{13}$, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -CN, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine, C_{1-3} hydroxyalkyl or C_{1-3} aminoalkyl.

13. The compound of Claim 5, wherein:

R^1 is a monocyclic aryl or heteroaryl group substituted with T_2 - V_2 - T_3 - M - R^Y and is further optionally substituted at any one or more substitutable ring carbon atoms with R^{11} ;
each R^{11} is independently halo, -OR¹², -SR¹², -CN, -NO₂, -N(R¹²R¹³), -N(R¹³)C(O)R¹², -N(R¹³)CO₂R^{12a}, -N(R¹³)C(O)N(R¹²R¹³), -C(O)N(R¹²R¹³), -OC(O)R¹², -OC(O)N(R¹²R¹³), -C(O)R¹², -CO₂R¹², -SO₂R^{12a}, -S(O)R^{12a}, -SO₂N(R¹²R¹³), -N(R¹³)SO₂R^{12a}, an optionally substituted group selected from a C_{1-8} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic group;

each R^{12} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;

each R^{12a} is an optionally substituted C_{1-6} aliphatic group; and

each R^{13} is independently hydrogen, a C_{1-6} aliphatic group, -CO₂R^{12a}, -SO₂R^{12a}, or -C(O)R¹², or -N(R¹²R¹³) is a monocyclic heteroaryl or non-aromatic heterocyclic group;

R^Y is -C(O)OR¹⁸, -C(O)R¹⁸, -OC(O)R¹⁸, -C(O)N(R¹⁹)₂, -NR¹⁹C(O)R¹⁸, -NR¹⁹C(O)OR^{18a}, -S(O)₂R^{18a}, -S(O)₂COR¹⁸, -S(O)₂N(R¹⁹)₂, -NR¹⁹S(O)₂R^{18a}, -NR¹⁹S(O)₂R^{18a}, S(O)₂OR¹⁸, -S(O)OR¹⁸, -S(O)R^{18a}, -SR¹⁸, -C(O)NR¹⁹S(O)₂R^{18a}, -CN, -NR¹⁹C(O)N(R¹⁹)₂, -OC(O)N(R¹⁹)₂, -N(R¹⁹)₂, -OR¹⁸, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group;

M is absent or an optionally substituted monocyclic arylene, an optionally substituted monocyclic non-aromatic carbocyclene or an optionally substituted monocyclic non-aromatic heterocyclene;

V_2 is absent, -O-, -C(O)-, -N(R¹⁹)-, -S-, -S(O)-, -C(O)NR¹⁹-, -NR¹⁹C(O)-, -S(O)₂NR¹⁹-, -NR¹⁹S(O)₂-, or -S(O)₂-;

T_2 is absent, or a C_{1-10} straight chain alkylene;

T_3 is C_{1-10} is a straight chain alkylene; provided that T_3 is a C_{2-10} straight chained alkylene when M is absent and V_2 is -O-, -S-, -N(R¹⁹)-, -C(O)N(R¹⁹)- or -S(O)₂N(R¹⁹)- and R^Y is -NR¹⁹S(O)₂R^{18a}, -NR¹⁹S(O)₂R^{18a}, -NR¹⁹C(O)R¹⁸, -NR¹⁹C(O)OR^{18a}, -NR¹⁹C(O)N(R¹⁹)₂, -CN, -OH, -SH, -N(R¹⁹)₂;

wherein T_2 and T_3 together contain no more than 10 carbon atoms, and wherein T_2 and T_3 are optionally and independently substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, alkoxy, haloalkoxy, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic

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group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

each R^{13} is independently hydrogen or C_{1-6} aliphatic group;

each R^{13a} is independently C_{1-6} aliphatic group; and

each R^{19} is independently selected from hydrogen, a C_{1-6} aliphatic group, $-CO_2R^{13}$, $-SO_2R^{13}$, or $-C(O)R^{13}$, or $-NR^{19}$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

14. The compound of Claim 13 wherein T_2 and M are absent.

15. The compound of Claim 14 wherein:

B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;

each R^{14} is independently C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, R^{14a} , R^{14b} , $-T-R^{14a}$, $-T-R^{14b}$, $-V-T-R^{14a}$, $-V-T_1-R^{14b}$, $-V_1-T-R^{14a}$ or $-V_1-T_1-R^{14b}$;

V is $-O-$, $-N(R)-$, $-C(O)N(R)-$ or $-S(O)_2N(R)-$;

V_1 is $-S(O)_2-$, $-C(O)-$, $-N(R)C(O)-$ or $-N(R)SO_2-$;

T is a C_1-C_4 optionally substituted alkylene;

T_1 is a C_2-C_4 optionally substituted alkylene;

each R^{14a} is independently selected from $-OR^{15a}$, $-SR^{15a}$, $-C(O)N(R^{16})_2$, $-CO_2R^{15}$, $-SO_2R^{15a}$, $-S(O)R^{15a}$, $-SO_2N(R^{16})_2$, an optionally substituted monocyclic aromatic group or an optionally substituted monocyclic non-aromatic heterocyclic group;

each R^{14b} is independently selected from halo, $-OH$, $-SH$, $-CN$, $-NO_2$, $-N(R^{16})_2$, $-N(R^{16})C(O)R^{15}$, $-N(R^{16})CO_2R^{15a}$ or $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)R^{15}$, $-OC(O)N(R^{16})_2$ or $-N(R^{16})SO_2R^{15a}$;

each R^{15} is independently hydrogen or a C_{1-6} aliphatic group;

each R^{15a} is a C_{1-6} aliphatic group; and

each R^{16} is independently selected from hydrogen, a C_{1-6} aliphatic group, $-CO_2R^{15a}$, $-SO_2R^{15a}$, or $-C(O)R^{15}$, or $N(R^{16})_2$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

16. The compound of Claim 15 wherein:

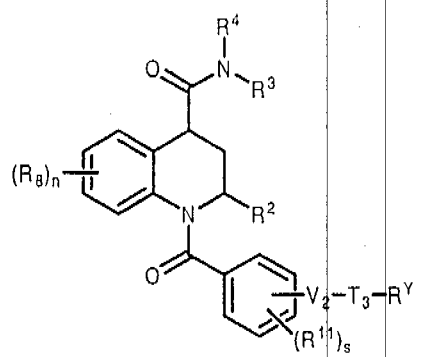
R^2 is C_1-C_2 alkyl or C_3-C_6 cycloalkyl ;

R^3 is a C_1-C_4 alkyl group, and

R^4 is $-(CH_2)_m-B$.

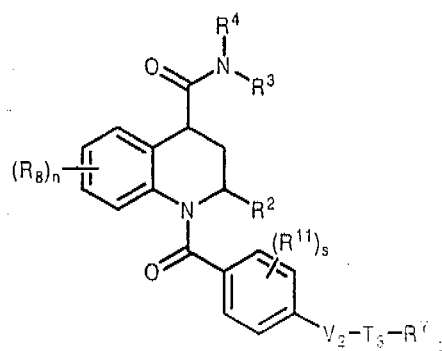
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17. The compound of Claim 16 wherein R^1 is a phenyl, pyridyl, pyrimidyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, furanyl, thiophenyl, imidazolyl, pyrazolyl, pyrrolyl, tetrazolyl, indolyl, benzotriazolyl, benzothiazolyl, benzimidazolyl, benzothienyl, benzofuranyl, benzmorpholinyl or benzpiperazinyl, each substituted with $-V_2-T_3-R^Y$, and each optionally substituted at any one or more substitutable ring carbon atoms with R^{11} .
18. The compound of Claim 17 wherein the compound is represented by structural formula:



or a pharmaceutically acceptable salt thereof, wherein s is 0, 1, 2, 3, or 4.

19. The compound of Claim 18 wherein $-C(O)NR^3R^4$ and $-R^2$ are *trans* relative to one another.
20. The compound of Claim 19 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

21. The compound of Claim 20 wherein:
- V_2 is a covalent bond or $-O-$;
 - T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro

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cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} ;

each R^{18} is independently H or C_1 - C_3 alkyl;

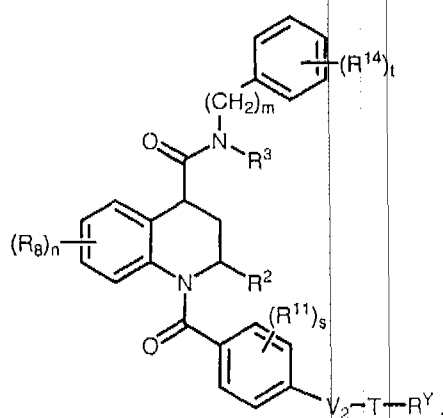
each R^{18a} is independently C_1 - C_3 alkyl;

each R^{19} is H or alkyl or $N(R^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group;

R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl.

22. The compound of Claim 21 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein t is 0, 1, 2, 3 or 4.

23. The compound of Claim 22 wherein:

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, optionally *N*-substituted tetrazolyl or optionally *N*-substituted imidazolyl; and

R^{18} and each R^{19} are independently-H, methyl, or ethyl.

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24. The compound of Claim 23 wherein R^8 , R^{11} and R^{14} , when present, are independently, halo, CO_2R^{12} , $CONR^{12}R^{13}$, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -CN, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine.
25. The compound of Claim 5 wherein:
 R^1 is a monocyclic aryl or heteroaryl group, substituted by $-V_3-R^{22}$ and wherein the aryl or heteroaryl group represented by R^1 optionally is further substituted at any one or more substitutable carbon atoms represented by R^{11} ;
 V_3 is a covalent bond, -O-, -C(O)-, -N(R^{13})-, -S-, -S(O)-, -C(O)N(R^{13})-, -N(R^{13})C(O)-, -S(O)₂N(R^{13})-, -N(R^{13})S(O)₂-, or -S(O)₂;
each R^{11} is independently halo, -OR¹², -SR¹², -CN, -NO₂, -N($R^{12}R^{13}$), -N(R^{13})C(O)R¹², -N(R^{13})CO₂R^{12a}, -N(R^{13})C(O)N($R^{12}R^{13}$), -C(O)N($R^{12}R^{13}$), -OC(O)R¹², -OC(O)N($R^{12}R^{13}$), -C(O)R¹², -CO₂R¹², -SO₂R^{12a}, -S(O)R^{12a}, -SO₂N($R^{12}R^{13}$), -N(R^{13})SO₂R^{12a}, or an optionally substituted group selected from a C_{1-8} aliphatic, a monocyclic aryl, a monocyclic heteroaryl, or a monocyclic non-aromatic group;
each R^{12} is independently hydrogen or an optionally substituted C_{1-6} aliphatic group;
each R^{12a} is an optionally substituted C_{1-6} aliphatic group; and
each R^{13} is independently hydrogen, a C_{1-6} aliphatic group, -CO₂R^{12a}, -SO₂R^{12a}, or -C(O)R¹², or -N($R^{12}R^{13}$) is an optionally substituted monocyclic heteroaryl or non-aromatic heterocyclic group; and
 R^{22} is an optionally substituted monocyclic or bicyclic non-aromatic carbocyclic or an optionally substituted monocyclic or bicyclic non-aromatic heterocyclic group.
26. The compound of Claim 25 wherein:
B is a monocyclic aryl or heteroaryl group or a monocyclic cycloalkyl group, each optionally substituted at any one or more substitutable ring carbon atoms with R^{14} ;
each R^{14} is independently C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, R^{14a} , R^{14b} , -T-R^{14a}, -T-R^{14b}, -V-T-R^{14a}, -V-T₁-R^{14b}, -V₁-T-R^{14a} or -V₁-T₁-R^{14b};
V is -O-, -N(R)-, -C(O)N(R)- or -S(O)₂N(R)-;
V₁ is -S(O)₂-, -C(O)-, -N(R)C(O)- or -N(R)SO₂;
T is a C_1 - C_4 optionally substituted alkylene;
T₁ is a C_2 - C_4 optionally substituted alkylene;
each R^{14a} is independently selected from -OR^{15a}, -SR^{15a}, -C(O)N(R^{16})₂, -CO₂R¹⁵, -SO₂R^{15a}, -S(O)R^{15a}, -SO₂N(R^{16})₂, an optionally substituted monocyclic aryl or heteroaryl group or an optionally substituted monocyclic non-aromatic heterocyclic group;

each R^{14b} is independently selected from halo, -OH, -SH, -CN, -NO₂, -N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁵, -N(R¹⁶)CO₂R^{15a}, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)R¹⁵, -OC(O)N(R¹⁶)₂ or -N(R¹⁶)SO₂R^{15a};

each R^{15} is independently hydrogen or a C₁₋₆ aliphatic group;

each R^{15a} is a C₁₋₆ aliphatic group; and

each R^{16} is independently selected from hydrogen, a C₁₋₆ aliphatic group, -CO₂R^{15a}, -SO₂R^{15a}, or -C(O)R¹⁵, or N(R¹⁶)₂ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

27. The compound of Claim 26 wherein:

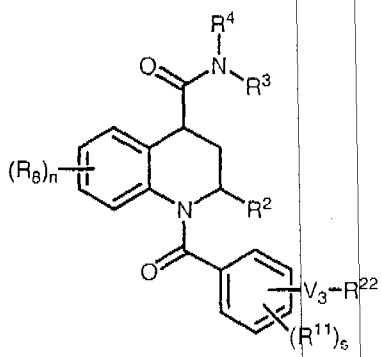
R^2 is C₁-C₂ alkyl or C₃-C₆ cycloalkyl;

R^3 is a C₁-C₄ alkyl group, and

R^4 is -(CH₂)_m-B.

28. The compound of Claim 27 wherein R^{22} is an optionally substituted monocyclic non-aromatic heterocyclic group.

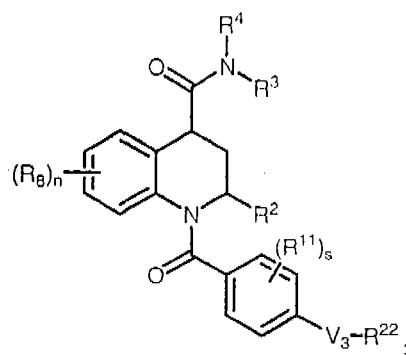
29. The compound of Claim 28 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein s is 0, 1, 2, 3, or 4.

30. The compound of Claim 29 wherein -C(O)NR³R⁴ and -R² are *trans* relative to one another.
31. The compound of Claim 30 wherein R^{22} is an optionally substituted cyclohexanyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothienyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazanyl, isothiazolidinyl S,S, dioxide, or piperidinyl.

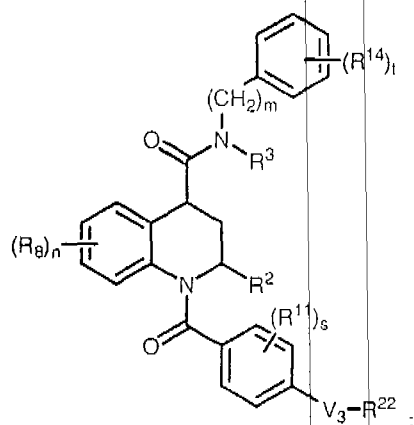
32. The compound of Claim 31 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

33. The compound of Claim 32 wherein V_3 is absent.
34. The compound of Claim 33 wherein R^{22} is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$, or $-C(O)N(R^{23})_2$, and each optionally substituted at any substitutable nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ or $-(CH_2)_qCH(CH_3)CO_2R^{23}$; q is an integer from 1-4; and each R^{23} is independently -H, alkyl, haloalkyl, or hydroxyalkyl.
35. The compound of Claim 34 wherein the compound is represented by the following structural formula:

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or a pharmaceutically acceptable salt thereof, wherein t is 0, 1, 2, 3 or 4.

36. The compound of Claim 35 wherein R^8 , R^{11} and R^{14} , when present, are independently, halo, C_{1-3} alkyl, C_{1-3} haloalkyl, hydroxyl, C_{1-3} alkoxy, C_{1-3} haloalkoxy, -CN, amine, C_{1-3} alkyl amine, C_{1-3} dialkylamine.

37. The compound of Claim 1 wherein:

R^1 is $T_2-V_2-T_3-M-R^Y$;

R^Y is $-C(O)OR^{18}$, $-C(O)R^{18}$, $-OC(O)R^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2R^{18a}$, $-S(O)_2COR^{18}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}S(O)_2R^{18a}$, $S(O)_2OR^{18}$, $-S(O)OR^{18}$, $-S(O)R^{18a}$, $-SR^{18}$, $-C(O)NR^{19}S(O)_2R^{18a}$, $-CN$, $-NR^{19}C(O)N(R^{19})_2$, $-OC(O)N(R^{19})_2$, $-N(R^{19})_2$, $-OR^{18}$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group;

M is absent or an optionally substituted monocyclic arylene, an optionally substituted monocyclic non-aromatic carbocyclene or an optionally substituted monocyclic non-aromatic heterocyclene;

V_2 is absent, $-O-$, $-C(O)-$, $-N(R^{19})-$, $-S-$, $-S(O)-$, $-C(O)NR^{19}-$, $-NR^{19}C(O)-$, $-S(O)_2NR^{19}-$, $-NR^{19}S(O)_2-$, or $-S(O)_2-$;

T_2 is absent, or a C_{1-10} straight chain alkylene.

T_3 is C_{1-10} is a straight chain alkylene; provided that T_3 is C_{2-10} straight chained alkylene when M is absent and V_2 is $-O-$, $-S-$, $-N(R^{19})-$, $-C(O)N(R^{19})-$ or $-S(O)_2N(R^{19})-$ and R^Y is $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, $-CN$, $-OH$, $-SH$, $-N(R^{19})_2$;

wherein T_2 and T_3 together contain no more than 10 carbon atoms, and wherein T_2 and T_3 are optionally and independently substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, alkoxy, haloalkoxy, spiro

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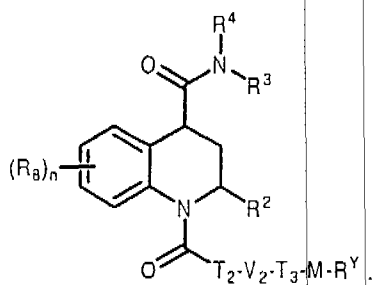
cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

each R^{18} is independently hydrogen or C_{1-6} aliphatic group;

each R^{18a} is independently C_{1-6} aliphatic group; and

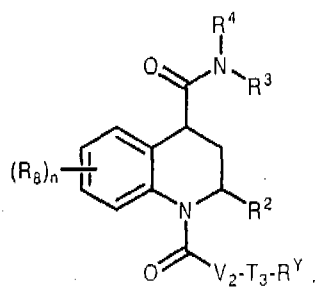
each R^{19} is independently selected from hydrogen, a C_{1-6} aliphatic group, $-\text{CO}_2R^{18}$, $-\text{SO}_2R^{18}$, or $-\text{C}(\text{O})R^{18}$, or $-\text{NR}^{19}$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

38. The compound of Claim 37 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

39. The compound of Claim 38 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof.

40. The compound of Claim 39 wherein:

V_2 is a covalent bond or $-\text{O}-$;

T_3 is C_{1-6} is a straight chain alkylene optionally substituted at any one or more substitutable carbon atoms with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic

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group, oxygen-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl

R^Y is $-C(O)OR^{13}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, an optionally substituted non-aromatic heterocyclic group represented by R^{20} or an optionally substituted heteroaryl group represented by R^{21} ;

each R^{18} is independently H or C_1 - C_3 alkyl;

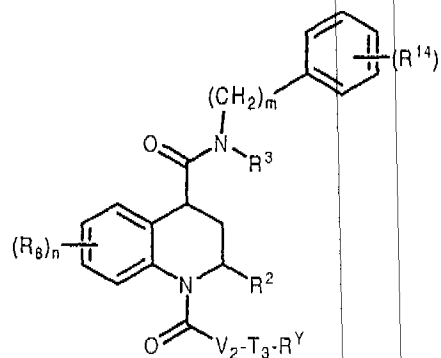
each R^{18} is independently C_1 - C_3 alkyl;

each R^{19} is H or C_1 - C_3 alkyl or $N(R^{19})_2$ is a nitrogen-containing non-aromatic heterocyclic group;

R^{20} is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahydrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^{21} is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl.

41. The compound of Claim 40 wherein the compound is represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

t is 0, 1, 2, 3 or 4;

each R^{14} is independently C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, R^{14a} , R^{14b} , $-T-R^{14a}$, $-T-R^{14b}$, $-V-T_1-R^b$, $-V-T-R^{14a}$, $-V_1-T-R^{14a}$ or $-V_1-T_1-R^{14b}$;

V is $-O-$, $-N(R)-$, $-C(O)N(R)-$ or $-S(O)_2N(R)-$;

V_1 is $-S(O)_2-$, $-C(O)-$, $-N(R)C(O)-$ or $-N(R)SO_2-$;

T is a C_1 - C_4 optionally substituted alkylene;

T_1 is a C_2 - C_4 optionally substituted alkylene;

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each R^{14a} is independently selected from $-OR^{15a}$, $-SR^{15a}$, $-C(O)N(R^{16})_2$, $-C(O)R^{15}$, $-CO_2R^{15}$, $-SO_2R^{15a}$, $-S(O)R^{15a}$, $-SO_2N(R^{16})_2$, an optionally substituted monocyclic aryl or heteroaryl group or an optionally substituted monocyclic non-aromatic heterocyclic group;

each R^{14b} is independently selected from halo, $-OH$, $-SH$, $-CN$, $-NO_2$, $-N(R^{16})_2$, $-N(R^{16})C(O)R^{15}$, $-N(R^{16})CO_2R^{15a}$, $-N(R^{16})C(O)N(R^{16})_2$, $-OC(O)R^{15}$, $-OC(O)N(R^{16})_2$ or $-N(R^{16})SO_2R^{15a}$,

each R^{15} is independently hydrogen or a C_{1-6} aliphatic group;

each R^{15a} is a C_{1-6} aliphatic group; and

each R^{16} is independently selected from hydrogen, a C_{1-6} aliphatic group, $-CO_2R^{15a}$, $-SO_2R^{15a}$, or $-C(O)R^{15}$, or $N(R^{16})_2$ is a monocyclic heteroaryl or a monocyclic non-aromatic heterocyclic group.

42. The compound of Claim 41 wherein:

R^Y is $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, optionally *N*-substituted tetrazolyl or optionally *N*-substituted imidazolyl; and

R^{18} and each R^{19} are independently $-H$, methyl, or ethyl.

43. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and an effective amount of a compound represented by the compound of Claim 1.
44. A method of treating an inflammatory disease in a subject, comprising the step of administering to the subject an effective amount of a compound represented by the compound of Claim 1.
45. The method of Claim 44, where the inflammatory disease is atopic dermatitis, allergic rhinitis, rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disorder (COPD), COPD exacerbations, or allergic asthma.
46. The method of Claim 45, where the inflammatory disease, disorder or symptom is atopic dermatitis, chronic obstructive pulmonary disorder (COPD), COPD exacerbations, allergic rhinitis, or allergic asthma.
47. A method of inhibiting CRTH2 activity in: (a) a subject; or (b) a biological sample; which method comprises administering to said subject, or contacting said biological sample with a compound represented by Claim 1.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2006/006287

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 44-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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International application No PCT/US2006/006287				
A. CLASSIFICATION OF SUBJECT MATTER INV. C07D215/50 C07D401/06 C07D413/06 C07D401/12 C07D409/06 C07D413/12 C07D471/04 C07D495/04 A61K31/47 A61K31/506 A61K31/4375 A61K31/4365 A61P19/00 A61P11/00				
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X	WO 2004/032848 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 22 April 2004 (2004-04-22) abstract; claims 1-10,18-24; tables 1-6	1-47		
X	EP 1 413 306 A (WARNER-LAMBERT COMPANY LLC) 28 April 2004 (2004-04-28) abstract; claims 1-23; examples 1-63	1-47		
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.				
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *F* 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 *G* document member of the same patent family				
Date of the actual completion of the international search 29 June 2006		Date of filing of the international search report 06/07/2006		
Name and mailing address of the ISA/ European Patent Office, P B 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tlx. 31 651 epon nl, Fax: (+31-70) 340-3016		Authorized officer van Laren, M		

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2006/006287

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004032848	A	22-04-2004	AU 2003277285 A1	04-05-2004
			BR 0315041 A	16-08-2005
			CA 2500582 A1	22-04-2004
			CN 1720047 A	11-01-2006
			EP 1556047 A2	27-07-2005
			JP 2006508077 T	09-03-2006
			MX PA05003456 A	05-07-2005
EP 1413306	A	28-04-2004	NONE	

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To:

See form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2006/006287

International filing date (day/month/year)
23.02.2006

Priority date (day/month/year)
24.02.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07D215/50 C07D401/06 C07D413/06 C07D401/12 C07D409/06 C07D413/12 C07D471/04 C07D495/04
A61K31/47 A61K31/506 A61K31/4375 A61K31/4365 A61P19/00 A61P11/00

Applicant
MILLENNIUM PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaag 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

van Laren, M

Telephone No. +31 70 340-9525



WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2006/006287

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No. **13²²**
PCT/US2006/006287

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

- ☐ the entire international application
- ☒ claims Nos. 44-47 (w.r.t. Industrial Applicability)

because:

- ☒ the said international application, or the said claims Nos. 44-47 relate to the following subject matter which does not require an international search (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No. **134**
PCT/US2006/006287

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-47
	No: Claims	-
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-47
Industrial applicability (IA)	Yes: Claims	1-43
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 44-47 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2. Reference is made to the following document:

D1: WO 2004/032848 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 22 April 2004 (2004-04-22)

3. The subject-matter of claims 1-47 is not disclosed in the prior art and therefore novel (Article 33(2) PCT).

4. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-47 does not involve an inventive step in the sense of Article 33(3) PCT.

4.1. The document D1 is regarded as being the closest prior art to the subject-matter of claim 1; and discloses (Tables 1-6): 1,2,3,4-tetrahydronaphthaquinolines as well as tetrahydropyridine compounds ortho condensed with other heteroaryl rings, the nitrogen situated in alpha position of the other ring, substituted on the nitrogen by a C(O)R¹ group, R¹ being an aromatic group, substituted on the 2-position by a methyl group and on the 4-position by an amide group, where the nitrogen of the amide is bonded directly to position 4 of the quinoline or condensed pyridine ring.

4.2. The subject-matter of claim 1 therefore differs from this known in D1 in that: on the 4-

position of the 1,2,3,4-tetrahydronaphthaquinoline as well as condensed tetrahydro-pyridine the amide group is bonded directly to the ring via the carbon of the amide.

4.3. In the absence of any enhanced activity as CRTH2 inhibitors of the compounds of the present application, the problem to be solved by the present invention is: the provision of further compounds useful as CRTH2 inhibitors.

4.4. The solution proposed in claim 1 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons.

The person skilled in the art would, when confronted with the problem as posed above, and starting from the closest prior art, consider changing the bonding mode of the amide group on position 4 of the bicyclic heterocyclic ring from being bonded via the nitrogen, as in the closest prior art, to being bonded via the carbon, thereby arriving at the subject-matter of the present application.

4.5. The same reasoning applies, mutatis mutandis, to the subject-matter of the corresponding independent claims 43,44 and 47 and dependent claims 2-42,45 and 46, which therefore are also considered not new/inventive.

Re Item VIII

Certain observations on the international application

5. The vague and imprecise statement in the description on page 102, paragraph 00316, implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

5.1. The expression "which is hereby incorporated by reference" implies that the subject-matter for which protection is sought may be different to that defined by the claims, thereby resulting in lack of clarity (Article 6 PCT) when used to interpret them.

PCT

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MPI05-005	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US2006/006287	International filing date (day/month/year) 23/02/2006	(Earliest) Priority Date (day/month/year) 24/02/2005
Applicant MILLENNIUM PHARMACEUTICALS, INC.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:



the international application in the language in which it was filed



a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the title,

the text is approved as submitted by the applicant



the text has been established by this Authority to read as follows:

5. With regard to the abstract,

the text is approved as submitted by the applicant



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

a. the figure of the **drawings** to be published with the abstract is: Figure (I), _____



as suggested by the applicant



as selected by this Authority, because the applicant failed to suggest a figure



as selected by this Authority, because this figure better characterizes the invention

b. ☐ none of the figures is to be published with the abstract

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A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D215/50	C07D401/06	C07D413/06	C07D401/12
	C07D413/12	C07D471/04	C07D495/04	A61K31/47
	A61K31/4375	A61K31/4365	A61P19/00	A61P11/00
According to International Patent Classification (IPC) or to both national classification and IPC				
B. FIELDS SEARCHED				
Minimum documentation searched (classification system followed by classification symbols)				
C07D A61K A61P				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)				
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BEILSTEIN Data				
C. DOCUMENTS CONSIDERED TO BE RELEVANT				
Category*	Citation of document, with indication, where appropriate, of the relevant passages			Relevant to claim No.
X	WO 2004/032848 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 22 April 2004 (2004-04-22) abstract; claims 1-10,18-24; tables 1-6			1-47
X	EP 1 413 306 A (WARNER-LAMBERT COMPANY LLC) 28 April 2004 (2004-04-28) abstract; claims 1-23; examples 1-63			1-47
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.				
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as explained) "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 which is cited to show that the invention involves an inventive step when the document is taken alone "Y" document of particular relevance which is cited to show that the invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family				
Date of the actual completion of the international search			Date of mailing of the international search report	
29 June 2006			06/07/2006	
Name and mailing address of the ISA: European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016			Authorized officer van Laren, M	

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 44-47 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, the international application is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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WO 2004032848 A	22-04-2004	AU 2003277285 A1	04-05-2004
		BR 0315041 A	16-08-2005
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		CN 1720047 A	11-01-2006
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EP 1413306 A	28-04-2004	NONE	

ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO DE ENFERMEDADES
INFLAMATORIAS

INFORMACIÓN DE PRIORIDAD

5 La presente solicitud reivindica prioridad según 35 U.S.C. § 119(e) para la solicitud provisional de Estados Unidos Nº 60/655.927, presentada el 24 de febrero de 2005, titulada "Antagonistas del Receptor de PGD2 para el Tratamiento de Enfermedades Inflamatorias", cuyo contenido entero se incorpora en este documento como referencia.

10 ANTECEDENTES DE LA INVENCION

CRTH2 es un receptor de quimioatrayentes acoplado a la proteína G expresado en células Th2 (Nagata *et al.*, *J. Immunol.*, **1999**, 162, 1278-1286), eosinófilos y basófilos (Hirai *et al.*, *J. Exp. Med.*, **2001**, 193, 255-261). La prostaglandina D2 (PGD2) es un ligando natural para CRTH2, y es el mediador inflamatorio principal producido por mastocitos. Se ha demostrado que la activación de CRTH2 por PGD2 induce la migración y la activación de células Th2 (Hirai *et al.*, *J. Exp. Med.* **2001**, 193, 255-261; Gervais *et al.*, *J. Allergy Clin. Immunol.* **2001**, 108, 982-988) que, a su vez, están implicadas en la creación de una respuesta inflamatoria alérgica por medio de la inducción directa o indirecta de la migración, activación, cebado y supervivencia prolongada de células efectoras tales como eosinófilos y basófilos (Sanz *et al.*, *J. Immunol.* **1998**, 160, 5637-5645; Pope *et al.*, *J. Allergy Clin. Immunol.* **2001**, 108, 594-601; Teran L. M., *Clin. Exp. Allergy* **1999**, 29, 287-290). El papel de PGD2 en el inicio y mantenimiento de la inflamación alérgica también se ha demostrado en modelos de asma en ratones demostrando que la sobreproducción de PGD2 *in vivo* por la PGD2 sintasa exacerba la inflamación de la vías respiratorias (Fujitani *et al.*, *J. Immunol.* **2002**, 168, 443-449).

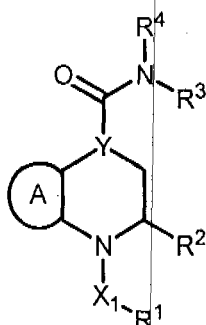
Por consiguiente, los compuestos que son moduladores, preferiblemente inhibidores, de la interacción entre CRTH2 y PGD2 deben ser útiles para el tratamiento de enfermedades y trastornos que están mediados por CRTH2, PGD2, células Th2 y eosinófilos y/o basófilos. Estas enfermedades incluyen, pero sin limitación, trastornos alérgicos, trastornos asmáticos y trastornos inflamatorios tales como rinitis alérgica, asma alérgica, broncoconstricción, dermatitis atópica y trastornos inflamatorios sistémicos.

Ahora se ha descubierto que los compuestos de esta invención y las composiciones farmacéuticamente aceptables de los mismos son eficaces como inhibidores de la interacción entre CRTH2 y su ligando natural PGD2. De esta

manera, los compuestos de la invención y las composiciones farmacéuticas de los mismos son útiles para tratar trastornos inflamatorios y trastornos con un componente inflamatorio.

DESCRIPCIÓN DETALLADA DE LA INVENCION

- 5 Esta invención proporciona compuestos que son inhibidores de CRTH2, y por consiguiente son útiles para el tratamiento de trastornos inflamatorios y/o trastornos con un componente inflamatorio. Los compuestos de esta invención se representan por la fórmula I:



(I);

o una sal farmacéuticamente aceptable de los mismos, donde:

El anillo A es un anillo arilo o heteroarilo, de 5-6 miembros, condensado, opcionalmente sustituido;

- 15 Y es >C(R^x)- o >N-;

X₁ es -C(=O)-, -SO₂-, -CONR-, -C(R)₂- o -CO₂-.

- R¹ es un grupo opcionalmente sustituido seleccionado entre un grupo alifático, un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico, un heterociclilo monocíclico o bicíclico no aromático o un grupo carbociclilo monocíclico o bicíclico no aromático.

R² es un grupo alquilo C₁-C₃, un grupo haloalquilo C₁-C₃ o un grupo cicloalquilo C₃-C₆ donde el grupo alquilo C₁-C₃ representado por R² está opcionalmente sustituido con R⁵;

- R³ es hidrógeno, alquilo C₁-C₆ opcionalmente sustituido con R⁶, fluoroalquilo C₁-C₆, o un grupo opcionalmente sustituido seleccionado entre un grupo cicloalquilo C₃-C₈, un grupo heterocíclico monocíclico no aromático, un arilo monocíclico o un grupo heteroarilo monocíclico;

- R⁴ es -[C(R⁷)₂]_m-B; o R³ y R⁴ se pueden tomar junto con el átomo de nitrógeno situado entre ellos para formar un grupo heteroarilo monocíclico o bicíclico, opcionalmente sustituido o un grupo heterocíclico no aromático; o

R^x y R⁴ se pueden tomar junto con los átomos de carbono y nitrógeno situados entre ellos para formar un grupo heterocíclico que contiene nitrógeno, no aromático, monocíclico, opcionalmente sustituido;

R⁵ es -OH, -O(grupo alifático C₁₋₄), -COOR' o -N(R')₂;

- 5 R⁶ es -OH, -O(grupo alifático C₁₋₄), -N(R')₂, -C(O)R', -COOR', C(O)N(R')₂, o un grupo opcionalmente sustituido seleccionado entre un cicloalquilo monocíclico, un arilo monocíclico, un heteroarilo monocíclico o un grupo heterocíclico no aromático monocíclico;

cada R⁷ es independientemente hidrógeno, flúor o alquilo C₁₋₃;

- 10 cada R, R^x o R' es independientemente hidrógeno o un grupo alifático C₁₋₄ o N(R')₂ es un grupo heterocíclico que contiene nitrógeno, no aromático, monocíclico;

m es cero o uno; y

- 15 B es -H, -C(R⁷)₃, -C(R⁷)₂-C(R⁷)₃, o un grupo opcionalmente sustituido seleccionado entre un cicloalquilo monocíclico o bicíclico, un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico o un grupo heterocíclico no aromático, monocíclico o bicíclico.

- En algunas realizaciones, los compuestos de la invención incluyen compuestos de fórmula (I) distintos de los compuestos en los que X₁ es -COO- y R¹ es etilo y el anillo A está sustituido con: a) dos apariciones de OMe, a) dos apariciones de Me, o c) una aparición de CF₃. En otras realizaciones, los compuestos de la invención incluyen aquellos compuestos en los que X₁ es distinto de -COO-
- 20

2. Compuestos y definiciones:

- 25 Los compuestos de esta invención incluyen los descritos anteriormente de forma general, y además se ilustran por las clases, subclases y especies descritas en este documento. Como se usan en este documento, se aplicarán las siguientes definiciones a menos que se indique otra cosa. Para los fines de esta invención, los elementos químicos se identifican de acuerdo con la Tabla Periódica de los Elementos, versión CAS, Handbook of Chemistry and Physics, 75ª Ed. Además, los principios generales de química orgánica se describen en "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, y "March's Advanced Organic Chemistry", 5ª Ed., Ed.: Smith, M. B. y March, J., John Wiley & Sons, New York: 2001.
- 30

- 35 El término "alifático" o "grupo alifático", como se usa en este documento, significa una cadena de hidrocarburos sustituida o sin sustituir, de cadena lineal (es

decir, no ramificada) o ramificada que está completamente saturada o que contiene una o más unidades de insaturación, o un hidrocarburo monocíclico o un hidrocarburo bicíclico que está completamente saturado o que contiene una o más unidades de insaturación, pero que no es aromático (también denominado en este documento "carbociclo", "cicloalifático", "cicloalquilo" o "cicloalquenilo"). Por ejemplo, los grupos alifáticos adecuados incluyen grupos alquilo, alquenilo y alquinilo lineales, ramificados o cíclicos, sustituidos o sin sustituir, e híbridos de los mismos, tales como (cicloalquil)alquilo, (cicloalquenil)alquilo o (cicloalquil)alquenilo. A menos que se especifique otra cosa, en diversas realizaciones, los grupos alifáticos tienen 1-20, 1-15, 1-12, 1-10, 1-8, 1-6, 1-4 ó 1-3 átomos de carbono.

Los términos "cicloalifático", "carbociclo", "carbocíclico", "carbociclo" o "carbocíclico", usados solos o como parte de un resto mayor, se refieren a un sistema de anillos alifáticos, cíclicos, saturados o parcialmente insaturados, que tienen de 3 a aproximadamente 14 miembros, donde el sistema de anillos alifáticos está opcionalmente sustituido. En algunas realizaciones, el grupo cicloalifático incluye sistemas de anillos saturados ("cicloalquilo") que tienen de aproximadamente 3 a aproximadamente 8 miembros. Los grupos cicloalifáticos incluyen, sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclohexilo, ciclohexenilo, cicloheptilo, cicloheptenilo, ciclooctilo, ciclooctenilo y ciclooctadienilo. En algunas realizaciones, el cicloalquilo tiene 3-6 carbonos. Los términos "cicloalifático", "carbociclo", "carbocíclico", "carbociclo" o "carbocíclico" también incluyen anillos alifáticos que se condensan a uno o más anillos aromáticos o no aromáticos, tales como decahidronaftilo o tetrahidronaftilo, donde el radical o punto de unión no es el anillo alifático.

El término "alcoxi" o "tioalquilo", como se usa en este documento, se refiere a un grupo alquilo, como se ha definido anteriormente, unido a la cadena principal de carbonos a través de un átomo de oxígeno ("alcoxi") o azufre ("tioalquilo").

Los términos "haloalifático", "haloalquilo", "haloalquenilo" y "haloalcoxi" se refieren a un grupo alifático, alquilo, alquenilo o alcoxi, como puede ser el caso, sustituido con uno o más átomos de halógeno. Como se usa en este documento, el término "halógeno" o "halo" significa F, Cl, Br o I. A menos que se indique otra cosa, los términos "alquilo", "alquenilo" y "alcoxi" incluyen grupos haloalquilo, haloalquenilo y haloalcoxi, incluyendo, en particular, aquellos con 1-5 átomos de flúor. A modo de ejemplo, los términos "alifático C₁₋₃" y "alquilo C₁₋₃" incluyen dentro de su alcance grupos trifluorometilo y pentafluoroetilo.

El término "heteroátomo" significa uno o más de oxígeno, azufre, nitrógeno, fósforo o silicio (incluyendo cualquier forma oxidada de nitrógeno, azufre, fósforo o silicio; la forma cuaternizada de cualquier nitrógeno básico o; un nitrógeno sustituible de un anillo heterocíclico, por ejemplo N (como en 3,4-dihidro-2H-pirrolilo), 5 - NH (como en pirrolidinilo) o NR⁺ (como en N-sustituido pirrolidinilo)).

Los términos "arilo" y "ar-", usados solos o como parte de un resto mayor, por ejemplo, "aralquilo", "aralcoxi" o "ariloxialquilo", se refieren a un resto aromático de C₆ a C₁₄ que comprende de uno a tres anillos aromáticos, que están opcionalmente sustituidos. Preferiblemente, el grupo arilo es un grupo arilo C₆₋₁₀. Los 10 grupos arilo incluyen, sin limitación, fenilo, naftilo y antracenilo. El término "arilo", como se usa en este documento, también incluye grupos en los que un anillo aromático se condensa a uno o más anillos heteroarilo, cicloalifático o heterocíclico, donde el radical o punto de unión está en el anillo aromático. Los ejemplos no limitantes de dichos sistemas de anillos condensados incluyen indolilo, isoindolilo, 15 benzotienilo, benzofuranilo, dibenzofuranilo, indazolilo, bencimidazolilo, benzotiazolilo, quinolilo, isoquinolilo, cinnolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo, fenoxazinilo, tetrahidroquinolinilo, tetrahidroisoquinolinilo, fluorenilo, indanilo, fenantridinilo, tetrahidronaftilo, indolinilo, fenoxazinilo, benzodioxanilo y benzodioxolilo. Un grupo arilo puede ser mono-, bi-, 20 tri- o policíclico, preferiblemente mono-, bi-, o trícíclico, más preferiblemente mono- o bicíclico. El término "arilo" puede usarse de forma intercambiable con los términos "grupo arilo", "anillo arilo" y "anillo aromático".

Un grupo "aralquilo" o "arilalquilo" comprende un grupo arilo unido covalentemente a un grupo alquilo, estando independientemente cualquiera de 25 ellos opcionalmente sustituido. Preferiblemente, el grupo aralquilo es aril C₆₋₁₀-alquilo (C₁₋₆), incluyendo, sin limitación, bencilo, fenetilo y naftilmetilo.

Los términos "heteroarilo" y "heteroar-", usados solos o como parte de un resto mayor, por ejemplo, heteroaralquilo o "heteroaralcoxi", se refieren a grupos que tienen de 5 a 14 átomos en el anillo, preferiblemente 5, 6, 9 ó 10 átomos en el 30 anillo; que tienen 6, 10 ó 14 electrones compartidos en una formación cíclica; y que tienen, además de átomos de carbono, de uno a cuatro heteroátomos. El término "heteroátomo" se refiere a nitrógeno, oxígeno o azufre, e incluye cualquier forma oxidada de nitrógeno o azufre, y cualquier forma cuaternizada de un nitrógeno básico. Los grupos heteroarilo incluyen, sin limitación, tienilo, furanilo, pirrolilo, 35 imidazolilo, pirazolilo, triazolilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, tiazolilo, isotiazolilo, tiadiazolilo, piridilo, piridazinilo, pirimidinilo, pirazinilo, indolizinilo, purinilo,

naffiridinilo y pteridinilo. Los términos "heteroarilo" y "heteroar-", como se usan en este documento, también incluyen grupos en los que un anillo heteroaromático se condensa a uno o más anillos arilo, cicloalifático o heterocíclico, donde el radical o punto de unión está en el anillo heteroaromático. Los ejemplos no limitantes

5 incluyen indolilo, isoindolilo, benzotienilo, benzofuranilo, dibenzofuranilo, indazolilo, bencimidazolilo, benzotiazolilo, quinolilo, isoquinolilo, cinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, 4H-quinolizinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo, fenoxazinilo, tetrahydroquinolinilo, tetrahydroisoquinolinilo y pirido[2,3-b]-1,4-oxazin-3(4H)-ona. Un grupo heteroarilo puede ser mono-, bi-, tri- o policíclico,

10 preferiblemente mono-, bi- o tricíclico, más preferiblemente mono- o bicíclico. El término "heteroarilo" puede usarse de forma intercambiable con los términos "anillo heteroarilo", "grupo heteroarilo" o "heteroaromático", donde cualquiera de dichos términos incluye anillos que están opcionalmente sustituidos. El término "heteroaralquilo" se refiere a un grupo alquilo sustituido con un heteroarilo, donde

15 las porciones alquilo y heteroarilo opcionalmente están independientemente sustituidas.

Como se usa en este documento, a menos que se indique otra cosa, las expresiones "heterociclo", "heterocíclico", "radical heterocíclico" y "anillo heterocíclico" se usan de forma intercambiable y se refieren a un resto

20 heterocíclico, monocíclico de 3 a 7 miembros o bicíclico de 7 a 10 miembros que está saturado o parcialmente insaturado y que tiene, además de átomos de carbono, uno o más, preferiblemente de uno a cuatro, heteroátomos, como se ha definido anteriormente. Cuando se usa con respecto a un átomo del anillo de un heterociclo, el término "nitrógeno" incluye un nitrógeno sustituido. Como ejemplo,

25 en un anillo saturado o parcialmente insaturado que tiene 0-3 heteroátomos seleccionados entre oxígeno, azufre o nitrógeno, el nitrógeno puede ser N (como en 3,4-dihidro-2H-pirrolilo), NH (como en pirrolidinilo) o ⁺NR (como en pirrolidinilo N-sustituido).

Un anillo heterocíclico puede unirse a su grupo colgante en cualquier

30 heteroátomo o átomo de carbono que dé como resultado una estructura estable y cualquiera de los átomos del anillo puede estar opcionalmente sustituido. Los ejemplos de dichos radicales heterocíclicos saturados o parcialmente insaturados incluyen, sin limitación, tetrahydrofuranoilo, tetrahidrotienilo, pirrolidinilo, pirrolidonilo, piperidinilo, pirrolinilo, tetrahydroquinolinilo, tetrahydroisoquinolinilo,

35 decahydroquinolinilo, oxazolidinilo, piperazinilo, dioxanilo, dioxolanilo, diazepinilo, oxazepinilo, tiazepinilo, morfolinilo y quinuclidinilo. Las expresiones "heterociclo",

"heterociclilo", "anillo heterociclilo", "grupo heterocíclico", "resto heterocíclico", y "radical heterocíclico", se usan de forma intercambiable en este documento, y también incluyen grupos en los que un anillo heterociclilo se condensa a uno o más anillos arilo, heteroarilo o cicloalifático, tales como indolinilo, 3H-indolilo, cromanilo, fenantridinilo o tetrahidroquinolinilo, donde el radical o punto de unión está en el anillo heterociclilo. Un grupo heterociclilo puede ser mono-, bi-, tri- o policíclico, preferiblemente mono-, bi- o tricíclico, más preferiblemente mono- o bicíclico. El término "heterociclilalquilo" se refiere a un grupo alquilo sustituido con un heterociclilo, donde las porciones alquilo y heterociclilo opcionalmente están independientemente sustituidas.

Como se usa en este documento, la expresión "parcialmente insaturado" se refiere a un resto del anillo que incluye al menos un doble enlace o triple enlace entre átomos del anillo. La expresión "parcialmente insaturado" pretende incluir anillos que tienen múltiples sitios de insaturación, pero no pretende incluir restos arilo o heteroarilo, como se han definido anteriormente.

El término "alquileno" se refiere a un grupo alquilo bivalente. Una "cadena alquileno" es un grupo polimetileno, es decir, $-(CH_2)_n-$, en el que n es un número entero positivo, preferiblemente de 1 a 6, de 1 a 4, de 1 a 3, de 1 a 2 o de 2 a 3. Una cadena alquileno sustituida es un grupo polimetileno en el que uno o más átomos de hidrógeno del metileno se reemplazan con un sustituyente. En general, a menos que se indique otra cosa, los sustituyentes adecuados incluyen los descritos a continuación para un grupo alifático sustituido.

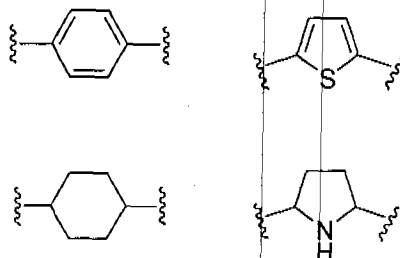
Una unidad metileno de la cadena alquileno también puede reemplazarse opcionalmente con un grupo funcional. En algunas realizaciones, una unidad metileno interna se reemplaza con el grupo funcional. En la memoria descriptiva y en las reivindicaciones de este documento se describen ejemplos de grupos funcionales adecuados.

Los términos "arileno", "heterociclono" y "carbociclono"/"cicloalquileno" se refieren a anillo(s) arilo, heteroarilo, heterocíclico no aromático o carbocíclico/cicloalquilo, respectivamente, en una molécula que está unida a dos grupos diferentes de la molécula mediante un enlace covalente sencillo de dos de sus átomos en el anillo. Los ejemplos de grupos arileno adecuados incluyen fenileno, pirrolileno, tienileno, furanileno, imidazolileno, triazolileno, tetrazolileno, oxazolileno, isoxazolileno, oxadiazolileno, pirazolileno, piridinileno, pirimidileno, pirazinileno, tiazolileno; los ejemplos de carbociclenos monocíclicos adecuados incluyen ciclopropileno, ciclopentileno, ciclohexileno y cicloheptileno; y los ejemplos de

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heterociclenos no aromáticos adecuados incluyen piperidinileno, piperazinileno, pirrolidinileno, pirazolidinileno, imidazolidinileno, tetrahidrofuranileno, tetrahidrotienileno, isooxazolidinileno, oxazolidinileno, isotiazolidinileno, tiazolidinileno, oxatiolanileno, dioxolanileno y ditiolanileno. A modo de ejemplo, la estructura de

5 1,4-fenileno, 2,5-tienileno, 1,4 ciclohexileno y 2,5-pirrolodinileno se muestra a continuación:



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El término "sustituido", como se usa en este documento, significa que se reemplazan uno o más hidrógenos del resto indicado, con la condición de que la sustitución dé como resultado un compuesto estable o químicamente viable. Un compuesto estable o un compuesto químicamente viable es uno en el que la

15 estructura química no se altera sustancialmente cuando se mantiene a una temperatura de aproximadamente -80°C a aproximadamente +40°C, en ausencia de humedad u otras condiciones químicamente reactivas, durante al menos una semana, o un compuesto que mantiene su integridad durante el tiempo suficiente para ser útil para la administración terapéutica o profiláctica a un paciente. La

20 expresión "uno o más sustituyentes", como se usa en este documento, se refiere a varios sustituyentes que varían de uno al número máximo de sustituyentes posibles en base al número de sitios de unión disponibles, con la condición de que se mantengan las condiciones anteriores de estabilidad y viabilidad química.

A menos que se indique otra cosa, un grupo arilo (incluyendo aralquilo, aralcoxi, ariloxialquilo y similares) o heteroarilo (incluyendo heteroaralquilo, heteroarilalcoxi y similares) puede contener uno o más sustituyentes y, por lo tanto puede estar "opcionalmente sustituido". Además de los sustituyentes definidos

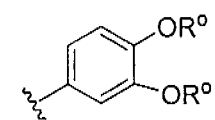
25 anteriormente y en este documento, los sustituyentes adecuados sobre el átomo de carbono insaturado de un grupo arilo o heteroarilo también incluyen y se seleccionan generalmente entre halógeno; -R°; -OR°; -SR°; -NO₂; -CN; -N(R°)₂; -NR°C(O)R°; -NR°C(S)R°; -NR°C(O)N(R°)₂; -NR°C(S)N(R°)₂; -NR°CO₂R°; -NR°NR°C(O)R°; -NR°NR°C(O)N(R°)₂; -NR°NR°CO₂R°; -C(O)C(O)R°; -C(O)CH₂C(O)R°; -CO₂R°; -C(O)R°; -C(S)R°; -C(O)N(R°)₂; -C(S)N(R°)₂; -OC(O)N(R°)₂; -OC(O)R°; -C(O)N(OR°)R°; -C(NOR°)R°; -S(O)₂R°; -S(O)₂OR°; -SO₂N(R°)₂; -S(O)R°; -NR°SO₂N(R°)₂; -NR°SO₂R°; -

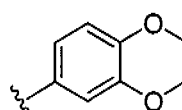
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- $N(OR^o)R^o$; $-C(=NH)-N(R^o)_2$; $-P(O)_2R^o$; $-PO(R^o)_2$; o $-OPO(R^o)_2$; donde cada aparición independiente de R^o se selecciona entre hidrógeno o un grupo opcionalmente sustituido seleccionado entre un grupo alifático C_{1-6} , arilo, heteroarilo, heterocíclico, o cicloalifático o, además de la definición anterior, dos apariciones independientes
- 5- de R^o , en el mismo sustituyente o en sustituyentes diferentes, tomados junto con los átomos situados entre ellos forman un anillo monocíclico o bicíclico, saturado, parcialmente insaturado o totalmente insaturado, de 3-12 miembros, opcionalmente sustituido, que tiene 0-4 heteroátomos seleccionados independientemente entre nitrógeno, oxígeno o azufre.
- 10 A menos que se indique otra cosa, un grupo alifático o heteroalifático, o un anillo heterocíclico no aromático puede contener uno o más sustituyentes y por lo tanto puede estar "opcionalmente sustituido". Además de los sustituyentes definidos anteriormente y en este documento, los sustituyentes adecuados sobre el carbono saturado de un grupo alifático o heteroalifático, o de un anillo heterocíclico no
- 15 aromático se seleccionan entre aquellos indicados anteriormente para el carbono insaturado de un grupo arilo o heteroarilo y además incluyen los siguientes: $=O$, $=S$, $=NNHR^*$, $=NN(R^*)_2$, $=NNHC(O)R^*$, $=NNHCO_2(\text{alquilo})$, $=NNHSO_2(\text{alquilo})$ o $=NR^*$, donde cada R^* se selecciona independientemente entre hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido.
- 20 Además de los sustituyentes definidos anteriormente en este documento, los sustituyentes opcionales sobre el nitrógeno de un anillo heterocíclico no aromático también incluyen y se seleccionan generalmente entre $-R^+$, $-N(R^+)_2$, $-C(O)R^+$, $-CO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-SO_2R^+$, $-SO_2N(R^+)_2$, $-C(=S)N(R^+)_2$, $-C(=NH)-N(R^+)_2$ o $-NR^+SO_2R^+$; donde R^+ es hidrógeno, o un grupo opcionalmente sustituido
- 25 seleccionado entre un grupo alifático C_{1-6} , arilo, heteroarilo, heterocíclico, o cicloalifático o, además de la definición anterior, dos apariciones independientes de R^+ , en el mismo sustituyente o en sustituyentes diferentes, tomados junto con los átomos situados entre ellos forman un anillo monocíclico o bicíclico, saturado, parcialmente insaturado o totalmente insaturado, de 3-12 miembros,
- 30 opcionalmente sustituido, que tiene 0-4 heteroátomos seleccionados independientemente entre nitrógeno, oxígeno o azufre.
- Como se ha detallado anteriormente, en algunas realizaciones, dos apariciones independientes de R^o (o R^+ o cualquier otra variable definida de manera similar en la memoria descriptiva y en las reivindicaciones de este
- 35 documento), se toman junto con los átomos de carbono situados entre ellos para formar un anillo monocíclico o bicíclico, saturado, parcialmente insaturado o

totalmente insaturado, de 3-12 miembros, opcionalmente sustituido, que tiene 0-4 heteroátomos seleccionados independientemente entre nitrógeno, oxígeno o azufre.

- Los anillos ejemplares que se forman cuando dos apariciones
 5 independientes de R^o (o R^+ , o cualquier otra variable definida de forma similar en la memoria descriptiva y en las reivindicaciones de este documento) se toman junto con los átomos de carbono situados entre ellos incluyen, pero sin limitación los siguientes: a) dos apariciones independientes de R^o (o R^+ , o cualquier otra variable definida de manera similar en la memoria descriptiva o en las reivindicaciones de
 10 este documento) que se unen al mismo átomo y se toman junto con ese átomo para formar un anillo, por ejemplo, $N(R^o)_2$, donde ambas apariciones de R^o se toman junto con el átomo de nitrógeno para formar un grupo piperidin-1-ilo, piperazin-1-ilo o morfolin-4-ilo; y b) dos apariciones independientes de R^o (o R^+ , o cualquier otra variable definida de manera similar en la memoria descriptiva o en
 15 las reivindicaciones de este documento) que se unen a átomos diferentes y se toman junto con los dos átomos para formar un anillo, por ejemplo cuando un anillo

fenilo está sustituido con dos apariciones de OR^o , estas dos apariciones de R^o se toman junto con los átomos de oxígeno a los que están unidos para formar un anillo de 6 miembros que contiene nitrógeno, condensado:

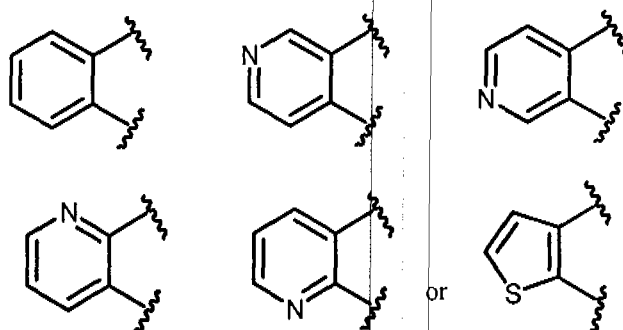
-  Se apreciará que puede formarse una diversidad de anillos
 20 diferentes (por ejemplo, también anillos espiro y enlazados) cuando dos apariciones independientes de R^o (o R^+ , o cualquier otra variable definida de manera similar en la memoria descriptiva y en las reivindicaciones de este documento) se toman junto con los átomos de carbono situados entre ellos, y que los ejemplos detallados
 25 anteriormente no pretenden ser limitantes.

- A menos que se indique otra cosa, las estructuras representadas en este documento también pretenden incluir todas las formas isoméricas (por ejemplo, enantioméricas, diastereoméricas y geométricas (o conformacionales)) de la estructura; por ejemplo, las configuraciones *R* y *S* de cada centro asimétrico,
 30 isómeros de doble enlace (*Z*) y (*E*) e isómeros conformacionales (*Z*) y (*E*). Por lo tanto, los isómeros estereoquímicos unitarios así como las mezclas enantioméricas, diastereoméricas y geométricas (o conformacionales) de los compuestos de este documento están dentro del alcance de la invención. A menos que se indique otra

cosa, todas las formas tautoméricas de los compuestos de la invención están dentro del alcance de la invención. Además, a menos que se indique otra cosa, las estructuras representadas en este documento también pretenden incluir compuestos que difieren únicamente en la presencia de uno o más átomos isotópicamente enriquecidos. Por ejemplo, los compuestos que tienen las estructuras mostradas en este documento, con la excepción del reemplazamiento del hidrógeno con deuterio o tritio, o el reemplazamiento de un carbono con un carbono enriquecido ^{13}C o ^{14}C , están dentro del alcance de esta invención.

3. Descripción de los compuestos ejemplares:

10 Como se ha descrito de forma general anteriormente para los compuestos de fórmula I, el anillo A es un anillo arilo o heteroarilo, de 5-6 miembros, condensado y opcionalmente sustituido. En algunas realizaciones, el anillo A es un grupo opcionalmente sustituido seleccionado entre:



15

Preferiblemente, el Anillo A es un grupo fenilo condensado, opcionalmente sustituido. En general, los sustituyentes del Anillo A adecuados son los que se proporcionan en la sección que describe los sustituyentes de grupo arilo y heteroarilo adecuados. Preferiblemente, el Anillo A, como se ha definido en general y en las realizaciones preferidas anteriormente, está sustituido con n sustituyentes representados por R^8 , donde n es 0, 1, 2, 3 ó 4, preferiblemente 0 ó 1. Cada R^8 es independientemente halo, $-\text{OR}^9$, $-\text{SR}^9$, $-\text{CN}$, $-\text{NO}_2$, $-\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{R}^9$, $-\text{N}(\text{R}^{10})\text{CO}_2\text{R}^{9a}$, $-\text{N}(\text{R}^{10})\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{OC}(\text{O})\text{R}^9$, $-\text{OC}(\text{O})\text{N}(\text{R}^{10})_2$, $-\text{C}(\text{O})\text{R}^9$, $-\text{CO}_2\text{R}^9$, $-\text{SO}_2\text{R}^{9a}$, $-\text{S}(\text{O})\text{R}^{9a}$, $-\text{SO}_2\text{N}(\text{R}^{10})_2$, $-\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{9a}$ o un grupo opcionalmente sustituido seleccionado entre un grupo alifático C_{1-8} , un arilo monocíclico, un heteroarilo monocíclico o un grupo heterocíclico monocíclico, donde cada R^9 es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido, cada R^{9a} es independientemente un grupo alifático C_{1-6} opcionalmente sustituido; y cada R^{10} es independientemente hidrógeno, un grupo alifático C_{1-6} , $-\text{CO}_2\text{R}^{9a}$, $-\text{SO}_2\text{R}^{9a}$ o $-\text{C}(\text{O})\text{R}^9$, o $\text{N}(\text{R}^{10})_2$ es un grupo heteroarilo monocíclico o heterocíclico no

aromático monocíclico. Preferiblemente, cada R^B es independientemente halo, alquilo C_{1-3} , haloalquilo C_{1-3} , hidroxilo, alcoxi C_{1-3} , haloalcoxi C_{1-3} , $-NO_2$, $-CN$, amina, alquilamina C_{1-3} , dialquilamina C_{1-3} , hidroxialquilo C_{1-3} o aminoalquilo C_{1-3} .

- 5 Como se ha descrito de forma general anteriormente para los compuestos de fórmula I, Y es $>C(R^x)-$ o $>N-$, donde R^x es hidrógeno o un grupo alifático C_{1-4} . Y es preferiblemente $>C(R^x)-$. Más preferiblemente Y es $>CH-$.

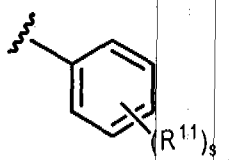
Como se ha descrito de forma general anteriormente para los compuestos de fórmula I, X_1 es $-C(=O)-$, $-SO_2-$, $-CONR-$, $-C(R)_2-$, o $-CO_2-$. Preferiblemente, X_1 es $-C(=O)-$.

- 10 Como se ha descrito de forma general anteriormente para los compuestos de fórmula I, R^1 es un grupo opcionalmente sustituido seleccionado entre un grupo alifático, un anillo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico, un grupo heterocíclico no aromático, monocíclico o bicíclico o un grupo carbocíclico no aromático, monocíclico o bicíclico. Preferiblemente, R^1 es un grupo arilo o
- 15 heteroarilo, monocíclico o bicíclico, opcionalmente sustituido. En otras realizaciones preferidas, R^1 es un grupo opcionalmente sustituido seleccionado entre fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo.
- 20 En otras realizaciones preferidas, R^1 es un grupo heterocíclico, monocíclico, no aromático, o carbocíclico no aromático, opcionalmente sustituido. En las realizaciones preferidas, R^1 es un grupo heterocíclico, monocíclico, no aromático, o carbocíclico no aromático, opcionalmente sustituido seleccionado entre ciclopropilo, ciclobutilo, azetidinio, ciclopentilo, pirrolidinilo, ciclohexilo, cicloheptilo,
- 25 morfolinilo, piperidinilo, piperazinilo o tiomorfolinilo. En otras realizaciones preferidas, R^1 es fenilo o piridilo opcionalmente sustituido. En otras realizaciones preferidas, R^1 es fenilo opcionalmente sustituido.

- En general, los sustituyentes adecuados para un átomo de carbono o nitrógeno sustituible del anillo aromático de un grupo arilo o heteroarilo
- 30 representado por R^1 son como se proporcionan en la sección que describe los sustituyentes adecuados para un grupo arilo o heteroarilo; los sustituyentes adecuados para un átomo de carbono o nitrógeno sustituible del anillo de un anillo heterocíclico no aromático del grupo representado por R^1 son como se proporcionan en la sección que describe los sustituyentes adecuados para un
- 35 grupo heterocíclico no aromático; y los sustituyentes adecuados para un grupo alifático o un carbono sustituible del anillo de un grupo carbocíclico representado

por R^1 son como se proporcionan en la sección que describe los sustituyentes adecuados para un grupo alifático.

- En algunas realizaciones, R^1 está sustituido con una o más apariciones de R^{11} , donde cada R^{11} es independientemente halo, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NO_2$, $-N(R^{12}R^{13})$, $-N(R^{13})C(O)R^{12}$, $-N(R^{13})CO_2R^{12a}$, $-N(R^{13})C(O)N(R^{12}R^{13})$, $-C(O)N(R^{12}R^{13})$, $-OC(O)R^{12}$, $-OC(O)N(R^{12}R^{13})$, $-C(O)R^{12}$, $-CO_2R^{12}$, $-SO_2R^{12a}$, $-S(O)R^{12a}$, $-SO_2N(R^{12}R^{13})$, $-N(R^{13})SO_2R^{12a}$ o un grupo opcionalmente sustituido seleccionado entre un grupo alifático C_{1-8} , un arilo monocíclico, un heteroarilo monocíclico, o un grupo carbocíclico, no aromático, monocíclico, donde cada R^{12} es independientemente hidrógeno o un grupo alifático C_{1-6} opcionalmente sustituido, cada R^{12a} es un grupo alifático C_{1-6} opcionalmente sustituido, y cada R^{13} es independientemente hidrógeno, un grupo alifático C_{1-6} , $-CO_2R^{12a}$, $-SO_2R^{12a}$ o $-C(O)R^{12}$, o $-N(R^{12}R^{13})$ es un grupo heteroarilo monocíclico o heterocíclico no aromático opcionalmente sustituido. Preferiblemente, cada R^{11} es independientemente halo, alquilo C_{1-3} , haloalquilo C_{1-3} , hidroxilo, alcoxi C_{1-3} , haloalcoxi C_{1-3} , $-NO_2$, $-CN$, amina, alquilamina C_{1-3} , dialquilamina C_{1-3} , hidroxialquilo C_{1-3} o aminoalquilo C_{1-3} . Más preferiblemente, R^1 es un grupo fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno opcionalmente sustituido en cualquier átomo de carbono sustituible del anillo con R^{11} . Aún más preferiblemente, R^1 es un grupo fenilo representado por la siguiente fórmula estructural:



s es 0, 1, 2, 3 ó 4, preferiblemente 0-2, y más preferiblemente 0 ó 1.

- Como alternativa, R^1 está sustituido con $T_2-V_2-T_3-M-R^Y$, y R^1 está opcionalmente sustituido además en uno o más de los átomos de carbono sustituibles del anillo con R^{11} .

- M está ausente o es un arileno monocíclico opcionalmente sustituido, un carbociclono no aromático, monocíclico, opcionalmente sustituido o un heterociclono no aromático, monocíclico, opcionalmente sustituido. Los ejemplos de grupos arileno adecuados incluyen fenileno, pirrolileno, tienileno, furanileno, imidazolileno, triazolileno, tetrazolileno, oxazolileno, isoxazolileno, oxadiazolileno, pirazolileno, piridinileno, pirimidileno, pirazinileno, tiazolileno; los ejemplos de carbociclenos monocíclicos adecuados incluyen ciclopropileno, ciclopentileno,

ciclohexileno y cicloheptileno; y los ejemplos de heterociclenos no aromáticos adecuados incluyen piperidinileno, piperazinileno, pirrolidinileno, pirazolidinileno, imidazolidinileno, tetrahydrofuranoileno, tetrahidrotienileno, isooxazolidinileno, oxazolidinileno, isotiazolidinileno, tiazolidinileno, oxatiolanileno, dioxolanileno y ditiolanileno. Se prefieren los grupos arileno fenileno, [2.5]tienileno y [2.5]furanileno. Los sustituyentes adecuados para un arileno son como se proporcionan en la sección que describe los sustituyentes de grupos arilo y heteroarilo; y los sustituyentes adecuados para heterociclono y carbociclono no aromáticos son como se describen en las secciones que proporcionan los sustituyentes adecuados para un grupo heterocíclico no aromático y un grupo alifático, respectivamente. Los sustituyentes preferidos para un carbono sustituible del anillo aromático de un grupo representado por M y un átomo de carbono o un átomo de nitrógeno sustituible del anillo de un anillo no aromático representado por M son como se ha descrito anteriormente para un grupo arilo o heteroarilo.

V_2 está ausente, o es $-O-$, $-C(O)-$, $-N(R^{19})-$, $-S-$, $-S(O)-$, $-C(O)NR^{19}-$, $-NR^{19}C(O)-$, $-S(O)_2NR^{19}-$, $-NR^{19}S(O)_2-$ o $-S(O)_2-$. Preferiblemente, V_2 está ausente o es $-O-$.

R^Y es $-C(O)OR^{18}$, $-C(O)R^{18}$, $-OC(O)R^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2R^{18a}$, $-S(O)_2COR^{18}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}S(O)_2R^{18a}$, $S(O)_2OR^{18}$, $-S(O)OR^{18}$, $-S(O)R^{18a}$, $-SR^{18}$, $-C(O)NR^{19}S(O)_2R^{18a}$, $-CN$, $-NR^{19}C(O)N(R^{19})_2$, $-OC(O)NR^{19}_2$, $-N(R^{19})_2$, $-OR^{18}$, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido. Los sustituyentes adecuados para el grupo heterocíclico no aromático y el grupo heteroarilo representado por R^Y son como se proporcionan en la siguiente sección que describe sustituyentes adecuados para un grupo heterocíclico y un grupo heteroarilo, respectivamente. Preferiblemente, R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^{20} o un grupo heteroarilo opcionalmente sustituido representado por R^{21} . Más preferiblemente, R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, tetrazolilo opcionalmente N -sustituido o imidazolilo opcionalmente N -sustituido.

Cada R^{18} es independientemente hidrógeno o un grupo alifático C_{1-6} . Preferiblemente, cada R^{18} es independientemente H o alquilo C_1-C_3 . Más preferiblemente, R^{18} es $-H$, metilo o etilo.

Cada R^{18a} es independientemente un grupo alifático C_{1-6} . Preferiblemente, cada R^{18a} es independientemente H o alquilo C_1-C_3 . Más preferiblemente, R^{18a} es $-H$, metilo o etilo.

Cada R^{19} se selecciona independientemente entre hidrógeno, un grupo alifático C_{1-6} , $-CO_2R^{18}$, $-SO_2R^{18}$ o $-C(O)R^{18}$, o $-NR^{19}$ es un grupo heteroarilo monocíclico o heterocíclico no aromático monocíclico. Preferiblemente, cada R^{19} es H o alquilo C_1-C_3 o $N(R^{19})_2$ es un grupo heterocíclico no aromático que contiene nitrógeno. Más preferiblemente, R^{19} es -H, metilo o etilo.

R^{20} es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiemo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido. R^{21} es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido.

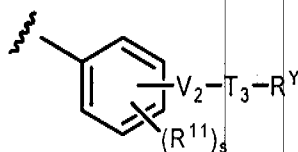
T_2 está ausente, o es un alquileo C_{1-10} de cadena lineal, y T_3 es un alquileo C_{1-10} de cadena lineal, donde T_2 y T_3 juntos no contienen más de 10 átomos de carbono, y con la condición de que T_3 sea un alquileo C_{2-10} de cadena lineal cuando M está ausente y V_2 es $-O-$, $-S-$, $-N(R^{19})-$, $-C(O)N(R^{19})-$ o $-S(O)_2N(R^{19})-$ y R^Y es $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, $-CN$, $-OH$, $-SH$, $-N(R^{19})_2$. T_2 y T_3 están opcional e independientemente sustituidos en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, una amina, alquilamina, dialquilamina o un hidroxilo. Preferiblemente, T_2 está ausente. Preferiblemente, T_3 es un alquileo C_{1-6} de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina, o un hidroxilo.

En algunas realizaciones, R^1 es un grupo arilo o heteroarilo monocíclico sustituido con $-T_2-V_2-T_3-M-R^Y$ y además está opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{11} .

Preferiblemente, R^1 es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos sustituido con $-V_2-T_3-R^Y$, y

cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{11} .

Más preferiblemente, R^1 es un grupo fenilo representado por la siguiente fórmula estructural:



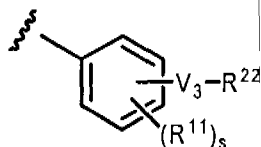
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$-V_2-T_3-R^Y$ está preferiblemente en posición para con respecto al resto X_1 como se ha descrito en los compuestos de fórmula I.

- En otra alternativa, R^1 está sustituido con $-V_3-R^{22}$; y además está opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con
- 10 R^{11} . V_3 es un enlace covalente, $-O-$, $-C(O)-$, $-N(R^{13})-$, $-S-$, $-S(O)-$, $-C(O)NR^{13}-$, $-NR^{13}C(O)-$, $-S(O)_2NR^{13}-$, $-NR^{13}S(O)_2-$ o $-S(O)_2-$. Preferiblemente, V_3 es un enlace covalente o $-O-$. R^{22} es un grupo carbocíclico, no aromático, monocíclico o bicíclico, opcionalmente sustituido, o un grupo heterocíclico no aromático monocíclico o bicíclico, opcionalmente sustituido. Preferiblemente, R^{22} es un grupo heterocíclico no
- 15 aromático monocíclico, opcionalmente sustituido. Más preferiblemente, R^{22} es un ciclohexanilo opcionalmente sustituido, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranoilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo, S,S-dióxido de isotiazolidinilo o piperidinilo.
- 20 Aún más preferiblemente, R^{22} es oxazolidinilo, tiazolidinilo, tetrahidrofuranoilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo. Los sustituyentes adecuados para el grupo carbocíclico no aromático y para el grupo heterocíclico no aromático representado por R^{22} son como se definen a continuación para grupos alifáticos y heterocíclicos no aromáticos,
- 25 respectivamente. Son sustituyentes preferidos en un átomo de carbono sustituible del anillo de un anillo carbocíclico no aromático o un átomo de carbono sustituible de un grupo heterocíclico no aromático representado por R^{22} , alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$ o $-C(O)NR^{23}_2$. Son
- 30 sustituyentes preferidos en un átomo de nitrógeno sustituible del anillo de un grupo heterocíclico no aromático representado por R^{22} , alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$; $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$; $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ o $-(CH_2)_qCH(CH_3)CO_2R^{23}$, donde q es un número entero de 1-4, y cada R^{23} es independientemente $-H$, alquilo, haloalquilo o hidroxialquilo.

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- En algunas realizaciones, R^1 es un grupo arilo o heteroarilo monocíclico, sustituido con $-V_3-R^{22}$; y el grupo arilo o heteroarilo monocíclico representado por R^1 está además opcionalmente sustituido con R^{11} en uno o más de los átomos de carbono sustituibles representados. Preferiblemente, R^1 es un grupo fenilo
- 5 representado por la siguiente fórmula estructural:



- $-V_3-R^{22}$ está preferiblemente en posición para con respecto al resto X_1 como se ha descrito en los compuestos de fórmula I.
- En otra alternativa más, R^1 es un grupo alifático sustituido o sin sustituir.
- 10 Preferiblemente, R^1 es $-T_2-V_2-T_3-M-R^Y$. Más preferiblemente, R^1 es $-V_2-T_3-R^Y$.

Como se ha descrito de forma general anteriormente, R^2 es un grupo alquilo C_1-C_3 , un grupo haloalquilo C_1-C_3 o un grupo cicloalquilo C_3-C_6 . El grupo alquilo C_1-C_3 representado por R^2 está opcionalmente sustituido con R^5 . Preferiblemente, R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 .

- 15 Como se ha descrito de forma general anteriormente, R^3 es hidrógeno, alquilo C_1-C_6 opcionalmente sustituido con R^6 , fluoroalquilo C_1-C_6 o un grupo opcionalmente sustituido seleccionado entre un cicloalquilo C_3-C_8 , un heterocíclico monocíclico no aromático, un arilo monocíclico o un grupo heteroarilo monocíclico. Los sustituyentes adecuados para el grupo heterocíclico no aromático
- 20 monocíclico y el grupo arilo o heteroarilo monocíclico representado por R^3 son como se proporcionan en la sección que describe sustituyentes adecuados para un grupo arilo o heteroarilo y un grupo heterocíclico no aromático, respectivamente. Preferiblemente, R^3 es un grupo alquilo C_1-C_4 .

- Como se ha descrito anteriormente de manera general, R^4 es $-[C(R^7)_2]_m-B$, o
- 25 R^3 y R^4 se pueden tomar junto con el átomo de nitrógeno situado entre ellos para formar un grupo heteroarilo monocíclico o bicíclico o heterocíclico no aromático, opcionalmente sustituido, o R^3 y R^4 se pueden tomar junto con los átomos de carbono y nitrógeno situados entre ellos para formar un grupo heterocíclico que contiene nitrógeno, no aromático, monocíclico, opcionalmente sustituido. En otra
- 30 alternativa, R^4 es $-(CH_2)_m-B$.

R^5 es $-OH$, $-O$ (grupo alifático C_{1-4}), $-COOR'$ o $-N(R')_2$.

R^6 es $-OH$, $-O$ (grupo alifático C_{1-4}), $-N(R')_2$, $-C(O)R'$, $-COOR'$, $C(O)N(R')_2$ o un grupo opcionalmente sustituido seleccionado entre un cicloalquilo monocíclico, un arilo monocíclico, un heteroarilo monocíclico, o un grupo heterocíclico no

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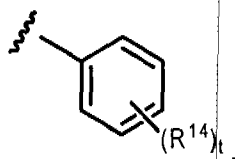
aromático monocíclico. Los sustituyentes adecuados para el grupo cicloalquilo monocíclico, el grupo heterocíclico no aromático monocíclico, el grupo arilo monocíclico y el grupo heteroarilo monocíclico representado por R^6 son como se proporcionan en la sección que describe sustituyentes adecuados para un grupo alifático, un grupo heterocíclico no aromático un grupo arilo, y un grupo heteroarilo, respectivamente.

Cada R^7 es independientemente hidrógeno, flúor o alquilo C_1 - C_3 . Preferiblemente, R^7 es hidrógeno o metilo, más preferiblemente hidrógeno.

Cada R , R^x o R' es independientemente hidrógeno o un grupo alifático C_1 - C_4 o $N(R')_2$ es un grupo heterocíclico que contiene nitrógeno, no aromático, monocíclico.

m es cero o uno.

B es $-H$, $-C(R^7)_3$, $-C(R^7)_2-C(R^7)_3$, un grupo opcionalmente sustituido seleccionado entre un cicloalquilo monocíclico o bicíclico, un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico o un grupo heterocíclico no aromático monocíclico o bicíclico. Los sustituyentes adecuados para estos grupos son como se proporcionan en la sección que describe sustituyentes adecuados para el grupo heteroarilo, monocíclico o bicíclico, el grupo arilo, monocíclico o bicíclico, el grupo heteroarilo, monocíclico o bicíclico y el grupo heterocíclico no aromático monocíclico o bicíclico. Los sustituyentes preferidos para un átomo de carbono sustituible del anillo de un grupo representado por B son R^{14} . Preferiblemente, B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} . Más preferiblemente, B es un grupo fenilo representado por la siguiente fórmula estructural:



t es 0, 1, 2, 3 ó 4, preferiblemente 0-2 y más preferiblemente 0-1.

Cada R^{14} es independientemente alquilo C_1 - C_4 , haloalquilo C_1 - C_4 , haloalcoxi C_1 - C_4 , R^{14a} , R^{14b} , $-T-R^{14a}$, $-T-R^{14b}$, $-V-T-R^b$, $-V-T-R^{14a}$, $-V_1-T-R^{14a}$ o $-V_1-T-R^{14b}$. Preferiblemente, cada R^{14} es independientemente halo, alquilo C_1 -3, haloalquilo C_1 -3, hidroxilo, alcoxi C_1 -3, haloalcoxi C_1 -3, $-NO_2$, $-CN$, amina, alquilamina C_1 -3, dialquilamina C_1 -3, hidroxialquilo C_1 -3 o aminoalquilo C_1 -3. R^{14} es independientemente halo, alquilo C_1 -3, haloalquilo C_1 -3, hidroxilo, alcoxi C_1 -3, haloalcoxi C_1 -3, $-NO_2$, $-CN$, amina, alquilamina C_1 -3, dialquilamina C_1 -3, hidroxialquilo C_1 -3 o aminoalquilo C_1 -3.

V es -O-, -N(R)-, -C(O)N(R)- o -S(O)₂N(R)-.

V₁ es -S(O)₂, -C(O)-, -N(R)C(O)- o -N(R)SO₂-.

T es un alquileo C₁-C₄ opcionalmente sustituido. Los ejemplos de sustituyentes adecuados para el grupo alquileo representado por T incluyen
 5 haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo.

T₁ es un alquileo C₂-C₄ opcionalmente sustituido. Los ejemplos de
 10 sustituyentes adecuados para el grupo alquileo representado por T₁ incluyen haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo.

15 Cada R^{14a} se selecciona independientemente entre -OR^{15a}, -SR^{15a}, -C(O)N(R¹⁶)₂, -C(O)R¹⁵, -CO₂R¹⁵, -SO₂R^{15a}, -S(O)R^{15a}, -SO₂N(R¹⁶)₂, un grupo arilo o heteroarilo, monocíclico, opcionalmente sustituido, o un grupo heterocíclico no aromático monocíclico, opcionalmente sustituido. Los sustituyentes adecuados para el grupo arilo o heteroarilo monocíclico y el grupo heterocíclico no aromático
 20 monocíclico representado por R^{14a} son como se proporcionan en la siguiente sección que describe sustituyentes adecuados para un arilo, heteroarilo, y un grupo heterocíclico no aromático respectivamente.

Cada R^{14b} se selecciona independientemente entre halo, -OH, -SH, -CN, -NO₂, -N(R¹⁶)₂, -N(R¹⁶)C(O)R¹⁵, -N(R¹⁶)CO₂R^{15a}, -N(R¹⁶)C(O)N(R¹⁶)₂, -OC(O)R¹⁵, -
 25 OC(O)N(R¹⁶)₂ o -N(R¹⁶)SO₂R^{15a}.

Cada R¹⁵ es independientemente hidrógeno o un grupo alifático C₁₋₆.

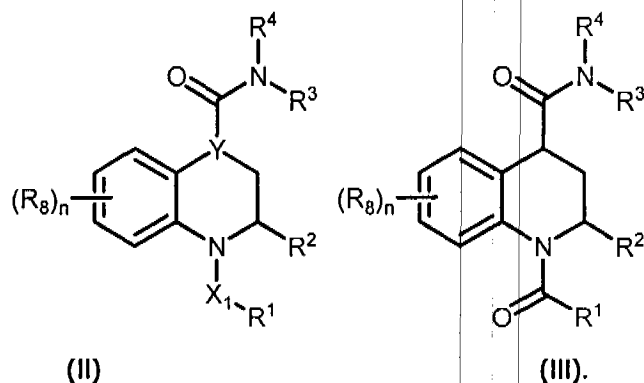
Cada R^{15a} es un grupo alifático C₁₋₆.

Cada R¹⁶ se selecciona independientemente entre hidrógeno, un grupo alifático C₁₋₆, -CO₂R^{15a}, -SO₂R^{15a} o -C(O)R¹⁵, o N(R¹⁶)₂ es un grupo heteroarilo
 30 monocíclico o heterocíclico no aromático monocíclico.

En una realización preferida, para compuestos de fórmula (I),

R¹ es un grupo opcionalmente sustituido seleccionado entre un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico, un grupo heterocíclico no aromático, monocíclico o bicíclico, o un grupo carbocíclico, no
 35 aromático, monocíclico o bicíclico, e Y es >CR^x.

En otra realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III):



- 5 Los valores y los valores preferidos para las variables de las Fórmulas estructurales (II) y (III) son como se ha descrito anteriormente para la Fórmula estructural (I). Preferiblemente, en la Fórmula estructural (II), R¹ es un grupo opcionalmente sustituido seleccionado entre un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico, un grupo heterocíclico no aromático, monocíclico o bicíclico, o un grupo carbocíclico, no aromático, monocíclico o
- 10 bicíclico, e Y es >CR^x-. Preferiblemente, en la Fórmula estructural (III), R¹ es un grupo opcionalmente sustituido seleccionado entre un arilo monocíclico o bicíclico, un heteroarilo monocíclico o bicíclico, un grupo heterocíclico no aromático, monocíclico o bicíclico, o un grupo carbocíclico, no aromático, monocíclico o
- 15 bicíclico.

Se apreciará que son de interés ciertas otras realizaciones:

En una primera realización preferida, un compuesto de la invención se representa por las Fórmulas estructurales (II) y (III), en las que:

- R¹ es un grupo arilo monocíclico o bicíclico o heteroarilo opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos opcionalmente sustituido en
- 20 uno o más de los átomos de carbono sustituibles del anillo con R¹¹; y
- 25 los valores y los valores preferidos para R¹¹ y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se ha descrito anteriormente para la Fórmula estructural (I).

- En una segunda realización preferida, un compuesto de la invención se representa por las Fórmulas estructurales (II) y (III), en las que:
- 30

R¹ es un grupo arilo o heteroarilo opcionalmente sustituido monocíclico o bicíclico, opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y

los valores y los valores preferidos para R¹¹, R¹⁴, y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una tercera realización preferida, un compuesto de la invención se representa por las Fórmulas estructurales (II) y (III), en las que:

R¹ es un grupo arilo o heteroarilo monocíclico o bicíclico, opcionalmente sustituido, opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹;

R² es alquilo C₁-C₂ o cicloalquilo C₃-C₆;

R³ es un grupo alquilo C₁-C₄;

R⁴ es -(CH₂)_m-B;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y

los valores y los valores preferidos para m, R¹¹, R¹⁴ y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una cuarta realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III) en la que:

R¹ es un grupo arilo monocíclico o bicíclico o heteroarilo sustituido con -T₂-V₂-T₃-M-R^Y y además está opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos sustituido con -T₂-V₂-T₃-M-R^Y, y cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹; y

los valores y los valores preferidos para R^Y, M, V₂, T₂, T₃, R¹¹ y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I). Preferiblemente, M y T₂ están ausentes.

En una quinta realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

R¹ es un grupo arilo monocíclico o bicíclico o heteroarilo sustituido con -T₂-V₂-T₃-M-R^Y y además está opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos sustituido con -T₂-V₂-T₃-M-R^Y, y cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y

los valores y los valores preferidos para R^Y, M, V₂, T₂, T₃, R¹¹, R¹⁴ y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I). Preferiblemente, M y T₂ están ausentes.

En una sexta realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

R¹ es un grupo arilo monocíclico o bicíclico o heteroarilo sustituido con -T₂-V₂-T₃-M-R^Y y además está opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹¹. Preferiblemente, R¹ es un fenilo, piridilo, pirimidilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, furanilo, tiofenilo, imidazolilo, pirazolilo, pirrolilo, tetrazolilo, indolilo, benzotriazolilo, benzotiazolilo, bencimidazolilo, benzotienilo, benzofuranilo, benzomorfolinilo o benzopiperazinilo, cada uno de ellos

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sustituido con $-T_2-V_2-T_3-M-R^Y$, y cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{11} ;

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

R^3 es un grupo alquilo C_1-C_4 ;

5 R^4 es $-(CH_2)_m-B$;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ; y

10 los valores y los valores preferidos para m , R^Y , M , V_2 , T_2 , T_3 , R^{11} , R^{14} y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I). Preferiblemente, M y T_2 están ausentes.

En una séptima realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

15 R^1 es un grupo arilo o heteroarilo monocíclico, sustituido con $-V_3-R^{22}$. El grupo arilo o heteroarilo representado por R^1 está además opcionalmente sustituido en uno o más átomos de carbono sustituibles representados con R^{11} ;

los valores y los valores preferidos para V_3 , R^{11} , R^{22} y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I).

20 En una octava realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

R^1 es un grupo arilo o heteroarilo monocíclico, sustituido con $-V_3-R^{22}$. El grupo arilo o heteroarilo representado por R^1 está además opcionalmente sustituido en uno o más átomos de carbono sustituibles representados con R^{11} ;

25 B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ; y

30 los valores y los valores preferidos para V_3 , R^{11} , R^{14} , R^{22} y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I).

En una novena realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

35 R^1 es un grupo arilo o heteroarilo monocíclico, sustituido con $-V_3-R^{22}$. El grupo arilo o heteroarilo representado por R^1 está además opcionalmente sustituido en uno o más átomos de carbono sustituibles representados con R^{11} ;

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

R³ es un grupo alquilo C₁-C₄;

R⁴ es -(CH₂)_m-B;

5 B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y

los valores y los valores preferidos para m, V₃, R¹¹, R¹⁴, R²² y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I).

10 En una décima realización preferida, un compuesto de la invención se representa por la Fórmula estructural (II) o (III), en la que:

R¹ es un grupo arilo o heteroarilo monocíclico, sustituido con -V₃-R²². El grupo arilo o heteroarilo representado por R¹ está además opcionalmente sustituido en uno o más átomos de carbono sustituibles representados con R¹¹;

R² es alquilo C₁-C₂ o cicloalquilo C₃-C₆;

15 R³ es un grupo alquilo C₁-C₄;

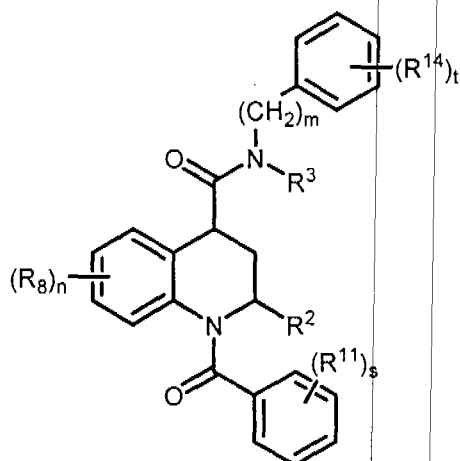
R⁴ es -(CH₂)_m-B;

R²² es un grupo heterocíclico no aromático monocíclico, opcionalmente sustituido;

20 B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y

los valores y los valores preferidos para m, V₃, R¹¹, R¹⁴ y el resto de las variables de las Fórmulas estructurales (II) y (III) son como se han descrito para la Fórmula estructural (I).

25 En la primera a décima realizaciones preferidas descritas inmediatamente antes, preferiblemente Y en la Fórmula estructural (II) es >CR^x-En otra realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (IV):



(IV).

Los valores y los valores preferidos para las variables de la Fórmula estructural (IV) son como se ha descrito anteriormente para la Fórmula estructural (I).

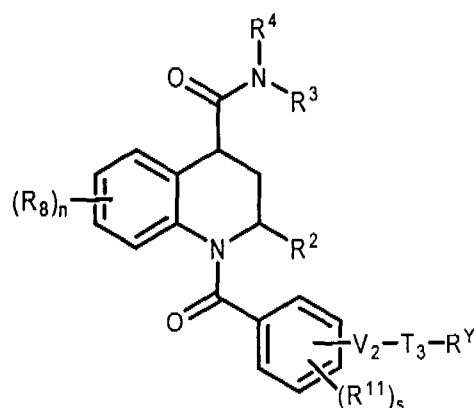
- 5 En una undécima realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (IV), en la que:

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

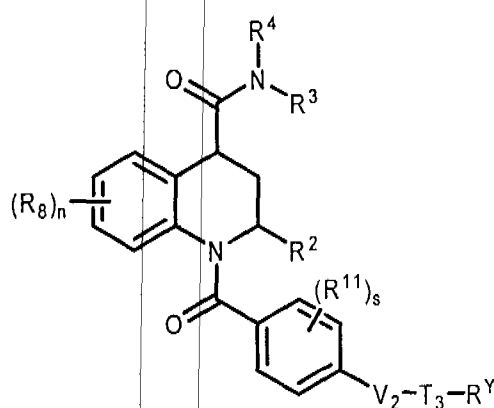
R^3 es un grupo alquilo C_1-C_4 ; y

- 10 los valores y los valores preferidos para el resto de las variables de la Fórmula estructural (IV) son como se ha descrito anteriormente para la Fórmula estructural (I).

En otra realización preferida adicional, un compuesto de la presente invención se representa por la Fórmula estructural (V) o (VI):



(V)



(VI).

Los valores y los valores preferidos para las variables de las Fórmulas estructurales (V) y (VI) son como se ha descrito anteriormente para la Fórmula estructural (I).

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En una décimosegunda realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (V) o (VI), en la que R² es alquilo C₁-C₂ o cicloalquilo C₃-C₆; R³ es un grupo alquilo C₁-C₄; R⁴ es -(CH₂)_m-B; B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴; y los valores y los valores preferidos para m, R¹⁴ y el resto de las variables de la Fórmula estructural (V) y (VI) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una decimotercera realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (V) o (VI), en la que:

R² es alquilo C₁-C₂ o cicloalquilo C₃-C₆;

R³ es un grupo alquilo C₁-C₄;

R⁴ es -(CH₂)_m-B;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R¹⁴;

V₂ es un enlace covalente o -O-;

T₃ es un alquileo C₁₋₆ de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo;

R^y es -C(O)OR¹⁸, -C(O)N(R¹⁹)₂, -NR¹⁹C(O)R¹⁸, -NR¹⁹C(O)OR^{18a}, -S(O)₂ N(R¹⁹)₂, -NR¹⁹S(O)₂R^{18a}, -NR¹⁹C(O)N(R¹⁹)₂, un grupo heterocíclico no aromático opcionalmente sustituido representado por R²⁰ o un grupo heteroarilo opcionalmente sustituido representado por R²¹. Preferiblemente, R^y es -C(O)OR¹⁸, -C(O) N(R¹⁹)₂, un tetrazolilo opcionalmente N-sustituido o un imidazolilo opcionalmente N-sustituido;

cada R¹⁸ es independientemente H o alquilo C₁-C₃. Preferiblemente, cada R¹⁸ es independientemente -H, metilo o etilo;

cada R^{18a} es independientemente alquilo C₁-C₃. Preferiblemente, cada R¹⁸ es independientemente metilo o etilo;

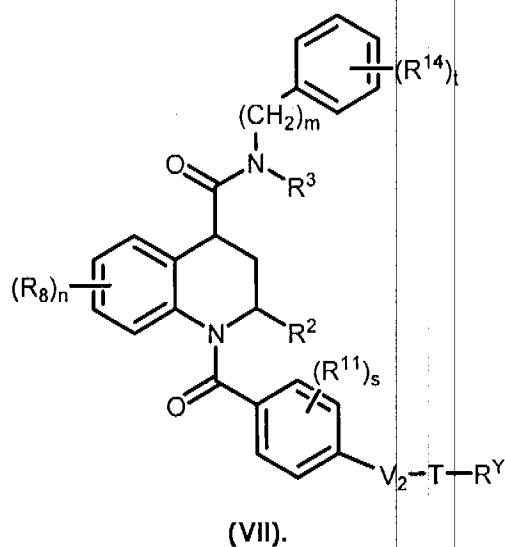
cada R¹⁹ es H o alquilo o NR^{19/2} es un grupo heterocíclico no aromático que contiene nitrógeno. Preferiblemente, cada R¹⁹ es independientemente -H, metilo o etilo;

R^{20} es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranoilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido;

5 R^{21} es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido; y

los valores y los valores preferidos para m , R^{14} y el resto de las variables de la Fórmula estructural (V) y (VI) son como se ha descrito anteriormente para la Fórmula estructural (I).

10 En otra realización preferida adicional, un compuesto de la presente invención se representa por la Fórmula estructural (VII):



Los valores y los valores preferidos para las variables de la Fórmula estructural (VII) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una decimocuarta realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (VII), en la que:

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

R^3 es un grupo alquilo C_1-C_4 ;

20 V_2 es un enlace covalente o $-O-$;

T_3 es un alquilenos C_{1-6} de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N -sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo;

R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^{20} o un grupo heteroarilo opcionalmente sustituido representado por R^{21} . Preferiblemente, R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, un tetrazolilo opcionalmente *N*-sustituido o un imidazolilo opcionalmente *N*-sustituido;

cada R^{18} es independientemente H o alquilo C_1 - C_3 . Preferiblemente, cada R^{18} es independientemente -H, metilo o etilo;

cada R^{18a} es independientemente alquilo C_1 - C_3 . Preferiblemente, cada R^{18} es independientemente metilo o etilo;

cada R^{19} es H o alquilo o $N(R^{19})_2$ es un grupo heterocíclico no aromático que contiene nitrógeno. Preferiblemente, cada R^{19} es independientemente -H, metilo o etilo;

R^{20} es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido;

R^{21} es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido; y

los valores y los valores preferidos para el resto de las variables de la Fórmula estructural (V) y (VI) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una decimoquinta realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (VII):

R^2 es alquilo C_1 - C_2 o cicloalquilo C_3 - C_6 ;

R^3 es un grupo alquilo C_1 - C_4 ;

V_2 es un enlace covalente o -O-;

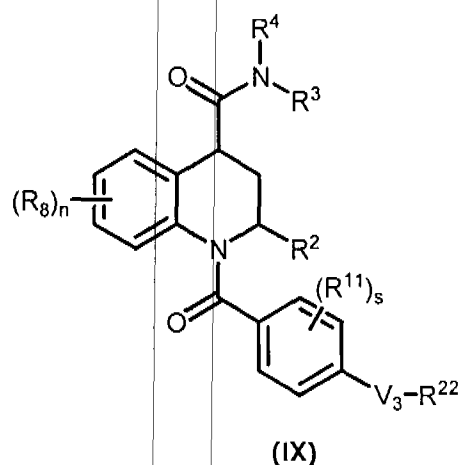
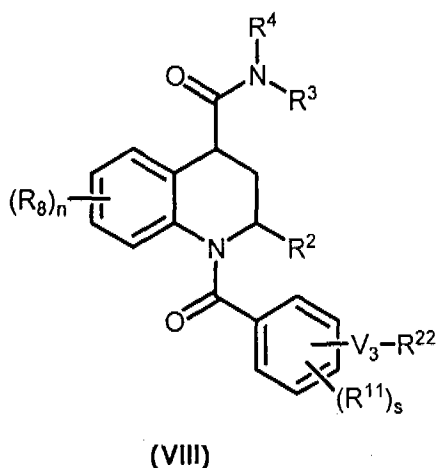
T_3 es un alquilenos C_{1-6} de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente *N*-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo;

R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, tetrazolilo opcionalmente *N*-sustituido o imidazolilo opcionalmente *N*-sustituido;

R^{18} y cada R^{19} son independientemente -H, metilo o etilo; y

los valores y los valores preferidos para el resto de las variables de la Fórmula estructural (V) y (VI) son como se ha descrito anteriormente para la Fórmula estructural (I).

En otra realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (VIII) o (IX):



Los valores y los valores preferidos para las variables de la Fórmula estructural (VIII) y (IX) son como se ha descrito anteriormente para la Fórmula estructural (I).

En una decimosexta realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (VIII) o (IX) en la que: R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ; R^3 es un grupo alquilo C_1-C_4 ; R^4 es $-(CH_2)_m-B$; R^{22} es un grupo heterocíclico no aromático monocíclico, opcionalmente sustituido; B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ; y los valores y los valores preferidos para m, R^{14} y el resto de las variables de las Fórmulas estructurales (VIII) y (IX) son como se han descrito para la Fórmula estructural (I).

En una decimoséptima realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (VIII) o (IX), en la que:

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

R^3 es un grupo alquilo C_1-C_4 ;

R^4 es $-(CH_2)_m-B$;

B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ;

R^{22} es un ciclohexanilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo,

- pirrolidinilo, pirrolidinonilo, piperazinilo, S,S-dióxido de isotiazolidinilo o piperidinilo opcionalmente sustituido. Preferiblemente, R^{22} es oxazolidinilo, tiazolidinilo, tetrahydrofuranoilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo, cada uno de ellos opcionalmente sustituido
- 5 en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$ o $-C(O)N(R^{23})_2$, y cada uno de ellos opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ o $-(CH_2)_qCH(CH_3)CO_2R^{23}$; y
- 10

los valores y los valores preferidos para m, c, R^{14} , R^{23} y el resto de las variables de las Fórmulas estructurales (VIII) y (IX) son como se han descrito para la Fórmula estructural (I).

- En una decimoctava realización preferida, un compuesto de la presente
- 15 invención se representa por la Fórmula estructural (VIII) o (IX), en la que:

V está ausente o -O-;

R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ;

R^3 es un grupo alquilo C_1-C_4 ;

R^4 es $-(CH_2)_m-B$;

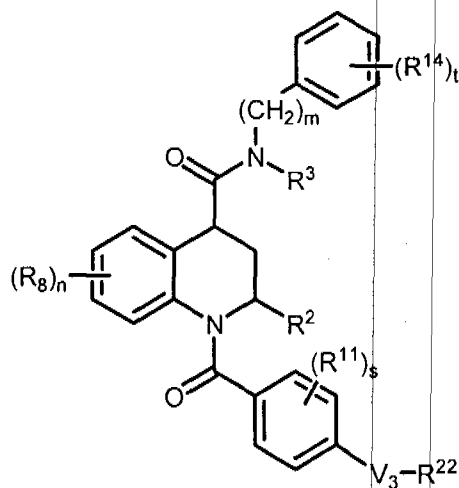
- 20 B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ;

- R^{22} es un ciclohexanilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo, S,S-dióxido de isotiazolidinilo o piperidinilo opcionalmente sustituido. Preferiblemente, R^{22} es oxazolidinilo, tiazolidinilo, tetrahydrofuranoilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo, cada uno de ellos opcionalmente sustituido
- 25 en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$ o $-C(O)N(R^{23})_2$, y cada uno de ellos opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ o $-(CH_2)_qCH(CH_3)CO_2R^{23}$; y
- 30
- 35

los valores y los valores preferidos para m , c , R^{14} , R^{23} y el resto de las variables de las Fórmulas estructurales (VIII) y (IX) son como se han descrito para la Fórmula estructural (I).

En ciertas realizaciones preferidas, V_3 está ausente.

- 5 En otra realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (X):



(X).

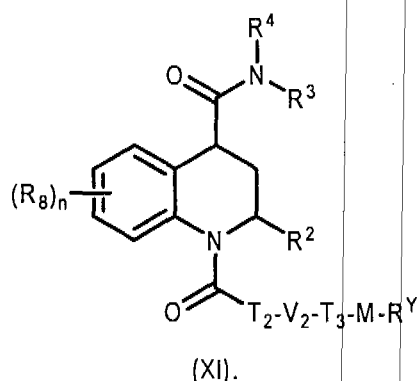
- 10 en la que los valores y los valores preferidos para las variables de la Fórmula estructural (X) son como se han descrito para la Fórmula estructural (I). En ciertas realizaciones preferidas, V_3 está ausente.

En una decimonovena realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (X) en la que:

V está ausente o $-O-$;

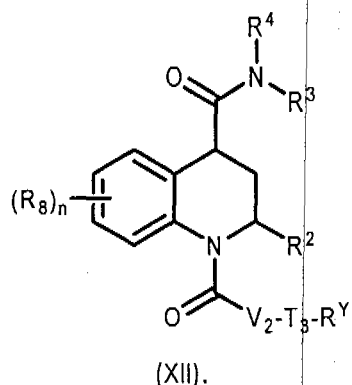
- 15 R^2 es alquilo C_1-C_2 o cicloalquilo C_3-C_6 ; R^3 es un grupo alquilo C_1-C_4 ; R^{22} es oxazolidinilo, tiazolidinilo, tetrahydrofuranoilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo, cada uno de ellos opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-OC(O)R^{23}$ o $-C(O)N(R^{23})_2$, y cada uno de ellos opcionalmente sustituido en cualquier átomo de
- 20 nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{23}$, $-C(O)R^{23}$, $-(CH_2)_qCO_2H$, $-(CH_2)_qC(O)N(R^{23})_2$, $-(CH_2)_qCH(CH_3)CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CON(R^{23})_2$, $-(CH_2)_qC(CH_3)_2CO_2R^{23}$ o $-(CH_2)_qCH(CH_3)CO_2R^{23}$; y los valores y los valores preferidos para m , c , R^{14} , R^{23} y el resto de las variables de las Fórmulas estructurales (X) son
- 25 como se han descrito para la Fórmula estructural (I).

En otra realización preferida adicional, un compuesto de la presente invención se representa por la Fórmula estructural (X):



en la que los valores y los valores preferidos para las variables de la Fórmula estructural (XI) son como se han descrito para la Fórmula estructural (I).

- 5 En otra realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (XII):



- 10 en la que los valores y los valores preferidos para las variables de la Fórmula estructural (XII) son como se han descrito para la Fórmula estructural (I).

En una vigésima realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (XII), en la que:

V₂ es un enlace covalente o -O-;

- 15 T₃ es un alquileo C₁₋₆ de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina o un hidroxilo;

- 20 R^Y es -C(O)OR¹⁸, -C(O)N(R¹⁹)₂, -NR¹⁹C(O)R¹⁸, -NR¹⁹C(O)OR^{18a}, -S(O)₂N(R¹⁹)₂, -NR¹⁹S(O)₂R^{18a}, -NR¹⁹C(O)N(R¹⁹)₂, un grupo heterocíclico no aromático opcionalmente sustituido representado por R²⁰ o un grupo heteroarilo opcionalmente sustituido representado por R²¹;

cada R¹⁸ es independientemente H o alquilo C₁-C₃;

cada R^{18a} es independientemente alquilo C_1-C_3 ;

cada R^{19} es H o alquilo o $N(R^{19})_2$ es un grupo heterocíclico no aromático que contiene nitrógeno;

5 R^{20} es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido; y

R^{21} es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido;

10 y los valores y los valores preferidos para el resto de las variables de la Fórmula estructural (XII) son como se han descrito para la Fórmula estructural (I).

En una vigésimo primera realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (XII), en la que:

15 B es un grupo arilo o heteroarilo monocíclico o un grupo cicloalquilo monocíclico, cada uno de ellos opcionalmente sustituido en uno o más de los átomos de carbono sustituibles del anillo con R^{14} ;

V_2 es un enlace covalente o $-O-$;

20 T_3 es un alquilenos C_{1-6} de cadena lineal opcionalmente sustituido en uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, un grupo heterocíclico no aromático espiro, que contiene nitrógeno, opcionalmente N-sustituido, un grupo heterocíclico no aromático espiro, que contiene oxígeno, una amina, alquilamina, dialquilamina, o un hidroxilo.

25 R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, $-NR^{19}C(O)R^{18}$, $-NR^{19}C(O)OR^{18a}$, $-S(O)_2N(R^{19})_2$, $-NR^{19}S(O)_2R^{18a}$, $-NR^{19}C(O)N(R^{19})_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^{20} o un grupo heteroarilo opcionalmente sustituido representado por R^{21} . Preferiblemente, R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, tetrazolilo opcionalmente N-sustituido o imidazolilo opcionalmente N-sustituido;

30 cada R^{18} es independientemente H o alquilo C_1-C_3 . Preferiblemente, cada R^{18} es independientemente -H, metilo o etilo;

cada R^{18a} es independientemente alquilo C_1-C_3 . Preferiblemente, cada R^{18} es independientemente metilo o etilo;

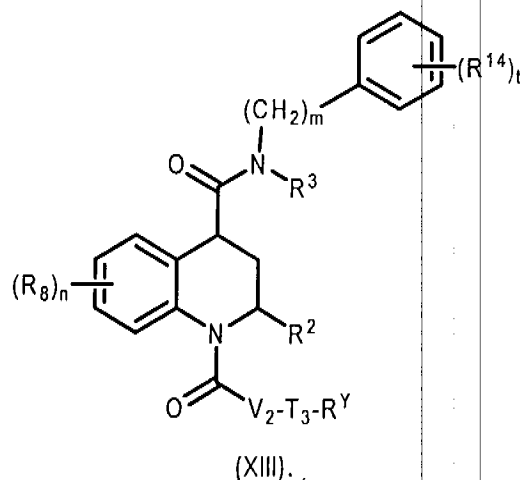
35 cada R^{19} es H o alquilo o $N(R^{19})_2$ es un grupo heterocíclico no aromático que contiene nitrógeno. Preferiblemente, cada R^{19} es independientemente -H, metilo o etilo;

R^{20} es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahydrofuranoilo, tetrahidropiranoilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido; y

- 5 R^{21} es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido;

y los valores y los valores preferidos para R^{14} y el resto de las variables de las Fórmulas estructurales (XII) son como se han descrito para la Fórmula estructural (I).

- 10 En otra realización preferida, un compuesto de la presente invención se representa por la Fórmula estructural (XIII):



- en la que V_2 , T_3 , R^Y , R^{18} , R^{18a} y R^{19} son como se han descrito para la Fórmula estructural (XII). Los valores y los valores preferidos para el resto de las variables de la
- 15 Fórmula estructural (XIII) son como se han descrito para la Fórmula estructural (I). Preferiblemente, R^Y es $-C(O)OR^{18}$, $-C(O)N(R^{19})_2$, tetrazolilo opcionalmente *N*-sustituido o imidazolilo opcionalmente *N*-sustituido; y R^{18} y cada R^{19} son independientemente -H, metilo o etilo.

- Más preferiblemente, en las Fórmulas estructurales (I)-(XIII), R^8 , R^{11} y R^{14} son
- 20 independientemente halo, alquilo C_{1-3} , haloalquilo C_{1-3} , hidroxilo, alcoxi C_{1-3} , haloalcoxi C_{1-3} , $-NO_2$, $-CN$, amina, alquilamina C_{1-3} , dialquilamina C_{1-3} , hidroxialquilo C_{1-3} o aminoalquilo C_{1-3} .

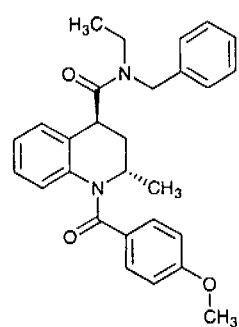
- Más preferiblemente, en las Fórmulas estructurales (III)-(XIII), R^2 y $C(O)NR^3R^4$
- son *trans*. En las Fórmulas estructurales (I) y (II), R^2 y $C(O)NR^3R^4$ son preferiblemente
- 25 *trans* cuando Y es $>C(R^x)-$.

La Tabla 1 que se muestra a continuación representa ciertos compuestos ejemplares de fórmula I.

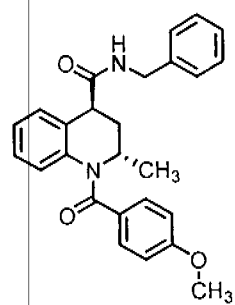
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Tabla 1. Ejemplos de compuestos de fórmula I

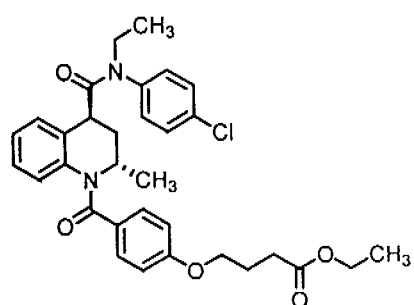
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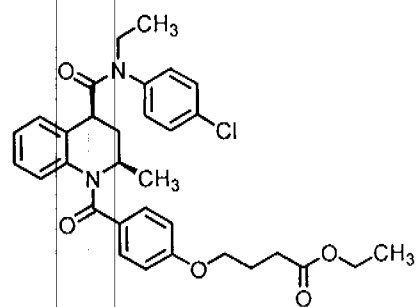
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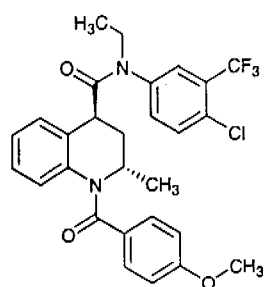
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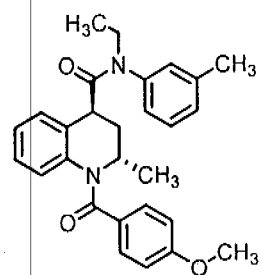
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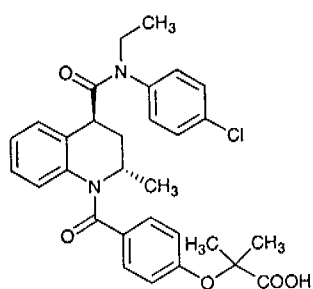
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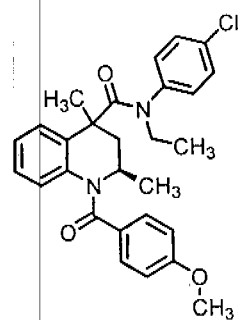
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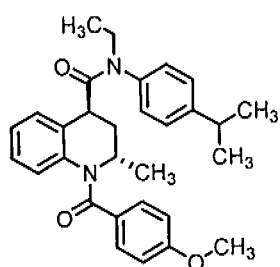
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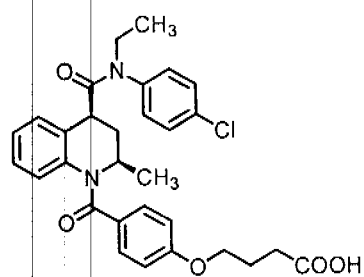
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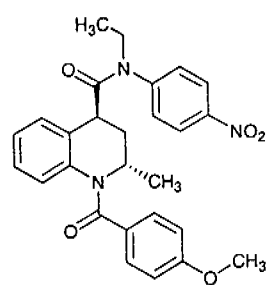
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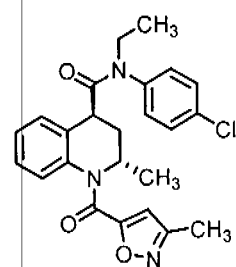
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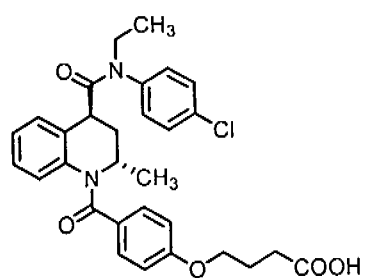
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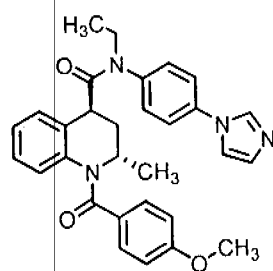
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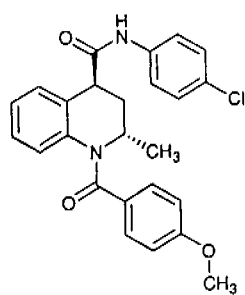
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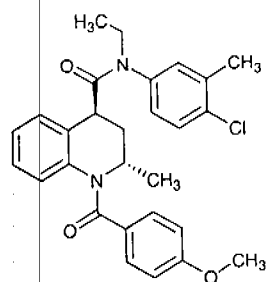
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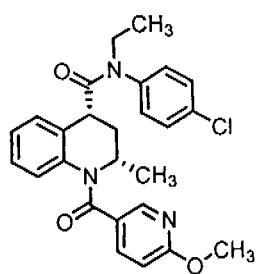
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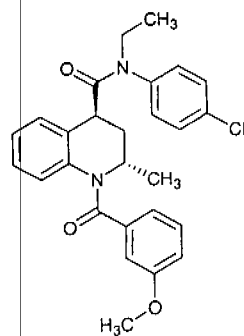
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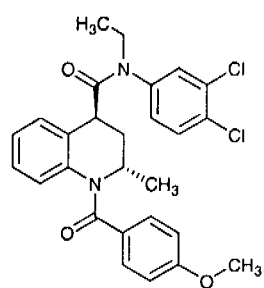


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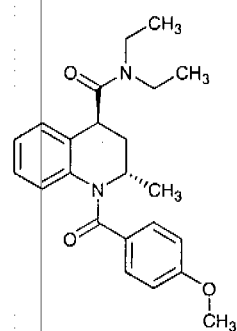


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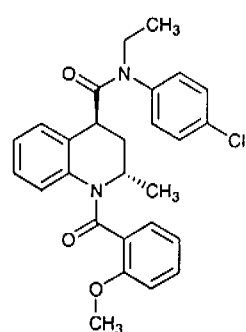
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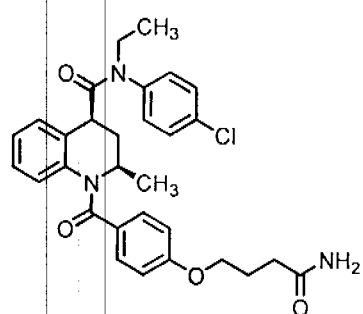
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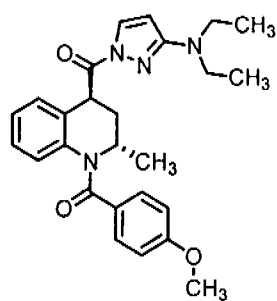
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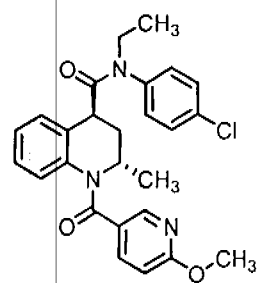
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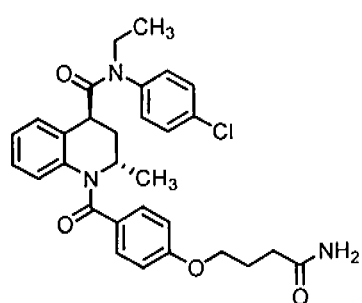


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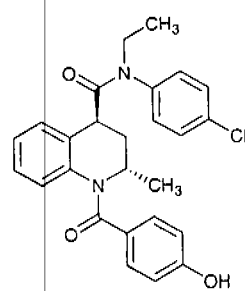


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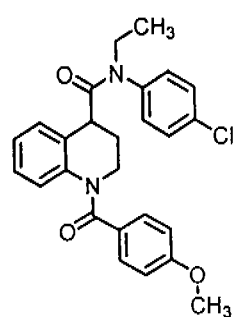
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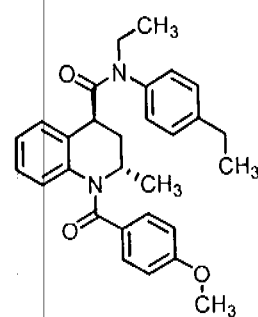
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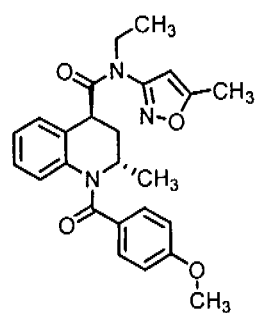
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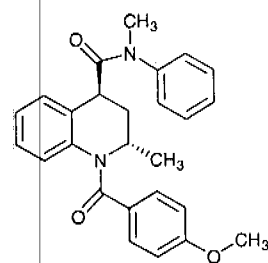
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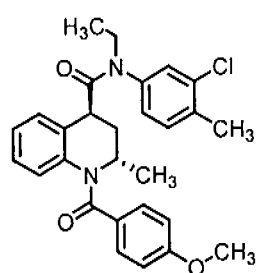


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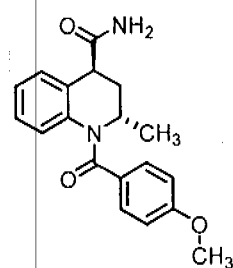


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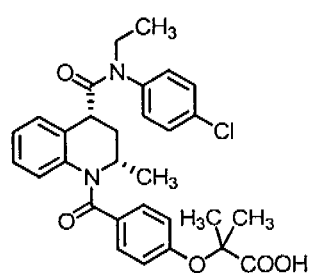
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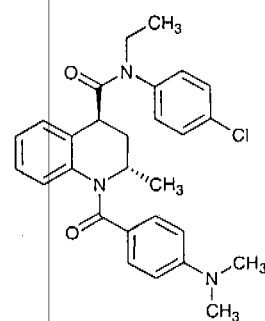
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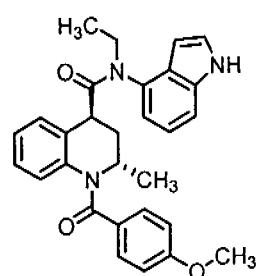
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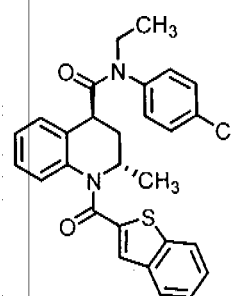
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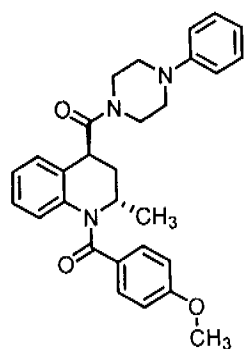


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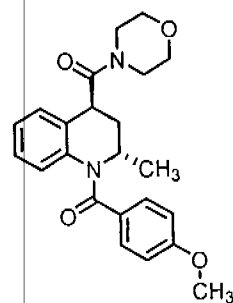


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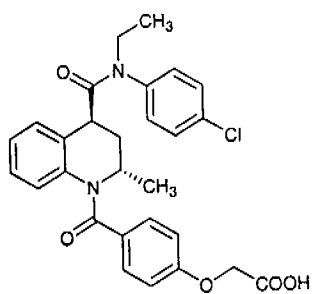
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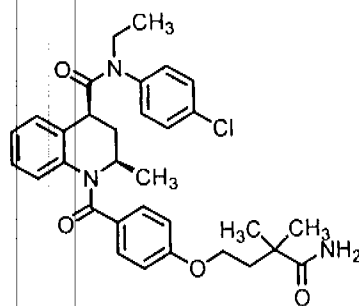
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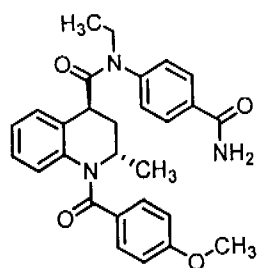
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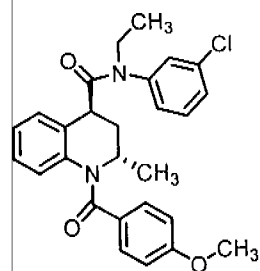
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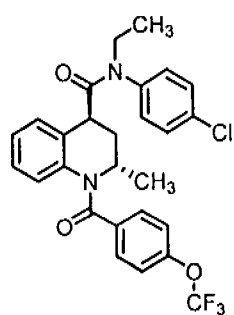
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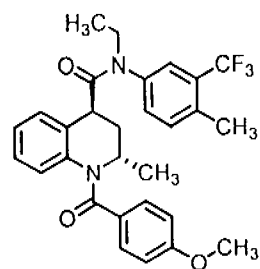
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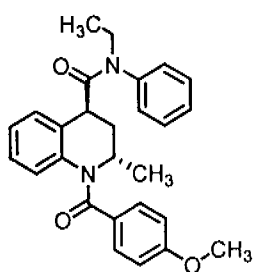
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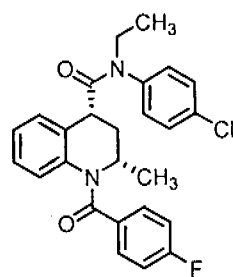
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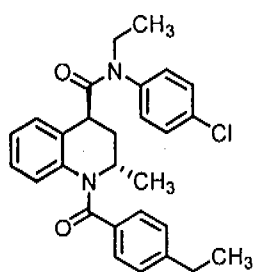
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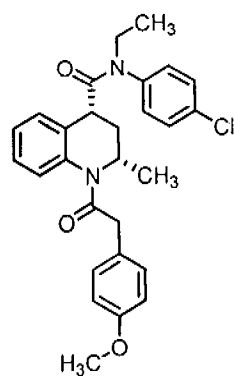
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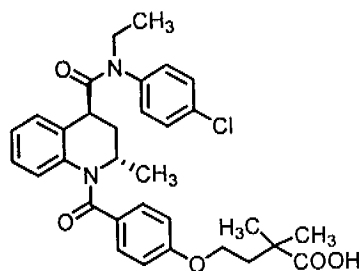
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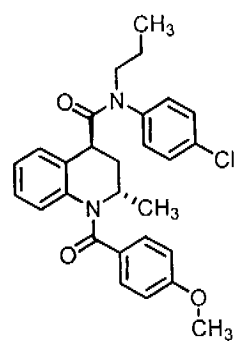
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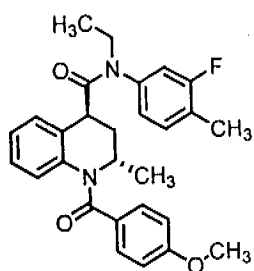
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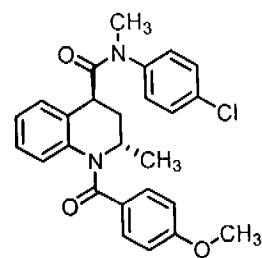
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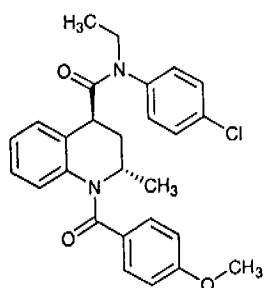
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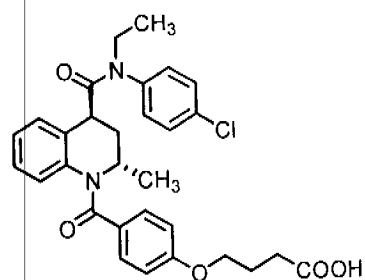
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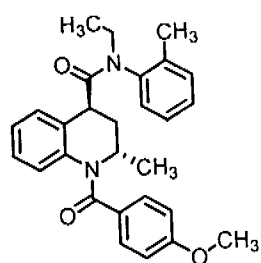
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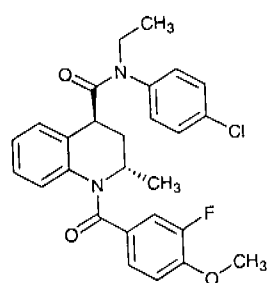
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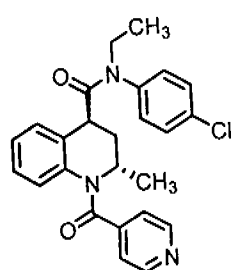
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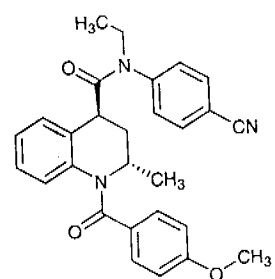
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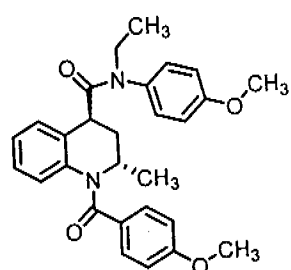
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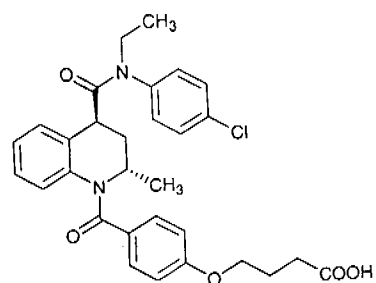
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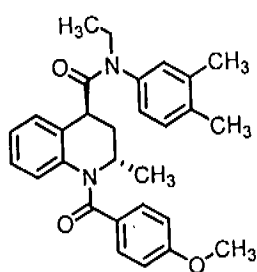
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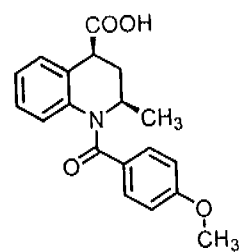
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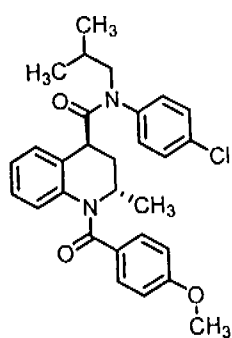
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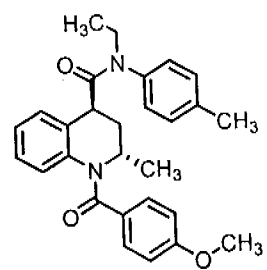
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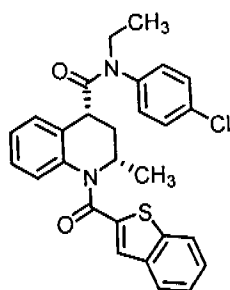
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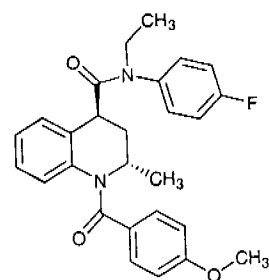
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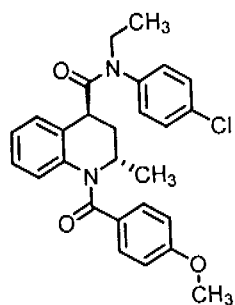
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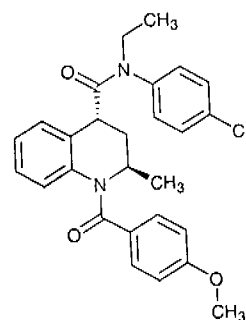
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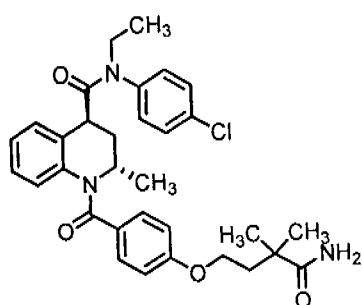
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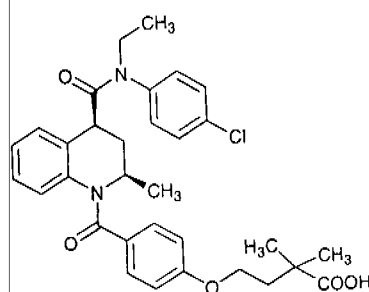
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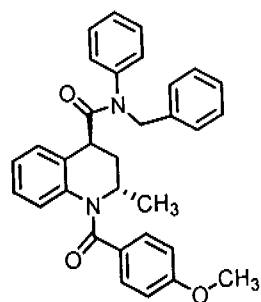
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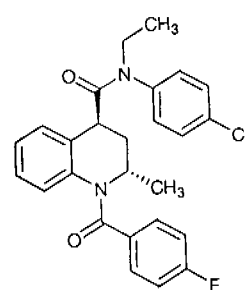
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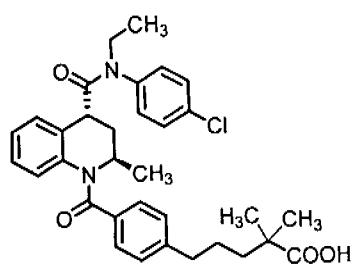
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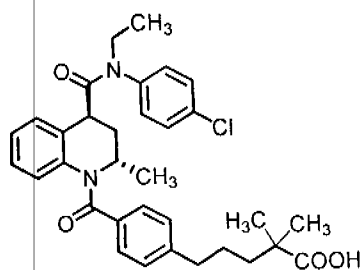
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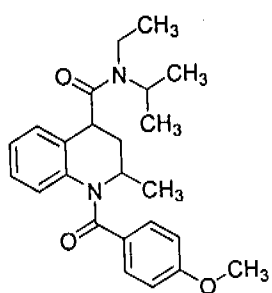
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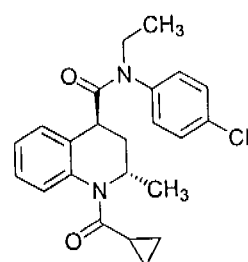
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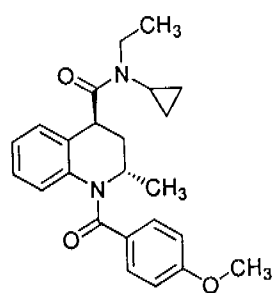
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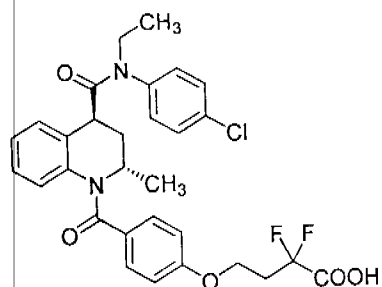
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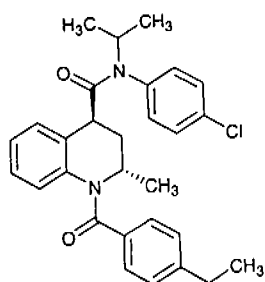
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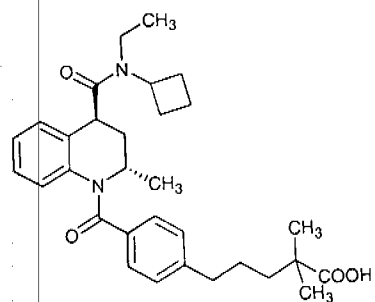
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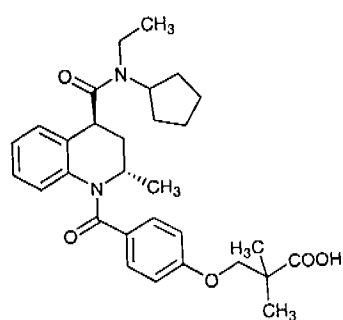
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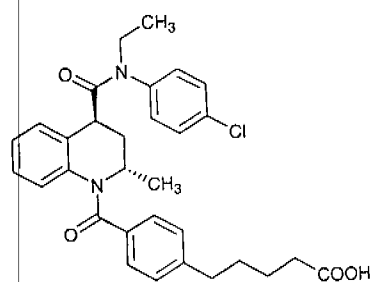
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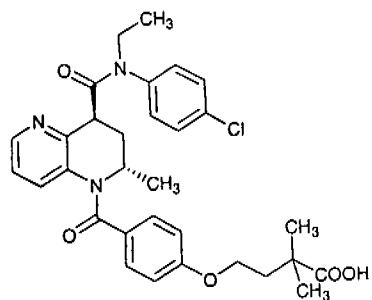
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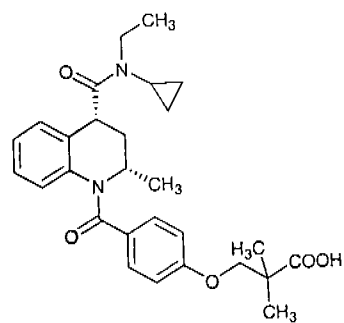
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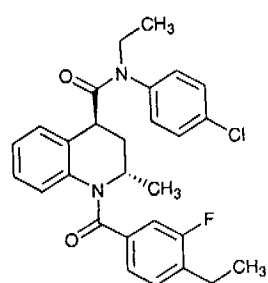
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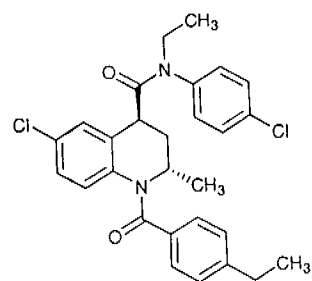
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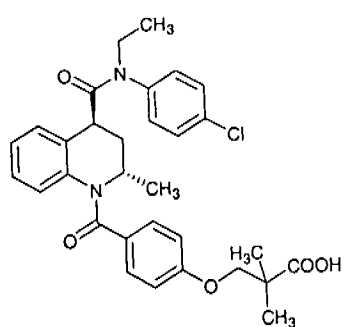
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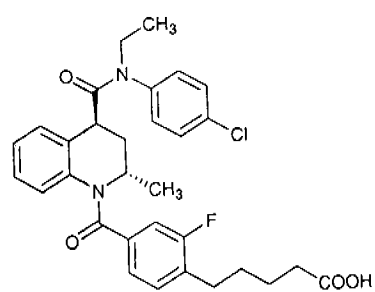
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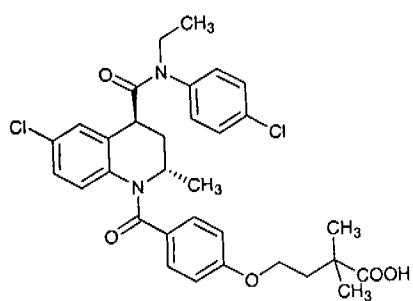
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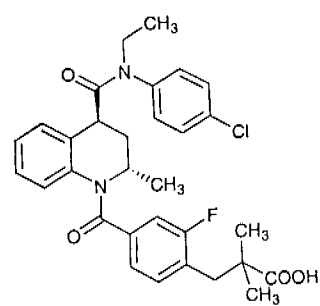
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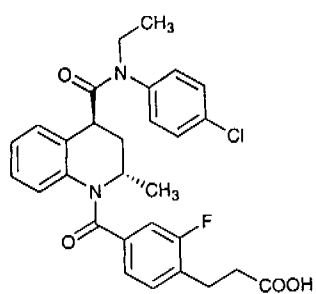
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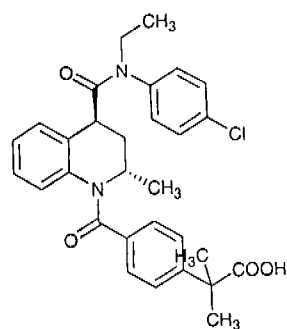
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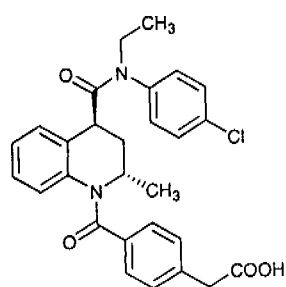
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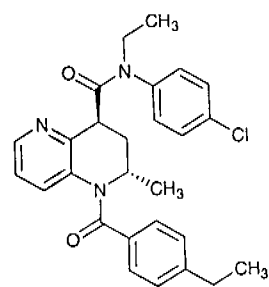
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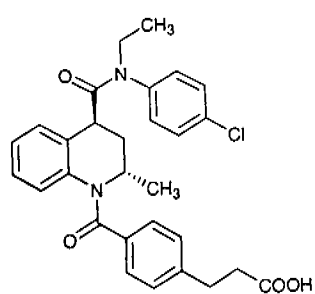
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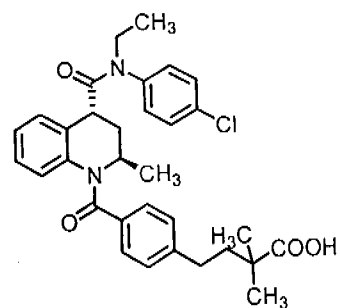
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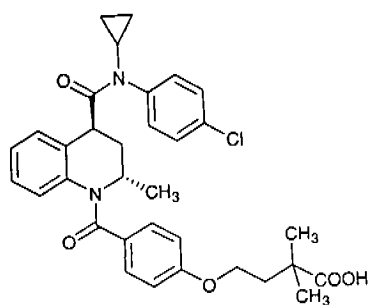
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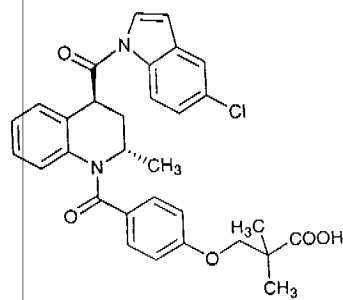
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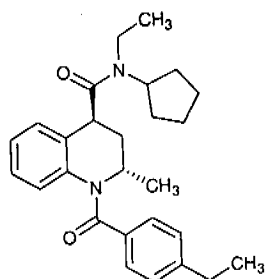
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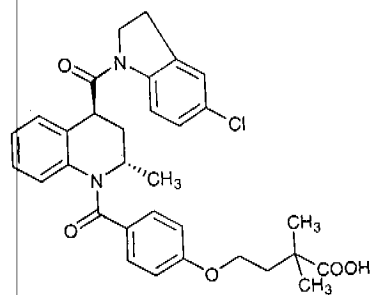
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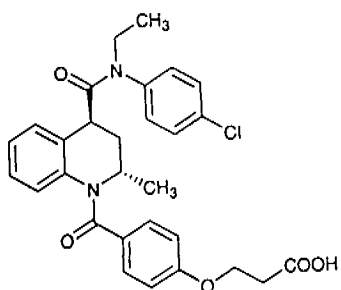
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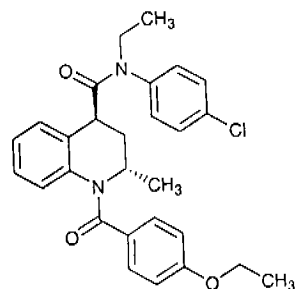
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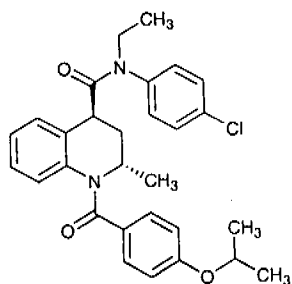
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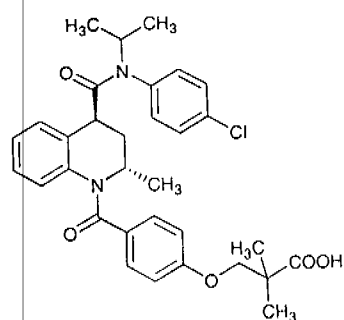
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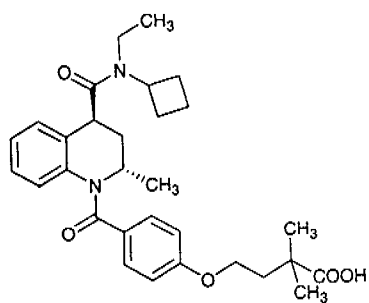
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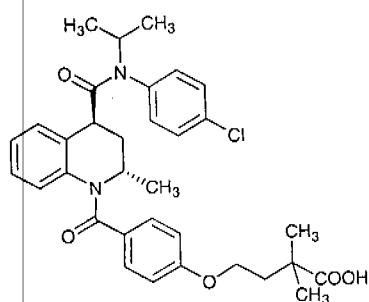
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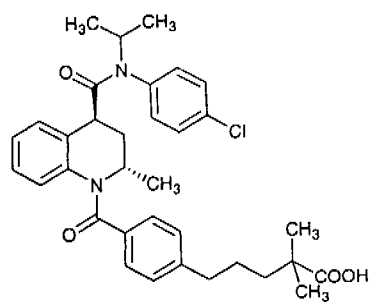
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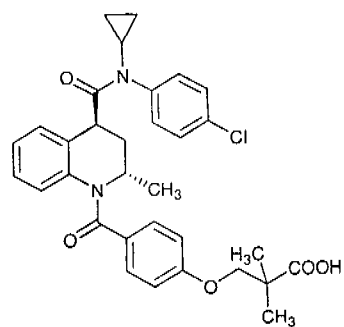
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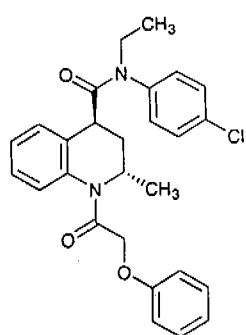
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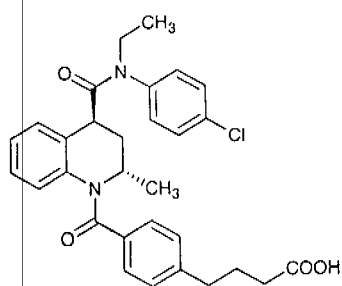
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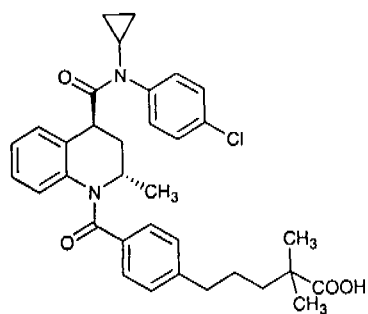
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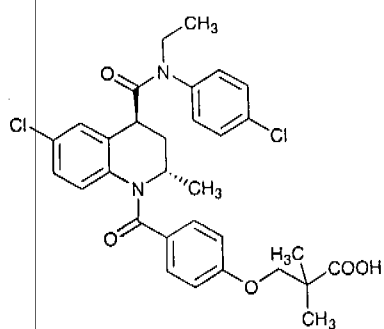
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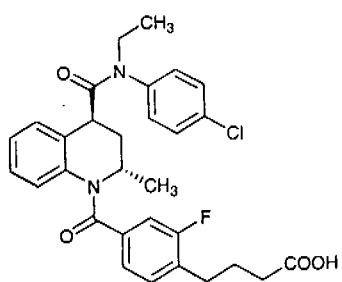
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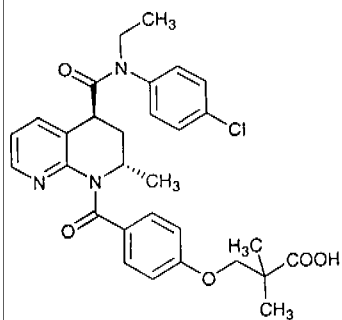
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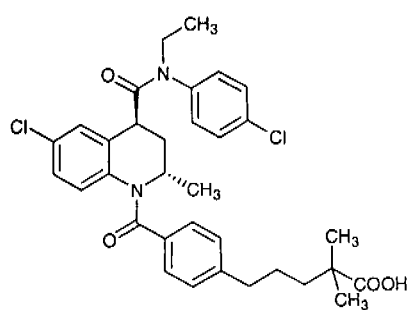
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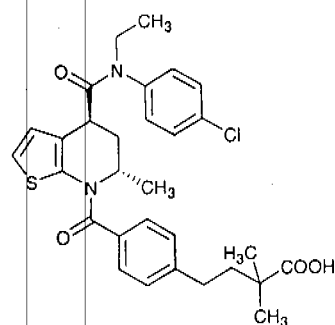
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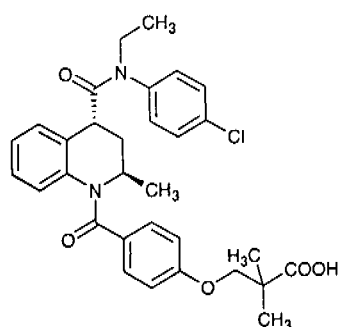
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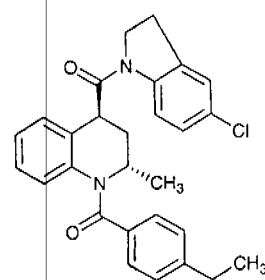
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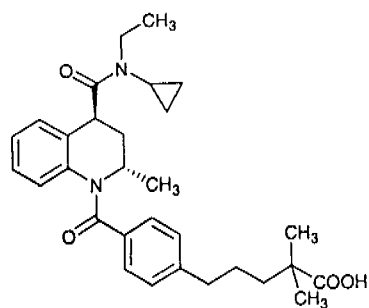
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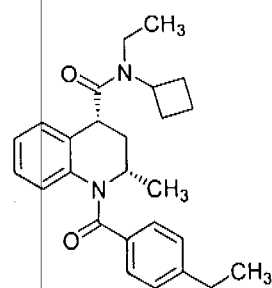
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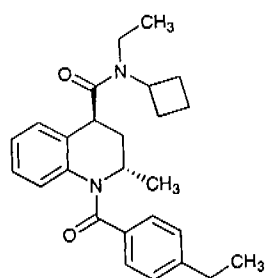
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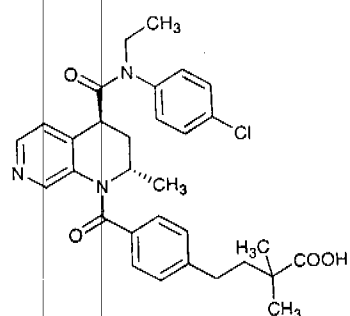
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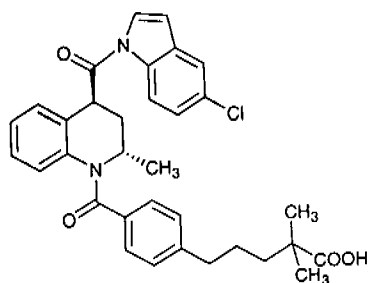
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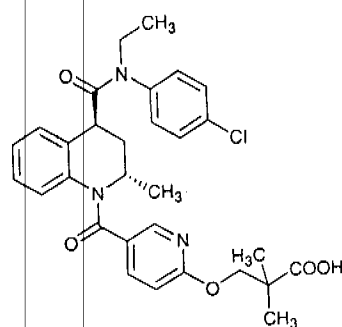
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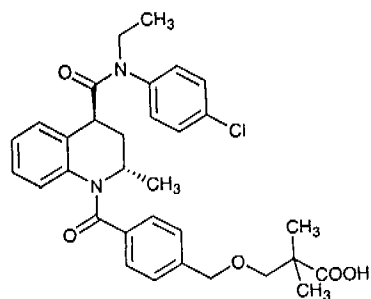
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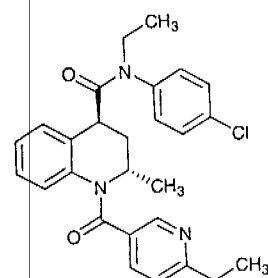
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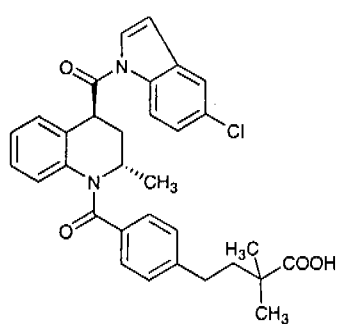
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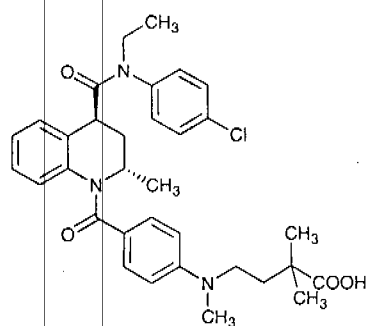
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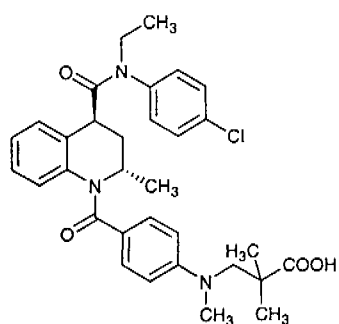
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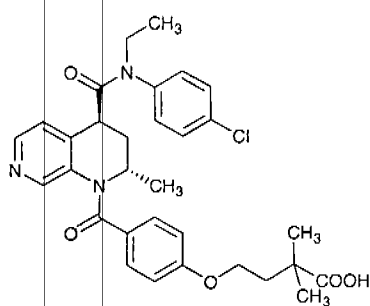
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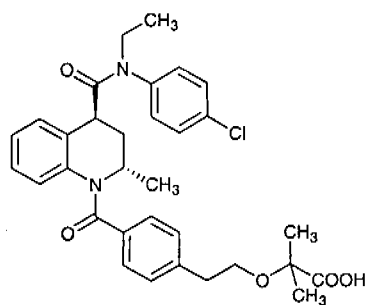
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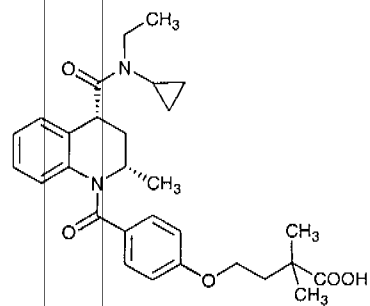
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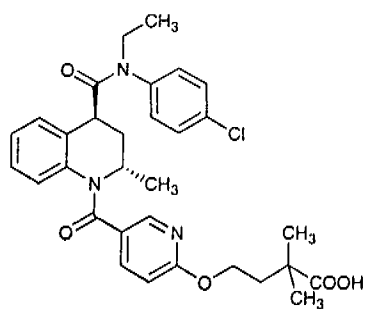
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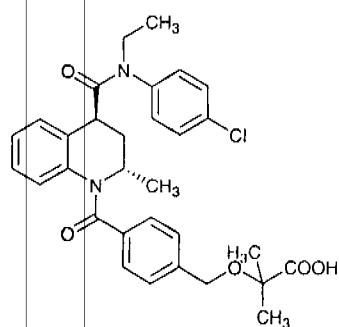
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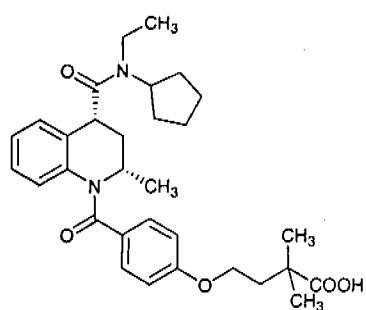
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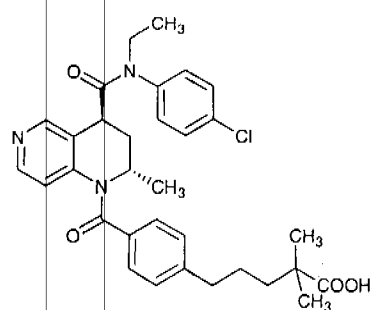
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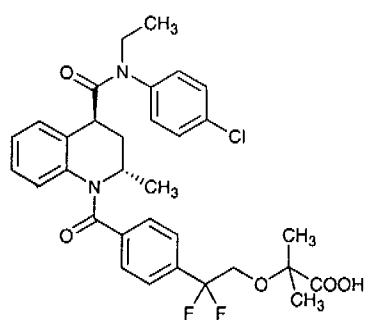
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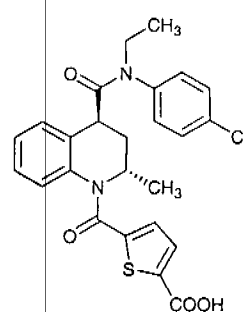
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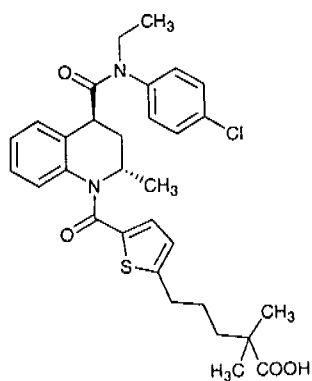


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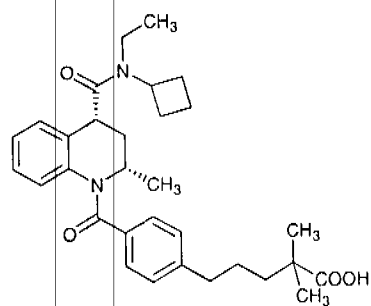


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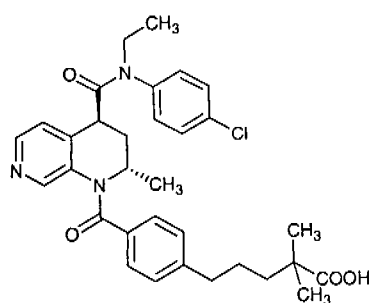
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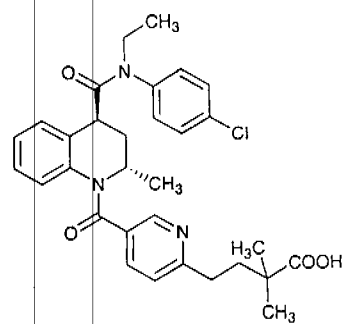
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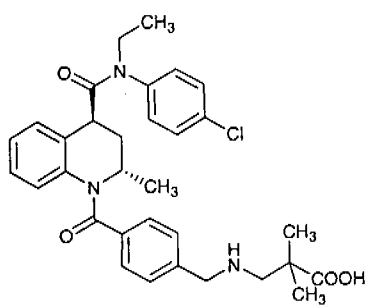
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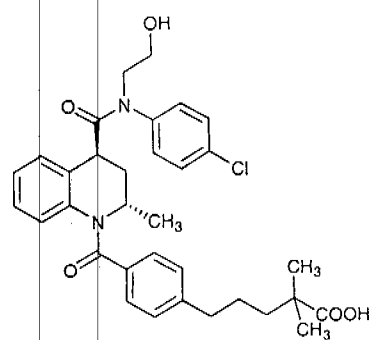
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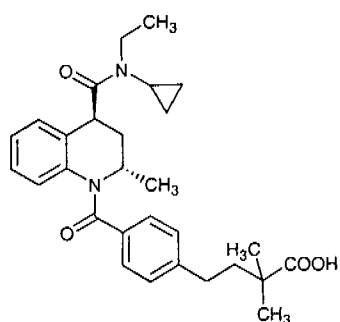
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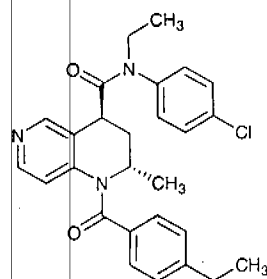
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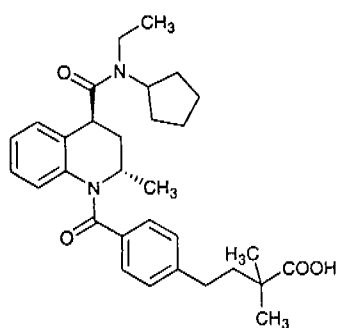
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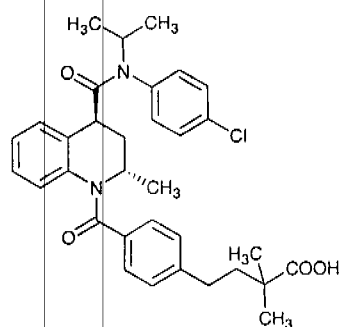
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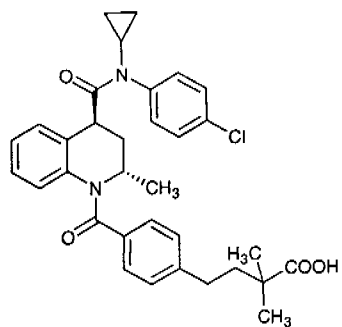
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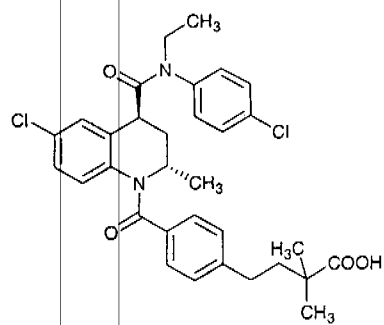
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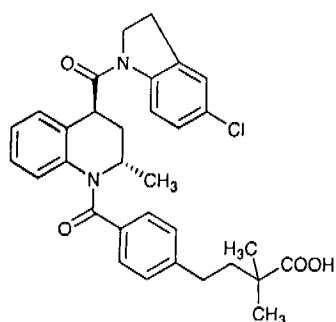
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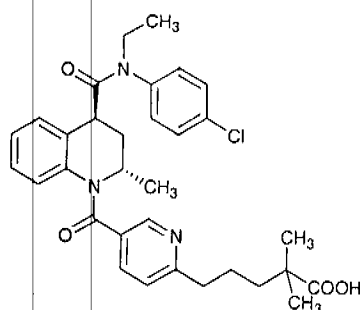
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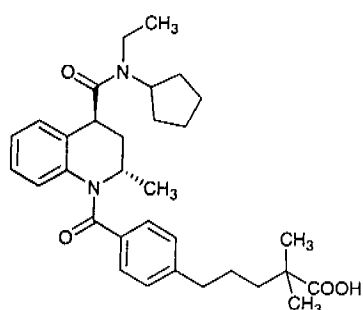
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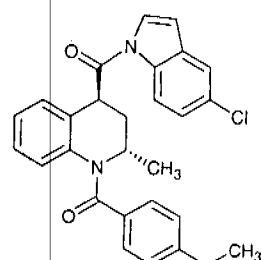
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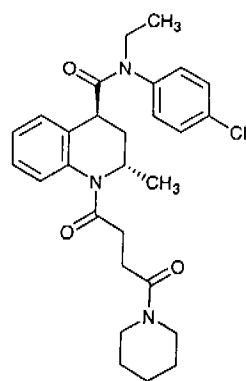
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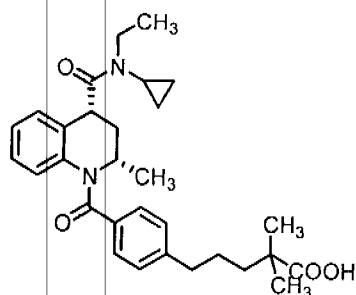
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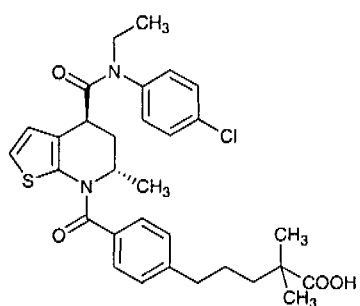
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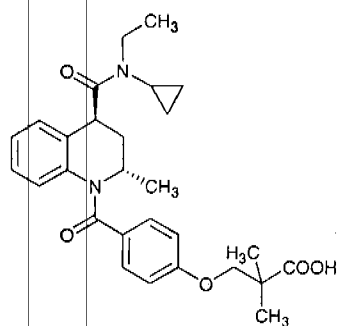
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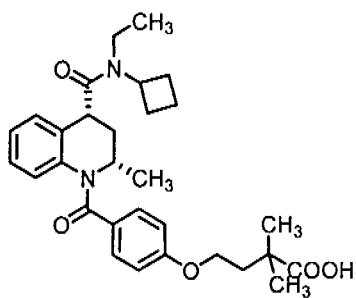
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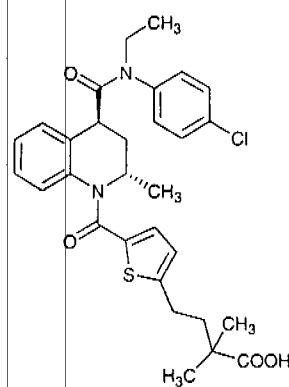
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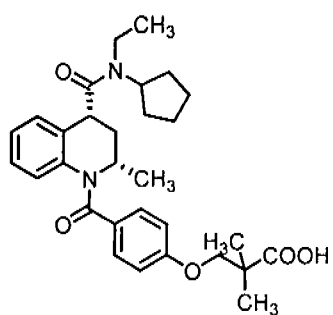
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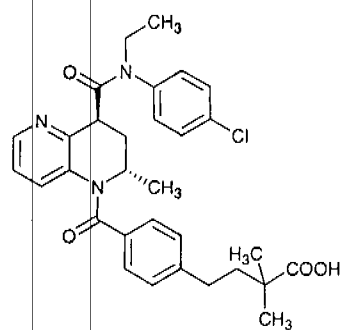
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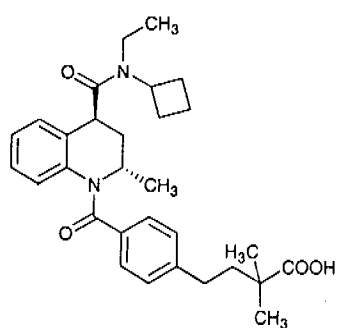


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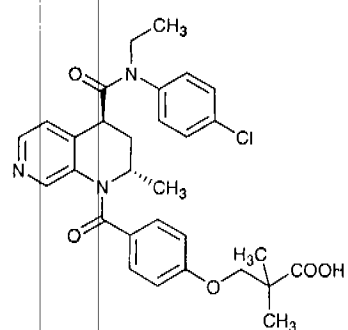


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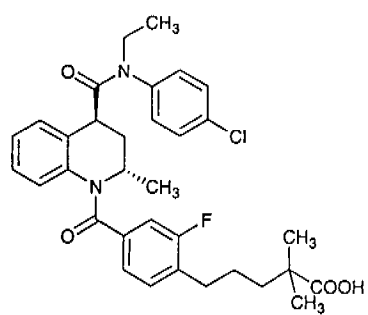
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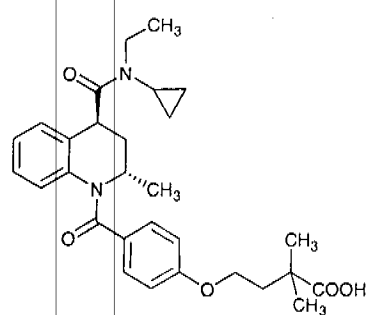
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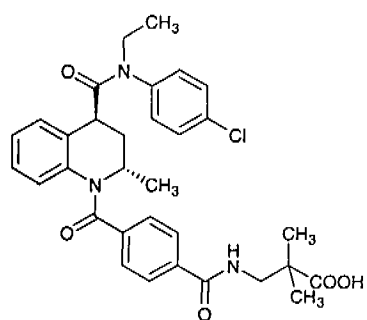
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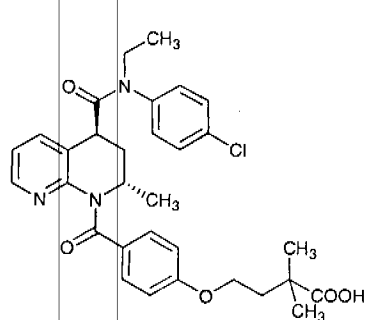
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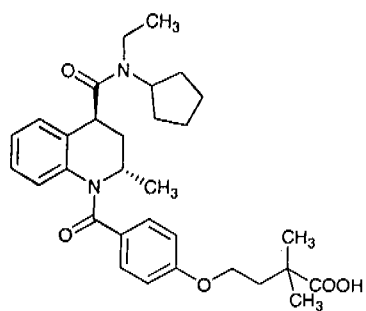


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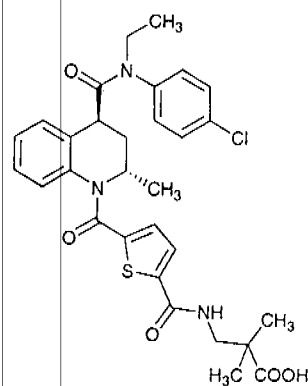


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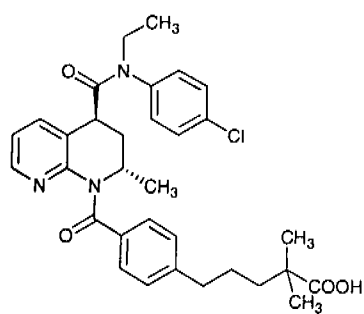
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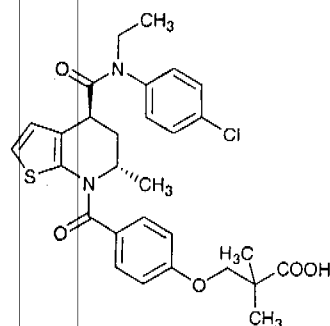
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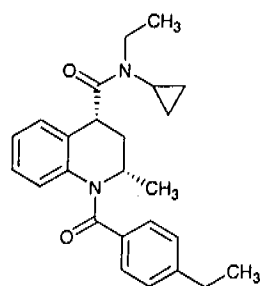
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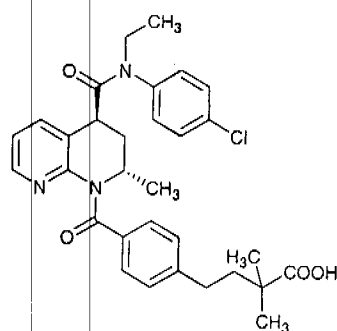
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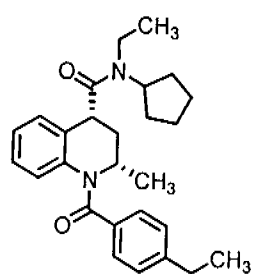
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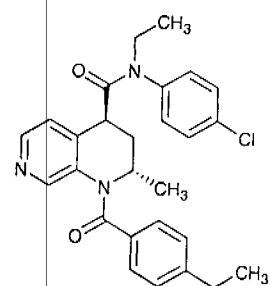
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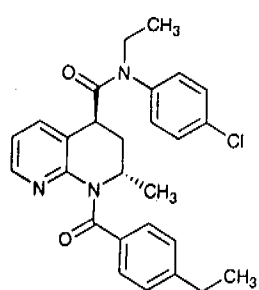
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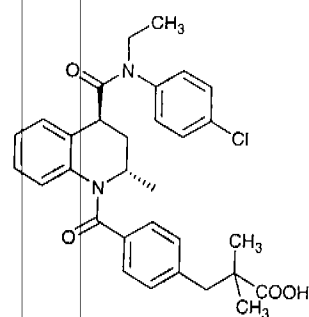
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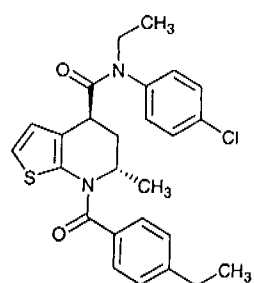
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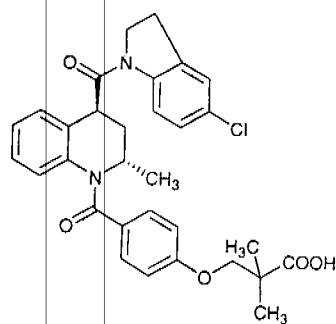
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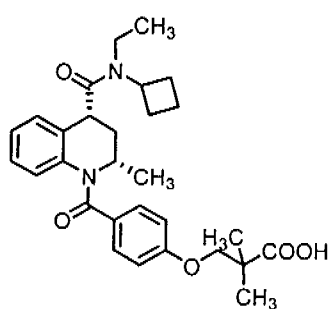
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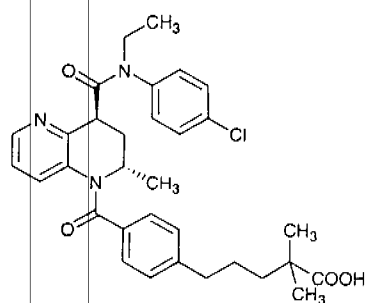
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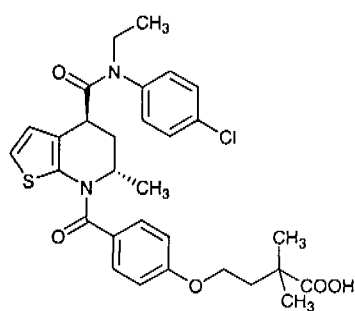
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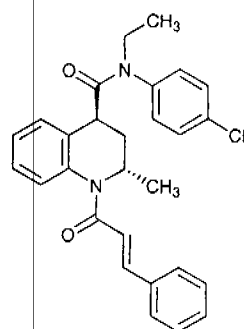
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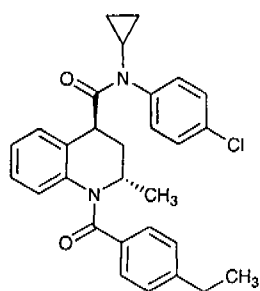
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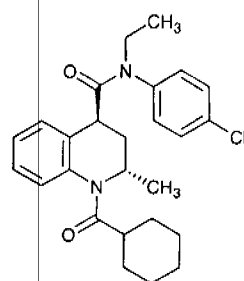
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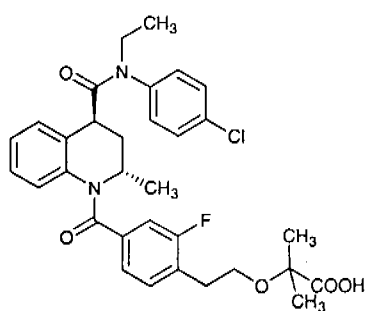


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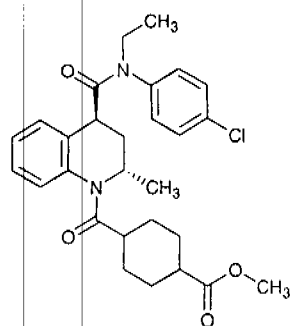


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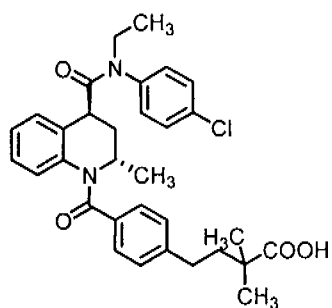
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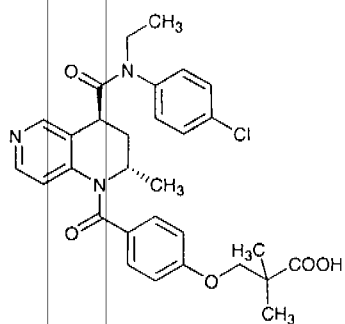
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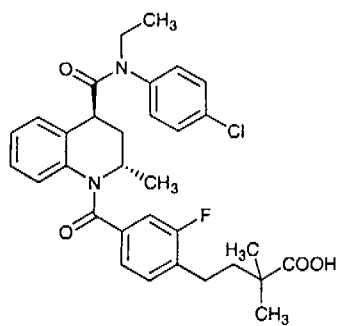
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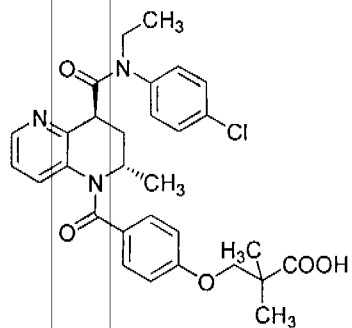
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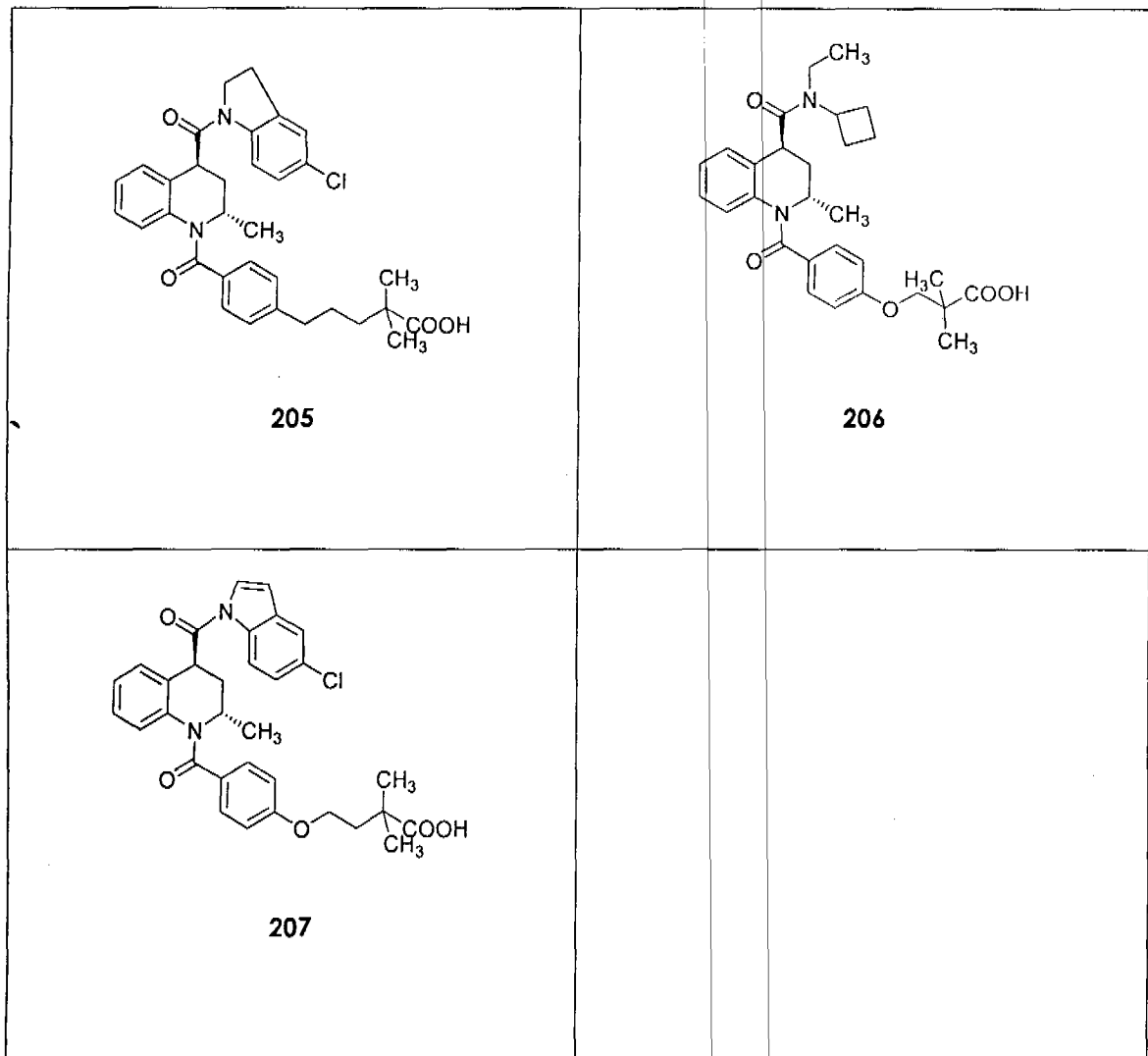


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4. Usos, formulación y administración

- Como se ha analizado anteriormente, la presente invención proporciona compuestos que son útiles como inhibidores de CRTH2, y por lo tanto los
- 5 compuestos de la invención son útiles para tratar (terapéutica o profilácticamente) trastornos con un componente inflamatorio y afecciones alérgicas. Los compuestos de la invención también pueden usarse para tratar trastornos inflamatorios y afecciones alérgicas mediadas por células Th2, eosinófilos y basófilos.

- Por consiguiente, en otro aspecto de la presente invención, se proporcionan
- 10 composiciones farmacéuticas, donde dichas composiciones comprenden cualquiera de los compuestos que se han descrito en este documento, y comprenden opcionalmente un excipiente, adyuvante o vehículo farmacéuticamente aceptable. En ciertas realizaciones, estas composiciones también comprenden además uno o más agentes terapéuticos adicionales.

- También se apreciará que ciertos de los compuestos de la presente invención pueden existir en forma libre para el tratamiento, o cuando sea apropiado, en forma de un derivado farmacéuticamente aceptable de los mismos. De acuerdo con la presente invención, un derivado farmacéuticamente aceptable
- 5 incluye, pero sin limitación, profármacos farmacéuticamente aceptables, sales, ésteres, sales de dichos ésteres o cualquier otro aducto o derivado que después de la administración a un paciente en necesidad del mismo sea capaz de proporcionar, directa o indirectamente, un compuesto como se ha descrito de otra forma en este documento, o un metabolito o resto del mismo.
- 10 Como se usa en este documento, la expresión "sal farmacéuticamente aceptable" se refiere a aquellas sales que, dentro del alcance del juicio médico razonable, son adecuadas para uso en contacto con los tejidos de seres humanos y animales inferiores sin toxicidad indebida, irritación, respuesta alérgica y similares, y tienen corresponden a una relación beneficio/riesgo razonable. Las sales
- 15 farmacéuticamente aceptables son bien conocidas en la técnica. Por ejemplo, S. M. Berte *et al.*, describe sales farmacéuticamente aceptables con detalle en *J. Pharmaceutical Sciences*, **1977**, 66, 1-19, incorporado en este documento como referencia. Las sales farmacéuticamente aceptables de los compuestos de esta invención incluyen las derivadas de ácidos y bases inorgánicos y orgánicos
- 20 adecuados. Los ejemplos de sales de adición de ácidos no tóxicas, farmacéuticamente aceptables, son sales de un grupo amino formadas con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido fosfórico, ácido sulfúrico y ácido perclórico o con ácidos orgánicos tales como ácido acético, ácido oxálico, ácido maleico, ácido tartárico, ácido cítrico, ácido succínico o
- 25 ácido malónico o mediante el uso de otros métodos usados en la técnica tales como intercambio iónico. Otras sales farmacéuticamente aceptables incluyen sales adipato, alginato, ascorbato, aspartato, bencenosulfonato, benzoato, bisulfato, borato, butirato, canforato, canforsulfonato, citrato, ciclopentanopropionato, digluconato, dodecilsulfato, etanosulfonato, formiato, fumarato, glucoheptonato,
- 30 glicerofosfato, gluconato, hemisulfato, heptanoato, hexanoato, hidroyoduro, 2-hidroxi-etanosulfonato, lactobionato, lactato, laurato, laurilsulfato, malato, maleato, malonato, metanosulfonato, 2-naftalenosulfonato, nicotinato, nitrato, oleato, oxalato, palmitato, pamoato, pectinato, persulfato, 3-fenilpropionato, fosfato, picrato, pivalato, propionato, estearato, succinato, sulfato, tartrato, tiocianato, p-
- 35 toluenosulfonato, undecanoato, valerato y similares. Las sales derivadas de bases apropiadas incluyen sales de metales alcalinos, metales alcalinotérreos, amonio y

N⁺(alquilo C₁₋₄)₄. Esta invención también incluye la cuaternización de cualquier grupo que contiene nitrógeno básico de los compuestos descritos en este documento. Otras sales farmacéuticamente aceptables incluyen, cuando es apropiado, cationes de amonio no tóxicos, de amonio cuaternario y de amina
5 formados usando contraiones tales como haluro, hidróxido, carboxilato, sulfato, fosfato, nitrato, alquilsulfato inferior y arilsulfonato.

Como se ha descrito anteriormente, las composiciones farmacéuticamente aceptables de la presente invención además comprenden un excipiente, adyuvante o vehículo farmacéuticamente aceptable que, como se usa en este
10 documento, incluye todos y cada uno de los disolventes, diluyentes u otros vehículos líquidos, adyuvantes de dispersión o suspensión, agentes tensioactivos, agentes isotónicos, agentes espesantes o emulsionantes, conservantes, aglutinantes sólidos, lubricantes y similares, adecuados para la forma de dosificación particular deseada. Remington's Pharmaceutical Sciences, Decimosexta Edición, E. W. Martin
15 (Mack Publishing Co., Easton, Pa., 1980) describe diversos excipientes usados en la formulación de composiciones farmacéuticamente aceptables y técnicas conocidas para su preparación. Excepto en la medida en la que cualquier medio excipiente convencional es incompatible con los compuestos de la invención, tal como por la producción de algún efecto biológico indeseable o la interacción de
20 otra manera de un forma perjudicial con cualquier otro componente de la composición farmacéuticamente aceptable, se contempla que su uso está dentro del alcance de esta invención. Algunos ejemplos de materiales que pueden servir como excipientes farmacéuticamente aceptables incluyen, pero sin limitación, intercambiadores iónicos, alúmina, estearato de aluminio, lecitina, proteínas séricas
25 tales como albúmina de suero humano, sustancias tamponantes tales como fosfatos, glicina, ácidos sórbico o sorbato potásico, mezclas de glicéridos parciales de ácidos grasos vegetales saturados, agua, sales o electrolitos, tales como sulfato de protamina, hidrógeno fosfato disódico, hidrógeno fosfato potásico, cloruro sódico, sales de cinc, sílice coloidal, trisilicato de magnesio, polivinil pirrolidona,
30 poliacrilatos, ceras, polímeros de bloque de polietileno-polioxipropileno, lanolina, azúcares tales como lactosa, glucosa y sacarosa; almidones tales como almidón de maíz y almidón de patata; celulosa y sus derivados tales como carboximetil celulosa sódica, etil celulosa y acetato de celulosa; tragacanto en polvo; malta; gelatina; talco; excipientes tales como manteca de cacao y ceras de supositorio; aceites
35 tales como aceite de cacahuete, aceite de semilla de algodón; aceite de cartamo; aceite de sésamo; aceite de oliva; aceite de maíz y aceite de soja;

- glicoles tales como propilenglicol o polietilenglicol; ésteres tales como oleato de etilo y laurato de etilo; agar; agentes tamponantes tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua sin pirógenos; solución salina isotónica; solución de Ringer; alcohol etílico; y soluciones tamponantes de fosfato, así como otros lubricantes compatibles no tóxicos tales como lauril sulfato sódico y estearato de magnesio, así como agentes colorantes, agentes de liberación, agentes de recubrimiento, edulcorantes, aromatizantes y perfumes; también pueden estar presentes en la composición, de acuerdo con el criterio del formulador, conservantes y antioxidantes.
- En otro aspecto, se proporciona un método para el tratamiento de una enfermedad inflamatoria o una enfermedad con un componente inflamatorio que comprende administrar una cantidad eficaz de un compuesto, o una composición farmacéutica del mismo, a un sujeto que lo necesite. Los compuestos y composiciones de la invención son inhibidores de CRTH2, y de esta manera, sin el deseo de limitarse por ninguna teoría particular, los compuestos y composiciones son particularmente útiles para tratar o reducir la gravedad de una enfermedad, afección o trastorno, cuando la activación de uno o más de CRTH2, PGD2 (incluyendo la actividad DP), células Th2, eosinófilos y/o basófilos está implicada en la enfermedad, afección o trastorno. Cuando la activación de uno o más de CRTH2, PGD2 (incluyendo la actividad DP), células Th2, eosinófilos y/o basófilos está implicada en una enfermedad, afección o trastorno particular, la enfermedad, afección o trastorno también puede denominarse "enfermedad o síntoma de enfermedad mediada por CRTH2". Por consiguiente, en otro aspecto, la presente invención proporciona un método para tratar o reducir la gravedad de una enfermedad, afección o trastorno cuando la activación de uno o más de CRTH2, PGD2 (incluyendo la actividad DP), células Th2, eosinófilos y/o basófilos está implicada en el estado de enfermedad.
- En ciertas realizaciones de la presente invención, una "cantidad eficaz" del compuesto o composición farmacéuticamente aceptable es la cantidad eficaz para tratar una enfermedad inflamatoria o enfermedad con un componente inflamatorio. En otras realizaciones, una "cantidad eficaz" de un compuesto es una cantidad que inhibe la unión de PGD2 a su receptor CRTH2 y, de esta manera, inhibe uno o más procesos mediados por la unión en un sujeto, por ejemplo, la liberación de mediadores proinflamatorios. Una "cantidad eficaz" de un compuesto puede conseguir un efecto terapéutico y/o profiláctico deseado, tal como una cantidad que tiene como resultado la prevención o una reducción en los síntomas

asociados con una enfermedad inflamatoria o una enfermedad mediada por uno o más de CRTH2, PGD2 (incluyendo la actividad DP), células Th2, eosinófilos y basófilos.

En una realización, la enfermedad inflamatoria es un estado alérgico. Los ejemplos de estados alérgicos para los que se cree que son particularmente eficaces los compuestos, composiciones farmacéuticas y métodos descritos incluyen dermatitis atópica, rinitis alérgica, artritis reumatoide, trastorno pulmonar obstructivo crónico (COPD), exacerbaciones de COPD, o asma alérgica. Otros estados alérgicos incluyen anafilaxis sistémica o respuestas de hipersensibilidad, alergias a fármacos (por ejemplo, a penicilina o cefalosporinas), alergias a picaduras de insectos y dermatosis tales como dermatitis, eccema, dermatitis atópica, dermatitis alérgica de contacto y urticaria.

Los ejemplos de enfermedades con un componente inflamatorio para las cuales se consideran particularmente eficaces los compuestos, composición farmacéutica y métodos descritos incluyen osteoartritis, enfermedad inflamatoria del intestino [por ejemplo, tal como colitis ulcerosa, enfermedad de Crohn, ileítis, enfermedad celíaca, Sprue no tropical, enteritis, enteropatía asociada con artropatías seronegativas, colitis microscópica o colagenosa, gastroenteritis eosinofílica o bursitis producida después de una proctocolectomía, y anastomosis ileoanal] y trastornos de la piel [por ejemplo, psoriasis, eritema, prurito y acné].

Muchas enfermedades autoinmunes también tienen un componente inflamatorio. Los ejemplos incluyen esclerosis múltiple, lupus sistémico eritematoso, miastenia grave, diabetes de inicio juvenil, glomerulonefritis y otras nefritis, tiroiditis autoinmune, enfermedad de Behcet y rechazo de injertos (incluyendo rechazo de aloinjertos o enfermedad de injerto contra hospedador). El componente inflamatorio de estos trastornos se considera mediado, al menos en parte, por CRTH2.

Las enfermedades caracterizadas por reperusión tienen un componente inflamatorio que se considera mediado, al menos en parte, por CRTH2. Los ejemplos incluyen apoplejía, isquemia cardíaca y similares. Los compuestos y composiciones descritas también pueden usarse para tratar estos trastornos.

Otras enfermedades y afecciones con un componente inflamatorio que se consideran mediadas por CRTH2 incluyen mastitis (glándula mamaria), vaginitis, colecistitis, colangitis o pericolangitis (conducto biliar y tejido circundante del hígado), bronquitis crónica, sinusitis crónica, enfermedades inflamatorias crónicas del pulmón que producen fibrosis intersticial, tales como enfermedades pulmonares

intersticiales (ILD) (por ejemplo, fibrosis pulmonar idiopática o ILD asociada con artritis reumatoide, u otros estados autoinmunes), neumonitis por hipersensibilidad, enfermedades del colágeno y sarcoidosis. Otras enfermedades o afecciones con componentes inflamatorios que son susceptibles de tratamiento de acuerdo con los métodos descritos en este documento incluyen vasculitis (por ejemplo, vasculitis necrosante, cutánea y de hipersensibilidad), espondiloartropatías, esclerodermia, aterosclerosis, reestenosis y miositis (incluyendo poliomiositis, dermatomiositis), pancreatitis y diabetes mellitus dependiente de insulina.

En una realización preferida, la invención proporciona un método para tratar asma que comprende administrar una cantidad eficaz de un compuesto de fórmula general I (y subseries del mismo como se describe en este documento) a un sujeto que lo necesita.

Los compuestos y composiciones de acuerdo con el método de la presente invención pueden administrarse usando cualquier cantidad y cualquier vía de administración eficaz para tratar una enfermedad inflamatoria o un estado alérgico. La cantidad exacta requerida variará de un sujeto a otro dependiendo de la especie, edad y estado general del sujeto, la gravedad de la infección, el agente particular, su modo de administración y similares. Los compuestos de la invención preferiblemente se formulan en forma de dosificación unitaria para facilitar la administración y la uniformidad de la dosificación. La expresión "forma de dosificación unitaria", como se usa en este documento, se refiere a una unidad físicamente discreta de un agente apropiada para el paciente a tratar. Sin embargo, se entenderá que el uso diario total de los compuestos y composiciones de la presente invención se decidirá por el médico correspondiente dentro del alcance del criterio médico razonable. El nivel de dosificación eficaz específico para cualquier paciente u organismo particular dependerá de una diversidad de factores que incluyen el trastorno a tratar y la gravedad del trastorno; la actividad del compuesto específico empleado; la composición específica empleada; la edad, peso corporal, salud general, sexo y dieta del paciente; el momento de administración, vía de administración y velocidad de excreción del compuesto específico empleado; la duración del tratamiento; los fármacos usados en combinación o que coinciden con el compuesto específico empleado y factores similares bien conocidos en la técnica médica. El término "paciente", como se usa en este documento, significa un animal, preferiblemente un mamífero y aún más preferiblemente un ser humano.

Las composiciones farmacéuticamente aceptables de esta invención pueden administrarse a seres humanos y otros animales por vía oral, rectal, parenteral, intracisternal, intravaginal, intraperitoneal, tópica (tal como por medio de polvos, pomadas o gotas), bucal, como una pulverización oral o nasal, o similares, dependiendo de la gravedad de la infección a tratar. En ciertas realizaciones, los compuestos de la invención pueden administrarse por vía oral o parenteral a niveles de dosificación de aproximadamente 0,01 mg/kg a aproximadamente 50 mg/kg y, preferiblemente, de aproximadamente 1 mg/kg a aproximadamente 25 mg/kg, de peso corporal del sujeto al día, una o más veces al día, para obtener el efecto terapéutico deseado.

Las formas de dosificación líquidas para administración oral, incluyen, pero sin limitación, emulsiones, microemulsiones, soluciones, suspensiones, jarabes y elixires farmacéuticamente aceptables. Además de los compuestos activos, las formas de dosificación líquidas pueden contener diluyente inertes usados comúnmente en la técnica tales como, por ejemplo, agua u otros disolventes, agentes solubilizantes y emulsionantes tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, dimetilformamida, aceites (en particular, aceite de semilla de algodón, de cacahuete, de maíz, de germen, de oliva, de ricino y de sésamo), glicerol, alcohol tetrahidrofurfurílico, polietilenglicoles y ésteres de ácido graso de sorbitán, y mezclas de los mismos. Además de diluyentes inertes, las composiciones orales también pueden incluir adyuvantes tales como agentes humectantes, agentes emulsionantes y de suspensión, edulcorantes, aromatizantes y perfumes.

Las preparaciones inyectables, por ejemplo, suspensiones acuosas u oleaginosas inyectables estériles pueden formularse de acuerdo con la técnica conocida usando agentes dispersantes o humectantes y agentes de suspensión adecuados. La preparación inyectable estéril también puede ser una solución, suspensión o emulsión inyectable estéril en un diluyente o disolvente parenteralmente aceptable no tóxico, por ejemplo, como una solución en 1,3-butanodiol. Entre los vehículos y disolventes aceptables que pueden emplearse se encuentran agua, solución de Ringer, solución de cloruro sódico U.S.P e isotónica. Además, convencionalmente se emplean aceites estériles fijos como disolvente o medio de suspensión. Para este fin, puede emplearse cualquier aceite fijo insípido incluyendo mono- o diglicéridos sintéticos. Además, en la preparación de inyectables se usan ácidos grasos tales como ácido oleico.

Las formulaciones inyectables pueden esterilizarse, por ejemplo, por filtración a través de un filtro que retiene bacterias o por la incorporación de agentes de esterilización en forma de composiciones sólidas estériles que pueden disolverse o dispersarse en agua estéril u otro medio inyectable estéril antes del uso.

- 5 Para prolongar el efecto de un compuesto de la presente invención, a menudo es deseable ralentizar la absorción del compuesto administrado por inyección subcutánea o intramuscular. Esto puede conseguirse por medio del uso de una suspensión líquida de un material cristalino o amorfo con baja solubilidad en agua. La velocidad de absorción del compuesto entonces depende de su
- 10 velocidad de disolución que, a su vez, puede depender del tamaño del cristal y de la forma cristalina. Como alternativa, la absorción retardada de una forma de compuesto administrada por vía parenteral se consigue disolviendo o suspendiendo el compuesto en un vehículo oleoso. Se obtienen formas de depósito inyectables formando matrices microencapsuladas del compuesto en polímeros
- 15 biodegradables tales como polilactida-poliglicolida. Dependiendo de la relación entre el compuesto y el polímero y de la naturaleza del polímero particular empleado, puede controlarse la velocidad de liberación del compuesto. Los ejemplos de otros polímeros biodegradables incluyen poli(ortoésteres) y poli(anhídridos). También se preparan formulaciones inyectables de depósito
- 20 introduciendo el compuesto en liposomas o microemulsiones que son compatibles con los tejidos corporales.

- Las composiciones para administración rectal o vaginal preferiblemente son supositorios que pueden prepararse mezclando los compuestos de esta invención con excipientes o vehículos no irritantes adecuados tales como manteca de
- 25 cacao, polietilenglicol o una cera de supositorio, que son sólidos a temperatura ambiente pero líquidos a la temperatura corporal y, por lo tanto, se funden en el recto o en la cavidad vaginal y liberan el compuesto activo.

- Las formas de dosificación sólidas para administración oral incluyen cápsulas, comprimidos, píldoras, polvos y gránulos. En estas formas de dosificación
- 30 sólidas, el compuesto activo se mezcla con al menos un excipiente o vehículo farmacéuticamente aceptable inerte tal como citrato sódico o fosfato dicálcico y/o a) cargas o diluyentes tales como almidones, lactosa, sacarosa, glucosa, manitol y ácido silícico, b) aglutinantes tales como, por ejemplo, carboximetilcelulosa, alginatos, gelatina, polivinilpirrolidona, sacarosa y goma
- 35 arábica, c) humectantes tales como glicerol, d) agentes disgregantes tales como agar-agar, carbonato cálcico, almidón de patata o tapioca, ácido algínico, ciertos

silicatos y carbonato sódico, e) agentes para retardar la solución tales como parafina, f) aceleradores de la absorción tales como compuestos de amonio cuaternario, g) agentes humectantes tales como, por ejemplo, alcohol cetílico y monoestearato de glicerol, h) absorbentes tales como caolín y arcilla de bentonita e i) lubricantes tales como talco, estearato cálcico, estearato de magnesio, polietilenglicoles sólidos, lauril sulfato sódico y mezclas de los mismos. En el caso de las cápsulas, comprimidos y píldoras, la forma de dosificación también puede comprender agentes tamponantes.

También pueden emplearse composiciones sólidas de un tipo similar como

10 cargas en cápsulas de gelatina rellenas blandas y duras usando excipientes tales como lactosa o azúcar de la leche así como polietilenglicoles de alto peso molecular y similares. Las formas de dosificación sólidas de comprimidos, grageas, cápsulas, píldoras y gránulos pueden prepararse con recubrimientos y envueltas

15 tales como recubrimientos entéricos y otros recubrimientos bien conocidos en la técnica de formulación farmacéutica. Opcionalmente, pueden contener agentes opacificantes y también pueden ser de una composición que liberen el ingrediente o ingredientes activos sólo, o preferentemente, en una cierta parte del tracto

intestinal, opcionalmente, de una forma retardada. Los ejemplos de composiciones de inclusión que pueden usarse incluyen sustancias poliméricas y ceras. También

20 pueden emplearse composiciones sólidas de un tipo similar como cargas en cápsulas de gelatina rellenas blandas y duras usando excipientes tales como lactosa o azúcar de la leche así como polietilenglicoles de alto peso molecular y similares.

Los compuestos activos también pueden estar en forma microencapsulada

25 con uno o más excipientes como se ha indicado anteriormente. Las formas de dosificación sólidas de comprimidos, grageas, cápsulas, píldoras y gránulos pueden prepararse con recubrimientos y envueltas tales como recubrimientos entéricos, recubrimientos de control de la liberación y otros recubrimientos bien conocidos en la técnica de formulación farmacéutica. En estas formas de dosificación sólidas, el

30 compuesto activo puede mezclarse con al menos un diluyente inerte tal como sacarosa, lactosa o almidón. Estas formas de dosificación también pueden comprender, como es normal en la práctica, otras sustancias distintas de diluyentes inertes, por ejemplo, lubricantes para la fabricación de comprimidos y otros adyuvantes para la fabricación de comprimidos tales como un estearato de

35 magnesio y celulosa microcristalina. En el caso de las cápsulas, comprimidos y píldoras, las formas de dosificación también pueden comprender agentes

tamponantes. Opcionalmente, pueden contener agentes opacificantes y también pueden ser de una composición tal que liberen el ingrediente o los ingredientes activos sólo, o preferentemente, en una cierta parte del tracto intestinal, opcionalmente, de una manera retardada. Los ejemplos de composiciones de
5 inclusión que pueden usarse incluyen sustancias poliméricas y ceras.

Las formas de dosificación para administración tópica o transdérmica de un compuesto de esta invención incluyen pomadas, pastas, cremas, lociones, geles, polvos, soluciones, pulverizaciones, inhalantes o parches. El componente activo se mezcla en condiciones estériles con un vehículo farmacéuticamente aceptable y
10 cualquier conservante necesario o tampón que pueda requerirse. También se contemplan dentro del alcance de esta invención formulaciones oftálmicas, gotas para los oídos y gotas para los ojos. Además, la presente invención contempla el uso de parches transdérmicos, que tienen la ventaja añadida de proporcionar la liberación controlada de un compuesto en el cuerpo. Estas formas de dosificación
15 pueden obtenerse disolviendo o dispersando el compuesto en el medio apropiado. También pueden usarse potenciadores de la absorción para aumentar el flujo del compuesto a través de la piel. La velocidad puede controlarse proporcionando una membrana de control de la velocidad o dispersando el compuesto en una matriz polimérica o gel.

También se apreciará que los compuestos y composiciones farmacéuticamente aceptables de la presente invención pueden emplearse en terapias de combinación, es decir, los compuestos y composiciones y farmacéuticamente aceptables pueden administrarse conjuntamente, antes o después de uno o más agentes terapéuticos o procedimientos médicos distintos
20 deseados. La combinación particular de terapias (agentes terapéuticos o procedimientos) a emplear en un régimen de combinación tendrá en cuenta la compatibilidad de los agentes terapéuticos y/o procedimientos deseados y el efecto terapéutico deseado a conseguir. También se apreciará que las terapias empleadas pueden conseguir un efecto deseado para el mismo trastorno (por
25 ejemplo, un compuesto de la invención puede administrarse junto con otro agente usado para tratar el mismo trastorno) o pueden conseguir diferentes efectos (por ejemplo, el control de cualquier efecto adverso). Como se usan en este documento, los agentes terapéuticos adicionales que se administran normalmente para tratar o prevenir una enfermedad o afección particular se conocen como
30 "apropiados para la enfermedad o afección a tratar".
35

Por ejemplo, los compuestos de la invención también pueden administrarse en combinación con uno o más agentes terapéuticos adicionales tales como teofilina, broncodilatadores β -adrenérgicos, corticosteroides, antihistamínicos, agentes antialérgicos, agentes inmunosupresores (por ejemplo, ciclosporina A, FK-506, prednisona, metilprednisolona), hormonas (por ejemplo, hormona adrenocorticotrópica (ACTH)), citoquinas (por ejemplo, interferones (por ejemplo, IFN β -1 α , IFN δ -1 β)) y similares.

La cantidad de agente terapéutico adicional presente en las composiciones de esta invención no será mayor que la cantidad administrada normalmente en una composición que comprende ese agente terapéutico como único agente activo. Preferiblemente, la cantidad de agente terapéutico adicional en las composiciones descritas en el presente documento variará de aproximadamente 50% a 100% de la cantidad presente normalmente en una composición que comprende ese agente como único agente terapéuticamente activo.

Los compuestos de esta invención o sus composiciones farmacéuticamente aceptables también pueden incorporarse en composiciones para el recubrimiento de dispositivos médicos implantables tales como prótesis, válvulas artificiales, injertos vasculares, stent y catéteres. Por consiguiente, la presente invención, en otro aspecto, incluye una composición para recubrir un dispositivo implantable que comprende un compuesto de la presente invención como se ha descrito en general anteriormente, y en clases y subclases en este documento, y un vehículo adecuado para recubrir dicho dispositivo implantable. En otro aspecto, la presente invención incluye un dispositivo implantable recubierto con una composición que comprende un compuesto de la presente invención como se ha descrito en general anteriormente, y en clases y subclases en este documento, y un vehículo adecuado para recubrir dicho dispositivo implantable.

Otro aspecto de la invención se refiere a la inhibición de la actividad CRTH2 en una muestra biológica o un paciente, comprendiendo dicho método administrar al paciente, o poner en contacto dicha muestra biológica con un compuesto de fórmula I o una composición que comprende dicho compuesto. La expresión "muestra biológica", como se usa en este documento, incluye, sin limitación, cultivos celulares o extractos de los mismos; material de biopsia obtenido a partir de un mamífero o extractos del mismo; y sangre, saliva, orina, heces, semen, lágrimas u otros fluidos corporales o extractos de los mismos.

La inhibición de la actividad CRTH2 en una muestra biológica es útil para una diversidad de fines conocidos para un especialista en la técnica. Los ejemplos

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de estos fines incluyen, pero sin limitación, transfusión de sangre, transplante de órganos, almacenamiento de muestras biológicas y ensayos biológicos.

PROCEDIMIENTOS EXPERIMENTALES

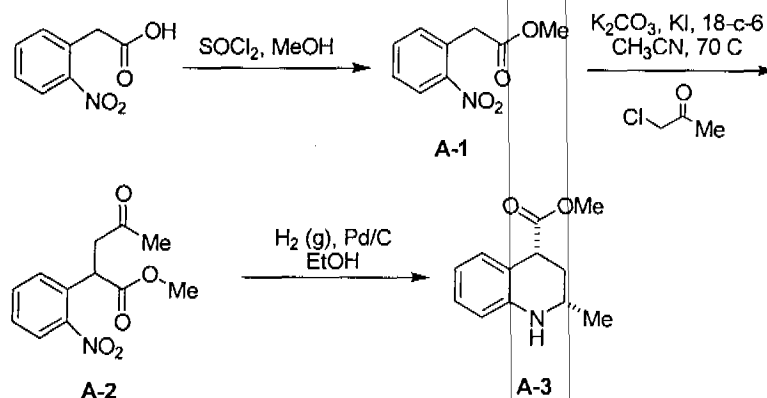
5 **General.** Todas las reacciones que implican reactivos sensibles al aire se realizaron en una atmósfera de nitrógeno. Los reactivos se usaron tal y como se recibieron de los proveedores comerciales a menos que se indique otra cosa. Los datos de ¹H RMN se registraron usando el instrumento Bruker UltraShield 300 MHz/54 mm equipado con Auto Muestreador Bruker B-ACS60 o el instrumento Varian 300
10 MHz. Los intermedios y compuestos finales se purificaron por cromatografía ultrarrápida usando uno de los siguientes instrumentos: 1. Recolector Ultrarrápido UV Biotage de 4-canales Quad equipado con un Módulo de Bomba Quad 1 y el Módulo de Cartucho Quad 12/25. 2. Recolector Ultrarrápido UV Biotage de 12-canales Quad equipado con un Módulo de Bomba Quad 3 y un Módulo de
15 Cartucho Quad 3. 3. Instrumento de cromatografía ultrarrápida ISCO combi. Los espectros de LC/MS se obtuvieron usando un MicroMass Platform LC (columna Phenomenex C18, 5 micrómetros, 50 x 4,6 mm) equipado con un Manipulador de Líquidos Gilson 215. Las condiciones de LC/MS convencionales son las siguientes:

% A (Agua)	95,0	Tabla de tiempos del Gradiente de Bomba						
% B (Acetonitrilo)	5,0	HP1100 LC						
% Acetato amónico	0,1							
Flujo (ml/min)	2,500	La Tabla de tiempos del gradiente contiene 4 entradas que son:						
Tiempo de parada (min)	3,8							
Presión mín. (bar)	0							
Presión máx. (bar)	400	Tiempo	%A	%B	%C	%D	Flujo	Presión
Temperatura izda. del	10,0	0,00	95,0	5,0	0,0	0,0	2,500	400
horno (°C)		2,00	0,0	100,0	0,0	0,0	2,500	400
Temperatura dcha. del	10,0	3,00	0,0	100,0	0,0	0,0	2,500	400
horno (°C)		3,05	95,0	5,0	0,0	0,0	2,500	400

20 Los datos de LC-MS se adquirieron usando el método de "Patrón de acetato amónico" a menos que se indique otra cosa.

Síntesis de éster metílico del ácido (±)-cis-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico

Esquema 1



Un matraz de fondo redondo con agitador magnético se cargó con ácido (2-nitro-fenil)-acético (10,0 g, 55,0 mmol) y metanol (70 ml) en una atmósfera de argón. A la solución amarilla resultante a temperatura ambiente se le añadió gota a gota cloruro de tionilo (12,1 ml, 166 mmol) mediante un embudo de adición (Nota: La reacción es muy exotérmica). La mezcla de reacción resultante se agitó a temperatura ambiente durante 12-18 horas y se concentró al vacío para producir 13,3 g de éster metílico del ácido (2-nitro-fenil)-acético bruto en forma de un aceite naranja. Este material se usó directamente en reacciones posteriores.

Un matraz de fondo redondo de tres bocas con agitador magnético se cargó con éster metílico del ácido (2-nitro-fenil)-acético bruto (7,23 g, 37,0 mmol), carbonato potásico (46,1 g, 33,3 mmol), 18-corona-6 (0,650 g), y yoduro potásico (0,650 g) en una atmósfera de argón. Al matraz se le añadió acetonitrilo (80 ml) y la mezcla se calentó a 70°C durante una hora. A la reacción se le añadió cloroacetona (3,50 ml, 44,0 mmol) y la reacción se agitó a 70°C en una atmósfera de argón durante 18-20 horas. La reacción se enfrió a temperatura ambiente y se filtró a través de una capa de celite. El filtrado resultante se concentró al vacío para producir 9,64 g de material bruto. La purificación por cromatografía ultrarrápida (eluyente de acetato de etilo al 0-40%/hexanos) produjo 4,74 g de éster metílico del ácido 2-(2-nitro-fenil)-4-oxo-pentanoico (51%).

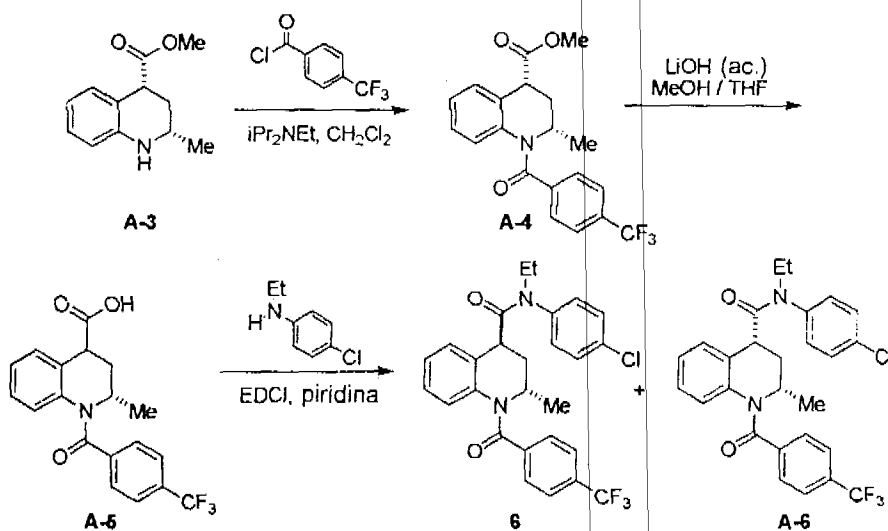
Un matraz de fondo redondo con agitador magnético se cargó con éster metílico del ácido 2-(2-nitro-fenil)-4-oxo-pentanoico (4,74 g, 19,1 mmol) y etanol anhidro (50 ml). A la reacción se le añadió paladio al 10% sobre carbono (0,948 g, 20% en peso) y la reacción se agitó a temperatura ambiente en una atmósfera de gas hidrógeno (globo) durante 18-20 horas. La reacción se filtró a través de una capa de celite y la capa de celite se lavó con etanol caliente. Los filtrados combinados se concentraron al vacío para producir un sólido de color blanquecino. Este material se purificó con un sistema ultrarrápido Isco (acetato de

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etilo al 0-20%/hexanos) para producir 2,64 g de éster metílico del ácido *cis*-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico en forma de un sólido blanco (68%). ^1H RMN (CDCl_3) δ : 1,23 (3H, d), 1,95 (1H, dd), 2,10 - 2,18 (1H, m), 3,34 - 3,46 (1H, m), 3,74 (3H, s), 3,94 (1H, dd), 6,51 (1H, dd), 6,60 - 6,67 (1H, m), 6,94-7,03 (2H, m). MS m/z : 206 (M+1).

Procedimiento general A

Esquema 2



10 (4-Cloro-fenil)-etil-amida del ácido ($\pm$)-*trans*-2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-tetrahidro-quinolina-4-carboxílico (6)

Un matraz de fondo redondo con agitador magnético se cargó con éster metílico del ácido *cis*-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico (556 mg, 2,71 mmol) en cloruro de metileno (8,00 ml) en una atmósfera de argón. A la reacción se le añadieron cloruro de 4-trifluorometil-benzoilo (0,61 ml, 4,07 mmol) y *N,N*-diisopropiletilamina (1,20 ml, 6,89 mmol). La reacción se agitó a temperatura ambiente durante 18-20 horas. La reacción se transfirió a un embudo de decantación que contenía una solución saturada de bicarbonato sódico (15 ml) y después se diluyó con cloruro de metileno (15 ml) y se agitó vigorosamente. La capa orgánica resultante se separó, se lavó con salmuera (1 x 20 ml), se secó sobre sulfato de magnesio y se filtró. El filtrado se concentró al vacío para producir un residuo naranja (1,359 g). El residuo se purificó por cromatografía ultrarrápida (eluyente de acetato de etilo al 20%/hexanos) para producir éster metílico del ácido *cis*-2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-tetrahidro-quinolina-4-carboxílico en forma de un sólido de color castaño (990 mg, 97%).

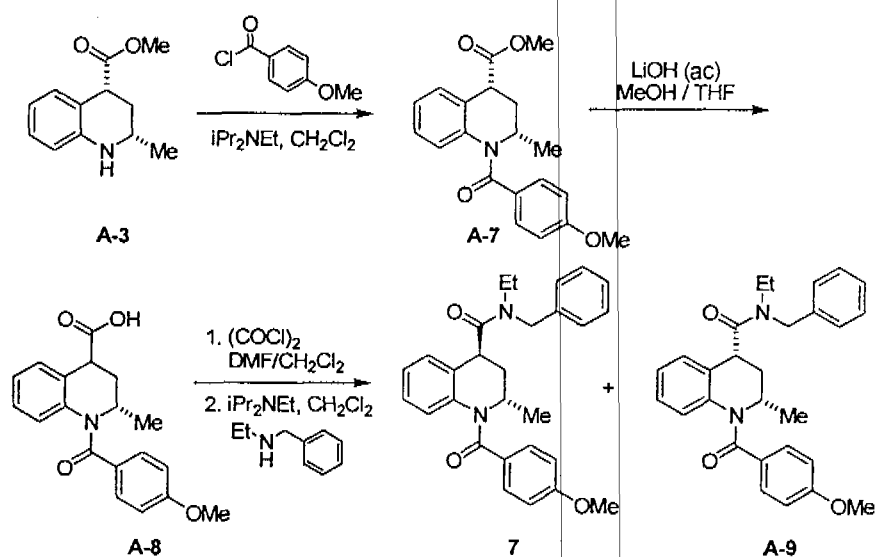
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- Un matraz de fondo redondo con agitador magnético se cargó con éster metílico del ácido *cis*-2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-tetrahidro-quinolina-4-carboxílico (980 mg, 2,60 mmol) en tetrahidrofurano (10,0 ml). A la reacción se le añadió una solución de hidróxido de litio (179 mg, 7,47 mmol) en agua (10 ml),
5 seguido de metanol (10 ml). La reacción se agitó a temperatura ambiente durante 18-20 horas en una atmósfera de argón. La reacción se transfirió a un embudo de decantación y el pH se ajustó a 2 mediante la adición de ácido clorhídrico 1 N. La mezcla se extrajo con acetato de etilo (3 x 35 ml) y las extracciones combinadas se lavaron con salmuera (1 x 50 ml), se secaron sobre sulfato de magnesio y se filtraron.
10 El filtrado se concentró al vacío para producir ácido 2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-tetrahidro-quinolina-4-carboxílico (mezcla de isómeros *cis* y *trans*) en forma de un sólido blanquecino (912 mg, 97%). La mezcla se usó sin purificación en posteriores reacciones.

- Un matraz de fondo redondo con agitador magnético se cargó con ácido
15 2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-tetrahidro-quinolina-4-carboxílico (886 mg, 2,44 mmol) en piridina anhidra (25,0 ml). A la reacción se le añadió *N*-etil-*p*-cloroanilina (0,410 ml, 2,95 mmol) seguido de EDCI (833 mg, 4,34 mmol). La reacción se agitó a temperatura ambiente en una atmósfera de argón durante 18-20 horas. La reacción se vertió en una mezcla 1:1 de agua/salmuera (50 ml) y se extrajo con
20 acetato de etilo (3 x 35 ml). Las extracciones combinadas se lavaron con salmuera (1 x 50 ml), se secaron sobre sulfato de magnesio y se filtraron. El filtrado se concentró al vacío para producir un residuo pardo. El residuo se purificó por cromatografía sobre gel de sílice (hexanos/acetato de etilo) para producir (4-clorofenil)-etil-amida del ácido ($\pm$)-*trans*-2-metil-1-(4-trifluorometil-benzoil)-1,2,3,4-
25 tetrahidro-quinolina-4-carboxílico (39%). ^1H RMN (CDCl_3) δ : 1,02 (d, 3H), 1,12 (t, 3H), 1,64-1,74 (m, 1H), 2,49-2,58 (m, 1H), 3,59-3,72 (m, 1H), 3,77-3,90 (m, 2H), 5,03-5,14 (m, 1H), 6,35-6,41 (m, 1H), 6,74-6,84 (m, 2H), 6,89-6,95 (m, 1H), 7,17-7,25 (m, 2H), 7,44-7,52 (m, 2H), 7,63-7,69 (m, 2H). MS m/z : 501 ($M+1$).

30 Procedimiento general B

Esquema 3



Bencil-etil-amida del ácido ($\pm$)-*trans*-1-(4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico (7)

5 Un matraz de fondo redondo con agitador magnético se cargó con éster metílico del ácido *cis*-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico (5,42 g, 26 mmol) en diclorometano (100 ml) en una atmósfera de argón a temperatura ambiente. A la reacción se le añadió *N,N*-diisopropiletilamina (11,8 ml, 68 mmol),
 10 seguido de cloruro de *p*-anisóilo (6,31 g, 37 mmol). La reacción se agitó a temperatura ambiente durante 18-20 horas y se vertió en bicarbonato sódico saturado (1000 ml), se diluyó con diclorometano (50 ml) y se agitó vigorosamente. La capa orgánica resultante se separó, se lavó con salmuera (1 x 100 ml), se secó sobre sulfato de magnesio y se filtró. El filtrado se concentró al vacío para producir un residuo oleoso. Al residuo se le añadió éter dietílico (50 ml) y el sólido blanco
 15 resultante se recogió por filtración por succión para producir éster metílico del ácido *cis*-1-(4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico (6,94 g, 78%).

Un matraz de fondo redondo con agitador magnético se cargó con éster metílico del ácido *cis*-1-(4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolina-4-carboxílico (3,00 g, 8,8 mmol) en tetrahidrofurano anhidro (70 ml). A la reacción se le
 20 añadió una solución de hidróxido de litio (423 mg, 18 mmol) en agua (24 ml), seguido de metanol (24 ml). La reacción se agitó a temperatura ambiente durante 18-20 horas en una atmósfera de argón. La reacción se transfirió a un embudo de decantación y el pH se ajustó a 2 mediante la adición de ácido clorhídrico 1 N. La mezcla se extrajo con acetato de etilo (3 x 35 ml) y las extracciones combinadas se
 25 lavaron con salmuera (1 x 50 ml), se secaron sobre sulfato de magnesio y se filtraron.