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PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-112392

54. **TÍTULO** Antagonistas del receptor de P2Y2 para el tratamiento de enfermedades inflamatorias

51. **CLASIFICACIÓN INTERNACIONAL** C07D 215/44
A61K 31/47 // A61P 37/00

71. **SOLICITANTE** Millennium Pharmaceuticals, Inc.

DOMICILIO Cambridge, Massachussets, Estados Unidos

74. **APODERADO** Luis Patiño Leyva

22. **BOGOTÁ, D. C.,** 03 de Noviembre de 2006

(FORMA P-10)

SS

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SUPERINTENDENCIA

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

7/11/06

① **SOLICITUD DE :**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capitulo I. ☐ Capitulo II.

② **SOLICITANTE (71)**	Nombre: **MILLENNIUM PHARMACEUTICALS, INC.** Dirección: 40 Landsdowne Street, Cambridge, MA 02139 Estados Unidos Nacionalidad o Domicilio: Cambridge, Massachussets Estados Unidos Lugar de Constitución Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C E. ☐ Otro ☐ Cual _____ Número _____
③ **REPRESENTANTE O APODERADO**	Nombre LUIS PATIÑO LEYVA Dirección Cra. 11ª No. 94-76 – Of. 308 Teléfono: 6161948 Fax: 6163976 E-mail.	**IDENTIFICACION** C C ☒ NIT ☐ C E. ☐ Otro ☒ Cual _____ Número 2.930 616 TP 2698
④ **INVENTOR (ES) (72)**	Nombre: GHOSH, Shomir Dirección 134 Sewall Avenue, Unit C, Nacionalidad o Domicilio: Brookline, Massachussetts 02446, Estados Unidos	

⑤ **PCT (86)**

Solicitud Internacional No. PCT/US2005/011643 Fecha: Abril 7 de 2005

Publicación Internacional No WO 2005/100321 A1 Fecha Octubre 27 de 2005

⑥ **Titulo (54)** **ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO DE ENFERMEDADES INFLAMATORIAS.**

⑦ **Clasificación Internacional (51)** C07D 215/44 A61K 31/47 // A61P 37/00

⑧ **PRIORIDAD:**	(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
SI ☒ NO ☐	Estados Unidos	Abril 7 de 2004	60/560,410

⑨ **Comprobante de pago No.** **Fecha**

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

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud
- [ ] Documento que acredita existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de deposito 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.
- [x] Otros Reporte de Búsqueda Internacional

(11) FIGURA CARACTERISTICA

(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA:

C.C. 2.930.616 Bogotá T.P. 2698

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

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REYNOLDS Dominic	304 Allston Street, Apt. 6	Cambridge, Massachussets 01239 Estados Unidos de América

Otros anexos que se acompañan a la solicitud.

Formulario No. PCT/RO/101 correspondiente a la solicitud de patente internacional, con su traducción al castellano.

Formulario PCT/IB/304 concerniente a la transmisión del documento de prioridad.

Formulario PCT/ISA/210 referente al reporte de Búsqueda Internacional.

Formulario PCT/ISA/220 correspondiente a la notificación o transmisión del Reporte de Búsqueda Internacional y la opinión escrita de la autoridad de búsqueda internacional o la declaración.

Formulario PCT/ISA/237 correspondiente a la opinión escrita de la autoridad de búsqueda internacional.

Apostille

(Convention de La Haye du 5 octobre 1961)

1. *District of Columbia*
   United States of America
2. This public document has been signed by ALBERT L. THEMES
3. acting in the capacity of NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA
4. bears the seal/stamp of ALBERT L. THEMES, NOTARY PUBLIC IN AND FOR THE DISTRICT OF COLUMBIA

CERTIFIED

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

10. Signature

Patricia Elwood (Interim)

86—F0136

G.HOLLMANN RESTREPO ABOGADOS LTDA

The undersigned , acting on behalf of and representing of **MILLENIUM 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

G. HOLLMANN RESTREPO ABOGADOS LTDA

Yo (nosotros) , obrando en nombre propio y representación de, con domicilio en , nombro(amos), **LUIS PATIÑO LEYVA y/o GUSTAVO HOLLMANN RESTREPO**, con domicilio en Bogotá D.C., Republica 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 traspasos, prorrogas, 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 obtencion 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 tomas 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.

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El Notario Cuarto del Circulo de Bogotá hace constar que esta copia concuerda con la copia auténtica de un documento que ha sido presentado a la vista.
NOTARIA CUARTA
GILBERTO CASTRO

CERTIFICATION
COMPANIES

The undersigned Diana E Gentile certifies that the preceding signature(s) reading Ian R Sloman, is (are) authentic, that the signer(s) at present fill(s) the position of Assistant General 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

DIANA E GENTILE
Notary Public
Commonwealth of Massachusetts
My Commission Expires Oct 2006

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

El Notario Cuarto del Círculo de Bogotá hace constar que esta copia coincide con el original que se le presentó y a la vista. 16 DIC 2005
GILBERTO CARRIZOSA CASTRO
NOTARIO CUARTO

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26 OCT 2006

GILBERTO CASTRO CASTRO
NOTARIO CUARTO

I HEREBY CERTIFY THAT THIS IS THE ORIGINAL DOCUMENT

Subscribed and sworn to before me, in my presence, this 8 day of Dec., 2005, a Notary Public in and for the District of Columbia

My commission expires 6/14, 2008.

Notary Public

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

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(74) Agents : SHAIR, Karoline, K., M. et al , Millenium Pharmaceuticals, Inc , 40 Landsdowne Street, Cambridge, MA 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, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, 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

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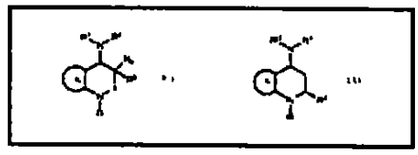
For information on time limits for entry into the national phase please click here

Published

-- *with international search report*

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

(57) Abstract



Disclosed herein are compounds represented by Structural Formula: (I) and (I-A) Also disclosed is the use of such compounds for inhibiting the G-protein coupled receptor referred to as chemoattractant receptor-homologous molecule expressed on Th2, or simply "CRTH2" for the treatment of inflammatory disorders The variables in Structural Formula (I) and (I-A) are defined herein.

PGD2 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES

BACKGROUND OF THE INVENTION

[0001] 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)

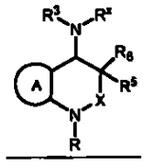
[0002] Accordingly, compounds which are modulators, preferably inhibitors, of the interaction between CRTH2 and PGD2 should be useful for the treatment of diseases and disorders that are mediated by CRTH2, PGD2, Th2 cells, eosinophils, and/or basophils These diseases include but are not limited to allergic disorders, asthmatic disorders, and inflammatory disorders such as allergic rhinitis, allergic asthma, bronchoconstriction, atopic dermatitis and systemic inflammatory disorders

DETAILED DESCRIPTION OF THE INVENTION

[0003] 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

[0004] *1 Description of Compounds of General Formula I (and subsets thereof).*

[0005] In one embodiment, the present invention relates to a compound of formula I·



I

or a pharmaceutically acceptable salt thereof, wherein.

Ring A is an optionally substituted monocyclic aromatic ring;

R is $-X_1-R^1$, wherein

X_1 is a bond, S(O), $S(O)_2$, C(O) or C(O)NH, provided that when X_1 is a bond, SO or SO_2, then R^1 is not H; and

R^1 is H or an optionally substituted, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group;

X is $-C(O)-$ or $-C(R^2)_2-$, wherein

each R^2 is independently -H, $-X_4-R^8$ or an optionally substituted, aliphatic group, cycloaliphatic group, aromatic group or a non-aromatic heterocyclic group,

R^x is $-X_2-R^4$, wherein

X_2 is a bond, S(O), $S(O)_2$, C(O) or C(O)NH, and

R^4 is -H, $-X_6-R^{10}$ or an optionally substituted, aliphatic group, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group;

provided that when X_2 is a bond, SO or SO_2, then R^4 is not H;

R^3 is an optionally substituted, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group, or $-NR^xR^3$, taken together, is an optionally substituted non-aromatic nitrogen containing heterocyclic group;

X_4 and X_6 are each independently a straight or branched hydrocarbyl group optionally substituted with one or more groups selected from the group consisting of halo, -OH, =O, C_1-C_3 alkoxy, nitro and cyano;

R^5 and R^6 are each independently H or C_1-C_3 alkyl,

R^8 and R^{10} are each independently H, -C(O)OR" or an optionally substituted, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group,

R" is H or R^{13}, and

R^{13} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl.

[0006] In another embodiment, the present invention relates to a compound of formula I or a pharmaceutically acceptable salt thereof, wherein

Ring **A** is an optionally substituted monocyclic aromatic ring;

R is $-X_1-R^1$;

R^x is $-X_2-R^4$, and R^3 is an optionally substituted aromatic group; or $-NR^xR^3$, taken together, is an optionally substituted non-aromatic nitrogen containing heterocyclic group,

X is $-C(O)-$ or $-C(R^2)_2-$;

X_1 and X_2 are each independently a bond, S(O), $S(O)_2$, C(O) or C(O)NH,

R^1 is H or an optionally substituted, cycloaliphatic group, aromatic group or non-aromatic

heterocyclic group,

provided that when X_1 is a bond, SO or SO_2, then R^1 is not H;

each R^2 is independently H, $-X_4-R^8$ or an optionally substituted, aliphatic group, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group,

R^4 is H, $-X_6-R^{10}$ or an optionally substituted, aliphatic group, cycloaliphatic group, aromatic group

or non-aromatic heterocyclic group;

provided that when X_2 is a bond, SO or SO_2, then R^4 is not H;

X_4 and X_6 are each independently a straight or branched hydrocarbyl group optionally substituted

with one or more groups selected from the group consisting of halo, -OH, =O, C_1-C_3 alkoxy, nitro and cyano;

R^5 and R^6 are each independently H or C_1-C_3 alkyl; and

R^8 and R^{10} are each independently H, -C(O)OR" or an optionally substituted, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group,

R" is H or R^{13}; and

R^{13} is C_1-C_6 alkyl or C_3-C_8 cycloalkyl

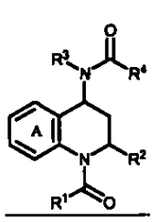
[0007] In one embodiment, compounds of formula I include compounds other than 2-Methyl-N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(2-methyl-1-oxobutyl)-4-quinolinyl]-butamide, N-(1-Acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-heptamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxo-3-phenylpropyl)-4-quinolinyl]- benzenepropanamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(3-nitrobenzoyl)-4-quinolinyl]- hexanamide, N-[1,1'-biphenyl]-3-yl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]-acetamide, N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-(4-nitrophenyl)- heptanamide; N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-(4-methoxyphenyl)-2-methyl- propanamide; N-[1-(4-fluorobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- butanamide, N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-methoxybenzoyl)-2-methyl-4-quinolinyl]-pentanamide, 2-ethyl-N-[1-(2-ethyl-1-oxobutyl)-1,2,3,4-tetrahydro-2,8-dimethyl-4-quinolinyl]-N-(2-methylphenyl)-butanamide; N-[1-[(4-fluorophenyl)acetyl]-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- propanamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(4-nitrobenzoyl)-4-quinolinyl]-octanamide, N-cyclohexyl-4-[(cyclohexylamino)carbonyl]phenylamino]-3,4-dihydro-2-methyl-1(2H)-quinolinecarboxamide; N-[1-(4-ethylbenzoyl)-1,2,3,4-tetrahydro-2,8-dimethyl-4-quinolinyl]-N-(2-methylphenyl)-3-(4-nitrophenyl)- 2-propenamide; 3-(4-methoxyphenyl)-N-phenyl-N-[1,2,3,4-tetrahydro-1-[3-(4-methoxyphenyl)-1-oxo-2-propenyl]-2-methyl-4-quinolinyl]-2-propenamide, 4-[(ethoxyoxoacetyl)phenylamino]-3,4-dihydro-2-methyl-∀-oxo-ethyl ester-1(2H)-quinolineacetic acid,

N-[1-(3-cyclohexyl-1-oxopropyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-cyclohexanepropanamide, 4-(acetylphenylamino)-3,4-dihydro-2-methyl-gamma-oxo-1(2H)-quinolinepentanoic acid, N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-2,2-dimethyl-N-phenyl- propanamide, N-(1-benzoyl-6-bromo-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-pentanamide; N-[1-(2-furanylcarbonyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, 2-methyl-N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-methoxybenzoyl)-2-methyl-4-quinolinyl]-propanamide; N-[1-[(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)acetyl]-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, 2,2,2-trifluoro-N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-methoxybenzoyl)-2-methyl-4-quinolinyl]- acetamide; 2-ethyl-N-[1-(2-ethyl-1-oxobutyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- butanamide; N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-(3-methoxyphenyl)- acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxohexyl)-4-quinolinyl]- acetamide, N-(1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-2-thiophenecarboxamide, N-[1-(2-fluorobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- hexanamide, N-phenyl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]-hexanamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]-hexanamide; N-[1-(cyclopropylcarbonyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-cyclopropanecarboxamide; N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-(4-methylphenyl)- acetamide; 2-methyl-N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(2-methyl-1-oxopropyl)-4-quinolinyl]- propanamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]- 2-thiophenecarboxamide; 1-(3,5-dinitrobenzoyl)-N-formyl-1,2,3,4-tetrahydro-2-methyl-N-phenyl-4-quinolinamine; N-[1-(4-chloro-3-nitrobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(3-nitrobenzoyl)-4-quinolinyl]-acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-methoxybenzoyl)-2-methyl-4-quinolinyl]- hexanamide, N-[1-(2-furanylcarbonyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-2-furancarboxamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxopropyl)-4-quinolinyl]-acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-[3-(4-methoxyphenyl)-1-oxo-2-propenyl]-2-methyl-4-quinolinyl]-acetamide, 3-(2-furanyl)-N-[1-[3-(2-furanyl)-1-oxo-2-propenyl]-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-2-propenamide, N-[1-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-octanamide; N-[1-(3-chlorobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, Relative stereochemistry N-phenyl-N-[(2R,4S)-1,2,3,4-tetrahydro-2-methyl-1-(1-oxopropyl)-4-quinolinyl]- acetamide, Relative stereochemistry N-[(2R,4S)-1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-2-methyl-N-phenyl-propanamide; Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-hexanamide; Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-propanamide, Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-

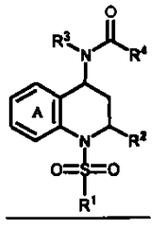
heptanamide; Relative stereochemistry N-[(2R,4S)-1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-2,2-dimethyl-N-phenyl-propanamide; N-[1-(3-fluorobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, N-[1-[4-(1,1-dimethylethyl)benzoyl]-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl- acetamide, N-(1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-2-methyl-N-phenyl- propanamide, 2,2,2-trifluoro-N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(trifluoroacetyl)-4-quinolinyl]- acetamide; Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-2,2-dimethyl-N-phenyl-propanamide, Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-butanamide, Relative stereochemistry N-[(2R,4S)-1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, Relative stereochemistry N-phenyl-N-[(2R,4S)-1,2,3,4-tetrahydro-2-methyl-1-(1-oxoheptyl)-4-quinolinyl]-acetamide, Relative stereochemistry N-phenyl-N-[(2R,4S)-1,2,3,4-tetrahydro-2-methyl-1-(1-oxohexyl)-4-quinolinyl]-acetamide, Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-pentanamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxo-3-phenyl-2-propenyl)-4-quinolinyl]-acetamide; Relative stereochemistry N-[(2R,4S)-1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-heptanamide, Relative stereochemistry N-[(2R,4S)-1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, Relative stereochemistry N-[(2R,4S)-1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-pentanamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(tricyclo[3.3 1 13,7]dec-1-ylcarbonyl)-4-quinolinyl]-acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxopropyl)-4-quinolinyl]- propanamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(2-thienylcarbonyl)-4-quinolinyl]- acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]- 2-furancarboxamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(4-methoxybenzoyl)-2-methyl-4-quinolinyl]- acetamide; N-[1-(3,5-dinitrobenzoyl)-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl]-N-phenyl-acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(4-nitrobenzoyl)-4-quinolinyl]-acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-1-(2-iodobenzoyl)-2-methyl-4-quinolinyl]-acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(2-methyl-1-oxopropyl)-4-quinolinyl]-acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-[(4-methylphenyl)sulfonyl]-4-quinolinyl]-acetamide, N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-[(4-nitrophenyl)methyl]-4-quinolinyl]-acetamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-methoxybenzoyl)-2-methyl-4-quinolinyl]-acetamide, N-(1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl- butanamide; N-phenyl-N-[1,2,3,4-tetrahydro-2-methyl-1-(1-oxobutyl)-4-quinolinyl]- acetamide, N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-hexanamide; N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-pentanamide; N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-propanamide, 1-benzoyl-1,2,3,4-tetrahydro-4-(N-phenylacetamido)quinaldine; N-(1-acetyl-6-bromo-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-acetamide, N-(1-acetyl-1,2,3,4-tetrahydro-2-methyl-6-nitro-4-quinolyl)-acetanilide; N-(1-acetyl-6-chloro-1,2,3,4-tetrahydro-2-

methyl-4-quinolyl)-acetanilide, N-(1-acetyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-acetamide, N-(1-benzoyl-6-bromo-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-acetamide; N-(1-benzoyl-6-chloro-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl-acetamide, N-(1-benzoyl-1,2,3,4-tetrahydro-2-methyl-4-quinolinyl)-N-phenyl- butanamide; N-phenyl-N-[1,2,3,4-tetrahydro-1-(3-fluorobenzoyl)-2-methyl-4-quinolinyl]-hexanamide N-[1-(3-Chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide; N-[1-(4-Fluoro-benzoyl)-2-methyl-6-nitro-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide; Pentanoic acid (1-benzoyl-6-bromo-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amide; N-(1-Benzoyl-6-chloro-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide; N-[6-Chloro-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide, N-[6-Bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide; N-(1-Benzoyl-6-nitro-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide, N-(1-Benzoyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-butyramide; or N-[1-(3-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2,2-dimethyl-N-phenyl-propionamide

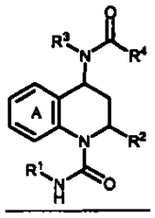
[0008] In a preferred embodiment of the present invention, X is $-CHR^2-$, R^2 is -H, methyl or ethyl, R^3 is a substituted or unsubstituted aromatic group; R^5 and R^6 are -H, and the remainder of the variables in Structural Formula **(I)** are as defined above. More preferably, the compound is represented by a structural formula selected from Structural Formulas **(II)-(VIII)**:



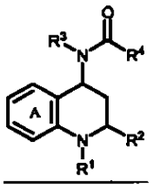
(II)



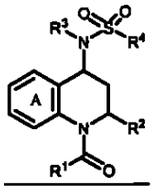
(III)



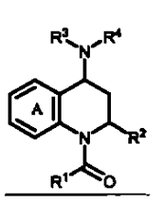
(IV)



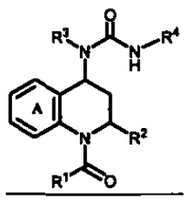
(V)



(VI)



(VII)



(VIII)

[0009] The variables in Structural Formulas (II)-(VIII) are as described above for Structural Formula (I). Preferred values for these variables are provided below

[0010] Phenyl Ring A is a substituted or unsubstituted phenyl group. Unless otherwise indicated suitable substituents for Phenyl Ring A are provided in the section below describing suitable aryl ring substituents

[0011] R^1 in Structural Formulas (II)-(IV) and (VI)-(VIII) is –H, optionally substituted, cycloaliphatic group, aromatic group or non-aromatic heterocyclic group, provided that R^1 in Structural Formulas (III) is not –H

[0012] R^2 in Structural Formulas (II)-(VIII) is –H, methyl or ethyl.

[0013] R^3 in Structural Formulas (II)-(VIII) is an optionally substituted phenyl group.

[0014] R^4 in Structural Formulas (II)-(VI) and (VIII) is –H, $-CH_2C(O)R^{14}$, $-CH_2R^{15}$, $-CH_2OR^{14}$ or an optionally substituted C_1-C_3 alkyl group or an optionally substituted cycloalkyl group, aromatic group or non-aromatic heterocyclic group, provided that R^4 in Structural Formula (VI) is not –H, and R^4 in Structural Formulas (VII) is $-(CH_2)_n-R^{13a}$

[0015] R^{13a} is –H, $-CH_2C(O)R^{14}$, $-CH_2R^{15}$, $-CH_2OR^{14}$ or an optionally substituted C_1-C_3 alkyl group or an optionally substituted cycloalkyl group, aromatic group or non-aromatic heterocyclic group

[0016] Each R^{14} is independently an –H or an optionally substituted alkyl group, aromatic group, cycloalkyl group or non-aromatic heterocyclic group

[0017] Each R^{15} is independently an optionally aromatic group, cycloalkyl group or non-aromatic heterocyclic group

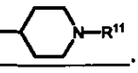
[0018] n is 0, 1, 2 or 3

[0019] More preferred values for R^1, R^4 and R^{13a} in Structural Formulas (II)-(VIII) are R^1 and R^{13a} are an optionally substituted, phenyl, pyridyl, furanyl, thiophenyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, benzofuranyl, tetrazolyl, thiazolyl, benzyl, benzothiazolyl, benzoimidazolyl, benzotriazolyl, benzomorpholinyl, benzopyrazolyl, indolyl, $-CH_2$-(*N*-pyridyl), $-CH_2$-furanyl, $-CH_2$-thiophienyl, $-CH_2$-isoxazolyl, $-CH_2$-imidazolyl, $-CH_2$-pyrazolyl, $-CH_2$-pyrollyl, $-CH_2$-benzofuranyl, $-CH_2$-tetrazolyl, $-CH_2$-thiazolyl, $-CH_2$-tetrazolyl, $-CH_2$-benzothiazolyl, $-CH_2$-benzimidazolyl, $-CH_2$-O-phenyl, $-CH_2C(O)$-phenyl, naphthalimidyl, tetrahydrofuranyl,

cyclohexyl, cyclopentyl or cyclopropyl group; and R^4 is C_1-C_4 alkyl, $-CH_2OH$, $-CH_2OCH_3$, $-CH_2OCH_2CH_3$, $-CH_2CH_2OCH_3$, $-CH_2CH_2OCH_2CH_3$ or an optionally substituted, phenyl, pyridyl, furanyl, thiophenyl, isoxazolyl, imidazolyl, pyrazolyl, pyrrolyl, benzofuranyl, tetrazolyl, benzyl, benzothiazolyl, benzoimidazolyl, benzotriazolyl, benzomorpholinyl, benzopyrazolyl, indolyl, $-CH_2$-(*N*-pyridyl), $-CH_2$-furanyl, $-CH_2$-thiophienyl, $-CH_2$-isoxazolyl, $-CH_2$-imidazolyl, $-CH_2$-pyrazolyl, $-CH_2$-pyrollyl, $-CH_2$-benzofuranyl, $-CH_2$-tetrazolyl, $-CH_2$-thiazolyl, $-CH_2$-tetrazolyl, $-CH_2$-benzothiazolyl, $-CH_2$-benzimidazolyl, $-CH_2$-O-phenyl, $-CH_2C(O)$-phenyl, naphthalimidyl, tetrahydrofuranyl, cyclohexyl, cyclopentyl or cyclopropyl group, wherein R^1, R^4 and R^{13} are independently selected; and Ring **A** is optionally substituted at the five, six, seven and/or the eight position

[0020] Even more preferably, the compounds in Structural Formulas **(II)-(VIII)** have one of the following features and preferably all of the following features. Phenyl Ring **A** is optionally substituted at the five, six, seven and/or eight position with R^{11}, wherein R^{11} is selected from substituents provided in the section below describing suitable aryl ring substituents unless otherwise indicated herein

[0021] R^1 is phenyl, thiophenyl, furanyl, pyridyl, oxazolyl, benzotriazole, pyrimidinyl, isoxazolyl or benzomorpholinyl, each group being optionally substituted with R^{11}; R^3 is [R^{11}]-phenyl; and R^4 is methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, $-CH_2OCH_3$ or $-CH_2OCH_2CH_3$.

[0022] Especially preferred are compounds represented by Structural Formulas **(II)-(VIII)** wherein Phenyl Ring **A** is optionally substituted at the six and/or seven position with R^{11}; R^1 is thiophenyl, [R^{11}]-thiophenyl, oxazolyl, [R^{11}]-oxazolyl, pyridinyl, [R^{11}]-pyridinyl, benzotriazolyl, [R^{11}]-benzotriazolyl, benzomorpholinyl, [R^{11}]-benzomorpholinyl, phenyl or phenyl substituted with one to four groups selected from the group consisting of halo, $-OR^o$ and $-N(R^{11})_2$, [R^{11}]-oxazolyl, oxazolyl and  .

[0023] R^3 is phenyl substituted with one to four atoms or groups selected from the group consisting of Br, Cl, $-CH_3$, $-N(R^{16})_2$, -NHC(O)OR", $-S(O)_2CH_3$, $-S(O)_2N(R^{16})_2$ and $-R^{13}C(O)N(R^{16})_2$, where R^{16} is C_1-C_6 alkyl.

[0024] In third preferred embodiment, Ring **A** in Structural Formulas **(I)** is a monocyclic heteroaryl group such as thiophene, furan, pyridine, pyrazole, pyrrole, [2,3]pyrimidine, [3,4]pyrimidine, [4,5]pyrimidine, [5,6]pyrimidine, oxazole, isoxazole or 1,2,3-triazole, each group being optionally substituted with R^{11}. When Ring **A** has these values, then the compound preferably has at least one and preferably all of the following features X is $-CHR^2$-, R^2 are –H, methyl or ethyl; R^5 and R^6 are –H; and R^3 is a substituted or unsubstituted phenyl group. When the compound has at

least one or all of these features, then preferably R^1 and R^4 are independently -H, $-CH_2C(O)R^{14}$, $-CH_2R^{15}$ or $-CH_2OR^{14}$ or an optionally substituted alkyl group, cycloalkyl group, aromatic group or non-aromatic heterocyclic group, and R^{14} and R^{15} are as described above for Structural Formula (II)

[0025] When Ring A in Structural Formula (I) is a monocyclic heteroaryl, as described in the preceding paragraph, commonly selected values for X_1 and X_2 are as follows X_1 and X_2 are both C(O); X_1 is $S(O)_2$ and X_2 is C(O), X_1 is C(O)NH and X_2 is C(O); X_1 is a bond and X_2 is C(O), and X_2 is C(O); X_1 is C(O) and X_2 is $S(O)_2$, X_1 is C(O) and; X_1 is C(O) and X_2 is a bond, or X_1 is C(O) and X_2 is C(O)NH Alternatively, Phenyl Ring A in Structural Formulas (II)-(VIII) is replaced with one of the monocyclic aromatic groups described in the preceding paragraph and the remainder of the variables are as described above.

[0026] In a fourth preferred embodiment, R^2 in Structural Formulas (I)-(VIII) is –H, C_1-C_4 alkyl, halogentated C_1-C_6 alkyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, phenyl, substituted phenyl, $-C(O)OR^{16}$, benzyl, substituted benzyl or $-(CH_2)_nO(CH_2)_m$, R^{16} is C_1-C_6 alkyl; n and m are positive integers such n+m=6; and the remainder of the variables are as described above

[0027] Also disclosed herein is a compound represented by Structural Formula (II) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 – 6 and R^3 and R^4 are as described above for Structural Formula (II).

[0028] Also disclosed herein is a compound represented by Structural Formula (II) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 – 6 and R^1 and R^4 are as described above for Structural Formula (II).

[0029] Also disclosed herein is a compound represented by Structural Formula (II) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (II).

[0030] Also disclosed herein is a compound represented by Structural Formula (III) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (III).

[0031] Also disclosed herein is a compound represented by Structural Formula (III) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (III).

[0032] Also disclosed herein is a compound represented by Structural Formula (III) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical

compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (III).

[0033] Also disclosed herein is a compound represented by Structural Formula (IV) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (IV).

[0034] Also disclosed herein is a compound represented by Structural Formula (IV) and methods of use thereof for inhibiting CRTH2, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (IV).

[0035] Also disclosed herein is a compound represented by Structural Formula (IV) and methods of use thereof for inhibiting CRTH2, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (IV).

[0036] Also disclosed herein is a compound represented by Structural Formula (V) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (V).

[0037] Also disclosed herein is a compound represented by Structural Formula (V) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (V).

[0038] Also disclosed herein is a compound represented by Structural Formula (V) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (V).

[0039] Also disclosed herein is a compound represented by Structural Formula (VI) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (VI).

[0040] Also disclosed herein is a compound represented by Structural Formula (VI) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (VI).

[0041] Also disclosed herein is a compound represented by Structural Formula (VI) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical

compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (VI).

[0042] Also disclosed herein is a compound represented by Structural Formula (VII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (VII).

[0043] Also disclosed herein is a compound represented by Structural Formula (VII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (VII).

[0044] Also disclosed herein is a compound represented by Structural Formula (VII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (VII).

[0045] Also disclosed herein is a compound represented by Structural Formula (VIII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^3 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^4 are as described above for Structural Formula (VIII).

[0046] Also disclosed herein is a compound represented by Structural Formula (VIII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^4 has the value corresponding to any one of the compounds in Table 1 - 6 and R^1 and R^3 are as described above for Structural Formula (VIII).

[0047] Also disclosed herein is a compound represented by Structural Formula (VIII) and methods of use thereof for inhibiting CRTH2 in a subject in need of treatment therefore and pharmaceutical compositions comprising the same, wherein R^1 has the value corresponding to any one of the compounds in Table 1 - 6 and R^3 and R^4 are as described above for Structural Formula (VIII).

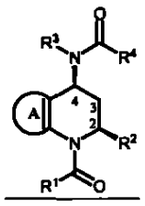
[0048] Specific examples of compounds of general formula I are shown in the Exemplification Section herein

[0049] It will be understood that the immediately following definitions and description apply to compounds of general formula I (and subsets thereof described above in this section 1 entitled *"Description of Compounds of General Formula I (and subsets thereof)"* 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,

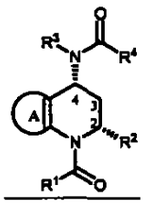
and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M. B and March, J , John Wiley & Sons, New York: 2001.

[0050] Many of the disclosed CRTH2 inhibitors contain one or more chiral centers The presence of chiral centers in a molecule gives rise to stereoisomers For example, a pair of optical isomers, referred to as "enantiomers", exist for every chiral center in a molecule; and a pair of diastereomers exist for every chiral center in a compound having two or more chiral centers. Even though Structural Formulas (I)-(VIII) do not explicitly depict stereochemistry, it is to be understood that these formulas encompass enantiomers free from the corresponding optical isomer, racemic mixtures, mixtures enriched in one enantiomer relative to its corresponding optical isomer, a diastereomer free of other diastereomers, a pair of diastereomers free from other diastereomeric pairs, mixtures of diasteromers, mixtures of diastereomeric pairs, mixtures of diasteromers in which one diastereomer is enriched relative to the other diastereomer(s) and mixtures of diastereomeric pairs in which one diastereomeric pair is enriched relative to the other diastereomeric pair(s)

[0051] A preferred diastereomeric pair is when R^2 and NR^xR^3 in Structural Formulas (I)-(VIII) are *cis* relative to one another By way of example, the *cis* diastereomeric pair for the compound represented by Structural Formula (II) is shown below in Structural Formulas (IX) and (X):



(IX)



(X).

[0052] The preferred configuration for R^2 and NR^xR^3 (depicted by $N(R^3)(COR^4)$ in Structural Formulas (IX) and (X) is (2*R*, 4*S*), as shown in Structural Formula (IX). Thus, Structural Formula (IX) represents a preferred optical isomer for the compound represented by Structural Formula (II) Similarly, the corresponding (2*R*,4*S*) optical isomer for the compounds represented by Structural Formulas (I) and (III)- (VIII) and Tables 1-6 are also specifically disclosed The more preferred configuration for R^2 and NR^xR^3 (depicted by $N(R^3)(COR^4)$) in Structural Formulas (IX) and (X) is (2*S*, 4*R*), as shown in Structural Formula (X). Thus, Structural Formula (X) represents a more preferred optical isomer for the compound represented by Structural Formulas (I) and (III)-(VIII) and in Tables 1- 6

[0053] As used herein, a structure depicting one optical isomer or a reference to one optical isomer is meant to include enantiomeric mixtures which are enriched with the depicted or referenced enantiomer relative to its optical isomer, for example, an enantiomeric excess of at least 50%, 75%, 90%, 95% 99% or 99.5%. As used herein, a structure depicting a diastereomeric pair or a reference to one diasteromeric pair is meant to include mixtures which are enriched with the depicted or

referenced diastereomeric pair relative to other diastereomers or diastereomeric pair(s) for the compound, for example, a molar excess of at least 50%, 75%, 90%, 95% 99% or 99 5%.

[0054] The enantiomers of the present invention may be resolved by methods known to those skilled in the art, for example by formation of diastereoisomeric salts which may be separated, for example, by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallization, gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with a bound chiral ligand or in the presence of a chiral solvent. Where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

[0055] The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above Specific procedures for chromatographically separating diastereomeric pairs of precursors used in the preparation of compounds disclosed herein are provided in Scheme 1 and 2

[0056] In certain instances compounds of the present invention may be associated in isolated form with solvent or water, as in a "solvate" or "hydrate". References to the disclosed compounds or structural formulas depicting the disclosed compounds are meant to include such solvates and hydrates.

[0057] The term "aliphatic" as used herein means straight-chain or branched hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic An aliphatic group is typically C_{1-8}, more typically C_{1-6}. For example, suitable aliphatic groups include substituted or unsubstituted linear or branched alkyl, alkenyl, alkynyl groups and hybrids thereof The terms "alkyl", "alkoxy", "hydroxyalkyl", "alkoxyalkylene", and "alkoxycarbonyl", used alone or as part of a larger moiety includes both straight and branched saturated chains containing one to eight carbon atoms. The terms "alkenyl" and alkynyl" used alone or as part of a larger moiety shall include both straight and branched chains containing two to eight carbon atoms and one or more double and/or triple bonds, respectively.

[0058] The term "cycloaliphatic" used alone or as part of a larger moiety shall include cyclic C_3-C_{10} hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic Cycloaliphatic groups are typically C_{3-10}, more typically C_{3-7}. A "cycloalkyl" is an cyclic aliphatic group that is completely saturated.

[0059] "Alkoxy" means (alkyl)-O-; "alkoxyalkylene" means (alkyl)-O-(alkylene) such as methoxymethylene (CH_3OCH_2); "hydroxyalkyl" means hydroxy substituted alkyl group; "alkoxy carbonyl means a carbonyl substituted with a carbonyl as in (alkyl)-O-C(O)-; and "aralkyl" mean alkyl substituted with an aromatic group. A "C_1-C_4 aralkyl group", for example, has a C_1-C_4 alkyl group substituted with an aromatic group

[0060] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring. 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).

[0061] The term "aromatic group" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", includes to carbocyclic aromatic ring groups and heteroaryl rings groups. The term "aromatic group" may be used interchangeably with the terms "aryl", "aryl ring" or "aromatic ring".

[0062] Carbocyclic aromatic ring groups have only carbon ring atoms and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl Also included within the scope of the term "carbocyclic aromatic ring", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings (aliphatic or heterocyclic), such as in an indanyl, phthalimidyl, naphthimidyl, phenantridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring.

[0063] The term "heteroaryl" or "heteroaromatic", used alone or as part of a larger moiety as in "heteroaralkyl" or "heteroarylalkoxy", refers to heteroaromatic ring groups having five to fourteen members, including monocyclic heteraromatic rings and polycyclic aromatic rings in which a monocyclic aromatic ring is fused to one or more other carbocyclic or heteroaromatic aromatic rings . Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl, benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisazolyl Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroaryl ring is fused to one or more cycloaliphatic or non-aromatic heterocyclic groups where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido [3,

4-d] pyrimidinyl. The term "heteroaryl" may be interchangeably with the term "heteroaryl ring" or the term "heteroaromatic"

[0064] The term "non-aromatic heterocyclic ring", used alone or as part of a larger moiety as in "hetercyclylalkyl", refers to non-aromatic ring systems typically having five to fourteen members, preferably five to ten, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Examples of non-aromatic heterocyclic rings include 3-1H-benzimidazol-2-one, 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, 4-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, 1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrorolidinyl, 1-piperazinyl, 2-piperazinyl, 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 4-thiazolidinyl, diazolonyl, N-substituted diazolonyl, 1-pthalimidinyl, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl

[0065] A "hydrocarbyl group" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer Preferably, n is an integer from 1 to 6, more preferably from 2 to 4 and more preferably from 2 to 3. A "substituted hydrocarbyl" is a hydrocarbyl group in which one or more methylene hydrogen atoms are replaced with a substituent Suitable substituents are as described below for a substituted aliphatic group Preferred substituents for the hydrocarbyl groups represented by X_3-X_6 are halo, -OH, =O, C_1-C_3 alkyl, C_1-C_3 alkoxy, nitro and cyano.

[0066] A hydrocarbyl group can be optionally interrupted by one or more functional groups. A hydrocarbyl is interrupted by a functional group when one of the internal methylenes is replaced with the functional group Examples of suitable "interrupting functional groups" include –O-, -S-, $-N(R^a)-$, -S(O)-, $-SO_2-$, -C(O)-, -OC(O)-, $-N(R^a)C(O)-$, $-C(O)N(R^a)-$, $-SO_2N(R^a)-$, and $-N(R^a)SO_2-$. R^a is –H or a C_1-C_3 alkyl group

[0067] An aromatic group (including Ring A, carbocyclic aromatic, heteroaryl, aralkyl, aralkoxy, aryloxyalkyl and heteroaralkyl and the like) group may contain one or more substituents. Examples of suitable substituents on an unsaturated carbon atom of an aromatic group include a halogen $-R^\circ$, $-OR^\circ$, $-SR^\circ$, 1,2-methylene-dioxy, 1,2-ethylenedioxy, protected OH (such as acyloxy), phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), $-CH_2(Ph)$, substituted $-CH_2(Ph)$, $-CH_2CH_2(Ph)$, substituted $-CH_2CH_2(Ph)$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, $-(CH_2)_yN(R')_2$, $-C(=NH)-N(R')_2$, $-(CH_2)_yNHC(O)R^\circ$, $-(CH_2)_yNHC(O)CH(V-R^\circ)(R^\circ)$ R' is R°, $-CO_2R^\circ$, $-SO_2R^\circ$ or $-C(O)R^\circ$ and preferably hydrogen, C_{1-6} aliphatic, CO_2R°, SO_2R° or $C(O)R^\circ$. R° is hydrogen or substituted or unsubstituted aliphatic, cycloaliphatic, arpmatic, aralkyl or non-aromatic heterocyclic group, and preferably hydrogen, C_{1-6} alkyl, phenyl (Ph), $-CH_2$ (Ph), aralkyl,

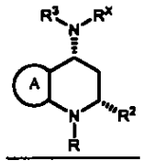
non-aromatic heterocyclic group or heteroaryl, y is 0-6; and V is C_1-C_6 alkylene group. Examples of substituents on the aliphatic group or the phenyl ring of R° include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, aminoalkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

[0068] An aliphatic group or a non-aromatic heterocycle may contain one or more substituents. Examples of suitable substituents on the saturated carbon of an aliphatic group of a non-aromatic heterocycle include those listed above for the unsaturated carbon of an aromatic group and the following: =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$ (alkyl), or =NR*. Each R* is independently selected from hydrogen, an unsubstituted aliphatic group or a substituted aliphatic group. Examples of substituents on the aliphatic group represented by R* include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

[0069] Suitable substitutents on the substitutable nitrogen of a heteroaryl or non-aromatic heterocyclic group include -R^+, -N(R^+)$_2$, -C(O)R^+, -CO$_2$ R^+, -C(O)C(O)R^+, -C(O)CH$_2$ C(O)R^+, -SO$_2$ R^+, -SO$_2$ N(R^+)$_2$, -C(=S)N(R^+)$_2$, -C(=NH)-N(R^+)$_2$, and -NR$^+$ SO$_2$ R^+; wherein R^+ is hydrogen, an aliphatic group, a substituted aliphatic group, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), CH$_2$(Ph), or an unsubstituted heteroaryl or non-aromatic heterocyclic ring Examples of substituents on the aliphatic group or the phenyl ring represented by R^+ include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl.

[0070] *2 Description of Compounds of General Formula I-A (and subsets thereof)*

[0071] Another embodiment of the present invention is a compound represented by Structural Formula **I-A:**



I-A

or a pharmaceutically acceptable salt thereof, wherein.

Ring A is an optionally substituted monocyclic aromatic;

R is –X_1-R^1,

R^X is –X_2-R^4,

X_1 and X_2 are each independently $-S(O)_2-$, -C(O)-, or -C(O)NH-;

R^1 is:

A) an aromatic group or heteroaromatic group having 5-6 ring atoms, fused to a monocyclic non-aromatic heterocyclic ring or monocyclic aromatic or heteroaromatic ring wherein the non-aromatic heterocyclic ring, the aromatic ring, or the heteroaromatic ring are optionally substituted; or

B) an aromatic group or heteroaromatic group having 5-6 ring atoms, substituted by:

i) T^1-V-T-R^Y;

ii) T^1-V-T-M-R^Y; or

iii) V-R^9, wherein R^9 is an optionally substituted non-aromatic carbocyclic or heterocyclic group,

and wherein the aromatic or heteroaromatic group having 5-6 ring atoms optionally is further substituted by 1-2 independently selected groups represented by R^Z;

each R^Z is independently selected from halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$,

each R' is independently hydrogen, alkyl, $-C(O)OR^\circ$, $S(O)_2R^\circ$, or $-C(O)R^\circ$;

each R° is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group and aromatic group represented by R° is optionally substituted with one or more independently selected groups represented by $R^\#$,

$R^\#$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$;

R^+ is –H, a C_1-C_3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine, or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups

represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated;

V is a covalent bond, -O-, -C(O)-, -N(R')-, -S-, -S(O)-, -C(O)NR^5-, -NR^{5}C(O)-, -S(O)$_2$NR^5-, -NR^{5}S(O)$_2$-, or –S(O)$_2$-;

T is C_{1-10} is a straight chain alkylene,

T^1 is a covalent bond, or a C_{1-10} straight chain alkylene, wherein T and T^1 together contain no more than 10 carbon atoms, and wherein T and T^1 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, O-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, alkoxy, or hydroxyl,

M is an optionally substituted group selected from monocyclic aromatic, heteroaromatic, monocyclic non-aromatic carbocyclic, or heterocyclic group;

R^Y is -C(O)OR^5, -C(O)R^5, -OC(O)R^5, -C(O)N(R^5)$_2$, -NR^{5}C(O)R^5, -NR^{5}C(O)OR^5, -S(O)$_2$R^5, -S(O)$_2$COR^5, -S(O)$_2$N(R^5)$_2$, -NR^{5}S(O)$_2$R^5, -NR^{5}S(O)$_2$R^5, S(O)$_2$OR^5, -S(O)OR^5, -S(O)R^5, -SR^5, -C(O)NR^{5}S(O)$_2$R^5, -CN, -NR^{5}C(O)N(R^5)$_2$, -OC(O)N(R^5)$_2$, -N(R^5)$_2$, -OR^5, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group,

provided that T is C_{2-10} when V is a covalent bond, and T is C_{2-10} when V is –O-, -S-, or -N(R')- and R^Y is –CN, –OH, -SH, -N(R^5)$_2$

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, -C(O)OCH$_2$C$_6$H$_5$, S(O)$_2$CH$_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, C(O)NH$_2$, benzyl, pyrrolidinyl, morpholinyl, or -N(R^5)$_2$ is a nitrogen-containing non-aromatic heterocyclic group;

R^2 is C_{1-3} alkyl,

R^3 is an optionally substituted monocyclic or bicyclic group selected from aromatic, heteroaromatic, non-aromatic carbocyclic, or non-aromatic heterocyclic, and

R^4 is optionally substituted C_{1-6}alkyl, C_{1-4}hydroxyalkyl, or optionally substituted C_{3-6}cycloalkyl.

[0072] In one embodiment, compounds of formula **I-A**, or a pharmaceutically acceptable salt thereof, are provided, wherein

Ring A is an optionally substituted monocyclic aromatic;

R is $-X_1-R^1$;

R^X is $-X_2-R^4$;

X_1 and X_2 are each independently $-S(O)_2-$, -C(O)-, or -C(O)NH-,

R^1 is: A) an aromatic group or heteroaromatic group having 5-6 ring atoms, substituted by:

i) T^1-V-T-R^Y,

ii) T^1-V-T-M-R^Y; or

iii) V-R^9 wherein R^9 is an optionally substituted non-aromatic carbocyclic or heterocyclic group;

and wherein the aromatic or heteroaromatic group represented by R^1 optionally is further substituted by 1-2 independently selected groups represented by R^Z; or

B) an aromatic group or heteroaromatic group having 5-6 ring atoms, fused to a monocyclic non-aromatic heterocyclic ring or monocyclic aromatic ring wherein the non-aromatic heterocyclic ring or the aromatic ring are optionally substituted;

each R^Z is independently selected from halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$;

each R' is independently hydrogen, alkyl, $-C(O)OR^\circ$, $S(O)_2R^\circ$, or $-C(O)R^\circ$,

each R° is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group and aromatic group represented by R° is optionally substituted with one or more independently selected groups represented by $R^\#$;

$R^\#$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$,

R^+ is –H, a C_1-C_3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine, or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated,

R^Y is $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)NR^5_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-S(O)R^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-OC(O)N(R^5)_2$, $-N(R^5)_2$, $-OR^5$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group,

V is a covalent bond, -O-, -C(O)-, -N(R')-, -S-, -S(O)-, $-C(O)NR^5-$, $-NR^5C(O)-$, $-S(O)_2NR^5-$, $-NR^5S(O)_2-$, or $-S(O)_2-$;

T is C_{1-10} is a straight chain alkylene, provided that T is C_{2-10} when V is a covalent bond, and T is C_{2-10} when V is –O-, -S-, or -N(R')- and R^Y is –CN, –OH, -SH, -$N(R^5)_2$;

T^1 is a covalent bond, or a C_{1-10} straight chain alkylene, wherein T and T^1 together contain no more than 10 carbon atoms, and wherein T and T^1 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, amine, alkylamine, dialkylamine, or hydroxyl,

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, -$C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or –$N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group;

M is an optionally substituted monocyclic aromatic, heteroaromatic or an optionally substituted monocyclic non-aromatic carbocyclic or heterocyclic group,

R^2 is C_{1-3} alkyl;

R^3 is an optionally substituted aromatic group having 5-6 ring atoms, and

R^4 is C_{1-3} alkyl or C_{1-3} hydroxyalkyl

[0073] The sections below defining the terms "aromatic group", "heteroaromatic group", "non-aromatic carbocycle" and "non-aromatic heterocyclic group" provide specific examples of suitable values for M Suitable substituents for aromatic rings represented by M are as defined for R^{11}, suitable substituents for carbocyclics and non-aromatics are as described in sections below defining suitable substituents for these two groups.

[0074] In certain aspects compounds of the invention are compounds other than one of the following compounds

[0075] When R^1 is phenyl *para* substituted with V-T-R^Y, R^2 is methyl, R^3 is *para* chlorophenyl, R^X is $C(O)CH_3$, X_1 is –C(O) and V is –O-, T-R^Y is -CH_2-CH_2-$C(CH_3)_2$-$CONH_2$, –CH_2-CH_2-$C(CH_3)_2$-OH, –CH_2-CH_2-CH_2-$C(CH_3)_2$-OH, -CH_2-CH_2-$C(CH_3)_2$-COOH, –CH_2-C (spiro cyclopropyl)-CH_2-COOH, or -CH_2-$C(CH_3)_2$-COOH.

[0076] When R^1 is phenyl *para* substituted with V-T-R^Y, R^2 is methyl, R^3 is *para* chlorophenyl, R^X is $C(O)CH_3$, X_1 is –C(O) and V is a covalent bond then, T-R^Y is -CH_2-CH_2-COOH.

[0077] When R^2 is methyl, R^3 is *para* chlorophenyl, R^X is $C(O)CH_3$, X_1 is C(O) and R^1 is phenyl *para* substituted with V-R^9 wherein R^9 is an optionally substituted non-aromatic heterocyclic group, V is a covalent bond R^1 is *N*-morpholinyl, *N*-ethoxycarbonyl-4-piperdinyl, *N*-acetyl-4-piperdinyl, *N*-ethoxycarbonyl-4-piperid-3-enyl, *N*-pyrrolidinyl, *N*-ethyl-*N'*-piperazinyl, *N*-acetyl-*N'*-piperazinyl, *N*-(2'-hydroxyacetyl)-*N'*-piperazinyl, *N*-($CH_2C(O)OH$-*N'*-piperazinyl, or *N*-($CH_2C(O)NH_2$)-*N'*-piperazinyl

[0078] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is phenyl *para* substituted with V-R^9 wherein R^9 is an optionally substituted non-aromatic heterocyclic group, V is –O-, R^1 is *N*-ethoxycarbonyl-4-piperdinyl or *N*-acetyl-4-piperdinyl.

[0079] When R^2 is methyl, R^3 is phenyl, R^x is $C(O)CH_2CH_3$, X_1 is C(O) and R^1 is phenyl *para* substituted with a non-aromatic heterocyclic group, R^1 is *N*-acetyl-4-piperdinyl, or *N*-morpholinyl

[0080] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is phenyl fused to an optionally substituted non-aromatic heterocyclic group, R^1 tetrahydrofuranyl, or N'-methyl morpholinyl.

[0081] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is pyridinyl *para* substituted with a non aromatic heterocyclic group, R^1 is *N*-morpholinyl

[0082] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is phenyl fused to an optionally substituted aromatic group, R^1 is *N*-isopropyl triazolyl, *N*-methyl triazolyl, *N*-isopropyl imidazolyl, 2, methyl N hydroxyethyl imidazolyl, 2, methyl N carboxymethyl imidazolyl, N carboxyethyl triazolyl *N*-isopropyl pyrazolyl.

[0083] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is imidazolyl fused to an optionally substituted aromatic group, R^1 is phenyl.

[0084] When R^2 is methyl, R^3 is *para* chlorophenyl, R^x is $C(O)CH_3$, X_1 is C(O) and R^1 is thiazolyl fused to an optionally substituted aromatic group, R^1 is phenyl

[0085] In some embodiments compounds of the invention are compounds other than compounds disclosed in our U S Patent Application 10/678,872 filed October 4, 2003 (the entire contents of which are incorporated herein by reference).

[0086] In other embodiments, compounds of the invention are compounds other than (±)-*Cis*-N-[1-(1H-indole-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-[1-(benzofuran-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester; (±)-*Cis*--{4-[2-Methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid, (±)-*Cis*-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide, (±)-*Cis*-N-[1-(4-carbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-{1-[4-(2-hydroxy-2-methyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide, (±)-*Cis*-N-[1-(4-dimethylcarbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-[1-(benzo[b]thiophene-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide; (±)-*Cis*-N-[1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-acetic acid, (±)-*Cis*-

N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester, (±)-*Cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-{1-[4-(1-acetyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide, (±)-*Cis*-N-{1-[4-(1-ethyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide; (±)-*Cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide, (±)-*Cis*-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-[2-Methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester, (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionamide, (±)-*Cis*-N-[1-(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-[1-(benzo[c]isoxazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester, (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid; (±)-*Cis*-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-propionamide, (±)-*Cis*-N-(4-chloro-phenyl)-N-{1-[4-(3-hydroxy-2,2-dimethyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide; (±)-*Cis*-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid methyl ester; (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-cyclopentyloxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (±)-*Cis*-N-{1-[4-(4-Acetyl-piperazin-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid, (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(6-morpholin-4-yl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-piperidine-1-carboxylic acid ethyl ester; (2*S* ,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide, (2*S* ,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid, (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide; (2*S* ,4*R*)-N-{1-[4-(1-Acetyl-piperidin-4-yloxy)-benzoyl]-2-methyl-1,2,3,4-

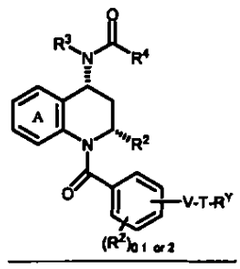
tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(pyridin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide; (2*S* ,4*R*)-4-(3-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid, (2*S*, 4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-1-carboxylic acid ethyl ester; (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide, (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-propionic acid; (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid, N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide, N-{(2R,4S)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-[(2S,4R)-2-methyl-1-(4-morpholin-4-ylbenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylpropanamide; N-[(2R,4S)-2-methyl-1-(4-morpholin-4-ylbenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylpropanamide; N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-{(2R,4S)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide, N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; (4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanoic acid; N-{(2S,4R)-1-[4-(2-amino-2-oxoethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; Ethyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate, N-[(2S,4R)-1-(1,3-benzodioxol-5-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylacetamide; N-{(2S,4R)-2-methyl-1-[(3-methyl-1-benzofuran-2-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylacetamide, 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N-ethylbutanamide, N-(4-Chlorophenyl)-N-[(2S,4R)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide, 4-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylbutanamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(4-oxo-4-pyrrolidin-1-ylbutoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; 4-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanamide; 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N-(methylsulfonyl)butanamide; Ethyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanoate; 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-

yl]carbonyl}phenoxy)-N-hydroxybutanamide, N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(3-cyanopropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[3-(1,2,4-oxadiazol-5-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, 3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propanamide, N-{(2S,4R)-1-[4-(3-aminopropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; N-{(2S,4R)-1-[4-(2-amino-2-oxoethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[2-(methylamino)-2-oxoethoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, 2-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N,N-dimethylacetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(2-morpholin-4-yl-2-oxoethoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[2-(2-oxopyrrolidin-1-yl)ethoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[2-(1H-imidazol-1-yl)ethoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-[(2S,4R)-1-(2,3-dihydro-1-benzofuran-5-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide; N-(4-Chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-pyrrolidin-1-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-morpholin-4-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[(4-oxopentyl)oxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; N-(4-Chlorophenyl)-N-{(2S,4R)-1-[4-(3-hydroxy-3-methylbutoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-Chlorophenyl)-N-((2S,4R)-1-{4-[(4-hydroxy-4-methylpentyl)oxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[(1-ethylpiperidin-4-yl)methoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[3-(1H-imidazol-1-yl)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, (2S,4R)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(4-ethylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-{(2S,4R)-1-[4-(4-acetylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(4-glycoloylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-morpholin-4-ylprop-1-yn-1-yl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)but-3-ynoic acid; N-

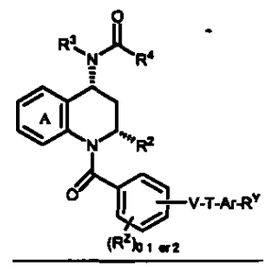
[(2S,4R)-1-(1H-benzimidazol-2-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-(4-chlorophenyl)acetamide; N-[(2S,4R)-1-(1,3-benzothiazol-2-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-(4-chlorophenyl)acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[(1-methyl-1H-1,2,3-benzotriazol-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-1-[(1-isopropyl-1H-benzimidazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, [4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)piperazin-1-yl]acetic acid; N-((2S,4R)-1-{4-[4-(2-amino-2-oxoethyl)piperazin-1-yl]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-N-(4-chlorophenyl)acetamide, 3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propanoic acid, 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid; {1-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)methyl]cyclopropyl}acetic acid, (2E)-4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)but-2-enoic acid; 3-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid; (2E)-4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-methylbut-2-enoic acid, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-{[(trifluoromethyl)sulfonyl]amino}propoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-1-{[1-(2-hydroxyethyl)-2-methyl-1H-benzimidazol-5-yl]carbonyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, 5-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}-2-methyl-1H-benzimidazol-1-yl)acetic acid, 3-(5-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}-1H-1,2,3-benzotriazol-1-yl)propanoic acid; (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; and (2S,4R)- N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(1H-tetrazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide

[0087] The classes and subclasses described in more detail below and in the specification herein apply to each of the embodiments for compound **I-A** as described above.

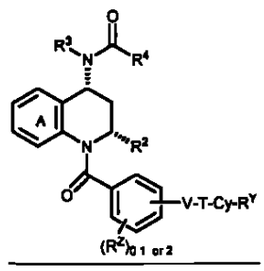
[0088] In one embodiment, the present invention is a compound represented by Structural Formulas **(II-A)**, **(III-A)** or **(IV-A)**



(II-A)



(III-A)



(IV-A)

[0089] Ar in Structural Formula **(III-A)** is a monocyclic aromatic ring Cy in Structural Formula (IV) is a monocyclic non-aromatic carbocyclic or heterocyclic group. All other variables in Structural Formulas **(II-A)-(IV-A)** are as described for Structural Formula **(I-A)**. Preferably, V in Structural Formulas **(II-A)-(IV-A)** is a covalent bond, -O-, or –N(R')-, and T in Structural Formulas **(II-A)-(IV-A)** 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, amine, alkylamine, dialkylamine, or hydroxyl

[0090] Alternatively, in Structural Formula **(II-A)-(IV-A)** V is a covalent bond, -NR'- or -O-; and T is a C_{1-10} straight chain alkylene (preferably C_{1-5}, more preferably C_{1-3}) optionally mono-substituted at any substitutable carbon atom with halide, alkyl, haloalkyl, amine, dialkylamine, or hydroxyl

[0091] Preferably, R^Y in Structural Formula **(I-A)** and **(II-A)** is $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-N(R^5)_2$, an optionally substituted non-aromatic heterocyclic group represented by R^7, or an optionally substituted heteroaryl group represented by R^8 R^7 is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahyrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl. R^8 is an optionally substituted furanyl,

tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl, and all the remainder of the variables are as described in the previous paragraph

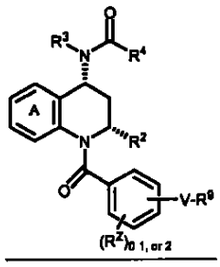
[0092] More preferably, R^Y in Structural Formula **(I-A)** and **(II-A)** is $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, an optionally substituted non-aromatic heterocyclic group represented by R^7 or an optionally substituted heteroaryl group represented by R^8. R^7 is piperidinonyl, morpholinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl. R^8 is tetrazolyl, oxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, or imidazolyl. R^5 is independently H or alkyl, or $N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group. V is a covalent bond, or -O-, and T is a C_{1-5} straight chain alkylene optionally substituted at the carbon atom adjacent to R^Y with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, amine, dialkylamine, or hydroxyl

[0093] More preferably, R^1 in Structural Formula **(I-A)-(III-A)** is a phenyl ring optionally substituted by at the *meta* and *para* positions (more preferably *para*) by V-T-R^Y or V-T-M-R^Y. Even more preferably R^Y is $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, *N*-substituted 2-imidazolidinyl, *N'*-substituted *N*-imidazolidinyl, *N*-substituted 4-imidazolidinyl, *N*-substituted 5-imidazolidinyl, *N*-imidazolidinonyl, 4-imidazolidinonyl, 5-imidazolidinonyl, *N*-substituted 4-imidazolidinonyl, *N*-substituted 5-imidazolidinonyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-pyrrolidin-2-onyl,, 3-pyrrolidin-2-onyl, 4-pyrrolidin-2-onyl, 5-pyrrolidin-2-onyl, *N*-substituted 3-pyrrolidin-2-only, *N*-substituted 4-pyrrolidin-2-only, *N*-substituted 5-pyrrolidin-2-onyl, *N*-pyrrolidin-3-onyl, 2-pyrrolidin-3-onyl, 4-pyrrolidin-3-onyl, 5-pyrrolidin-3-onyl, *N*-substituted 2-pyrrolidin-3-onyl *N*-substituted 4-pyrrolidin-3-onyl, *N*-substituted 5-pyrrolidin-3-onyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperidin-2-onyl, 3-piperidin-2-onyl, 4-piperidin-2-onyl, 5-piperidin-2-onyl, 6-piperidin-2-onyl, *N*-substituted 3-piperidin-2-onyl, *N*-substituted 4-piperidin-2-onyl, *N*-substituted 5-piperidin-2-onyl, *N*-substituted 6-piperidin-2-onyl, *N*-piperidin-3-onyl, 2-piperidin-3-onyl, 4-piperidin-3-onyl, 5-piperidin-3-onyl, 6-piperidin-3-onyl, *N*-substituted 2-piperidin-3-onyl, *N*-substituted 4-piperidin-3-onyl, *N*-substituted 5-piperidin-3-onyl, *N*-substituted 6-piperidin-3-onyl, *N*-piperidin-4-onyl, 2-piperidin-4-onyl, 3-piperidin-4-onyl, 5-piperidin-4-onyl, 6-piperidin-4-onyl, *N*-substituted 2-piperidin-4-onyl, *N*-substituted 3-piperidin-4-onyl, *N*-substituted 5-piperidin-4-onyl, *N*-substituted 6-piperidin-4-onyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-substituted 2-piperazinyl, furanyl, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, 4-(1,2,3)oxadiazolyl, 5-(1,2,3)oxadiazolyl, 3-(1,2,4)oxadiazolyl, 5-(1,2,4)oxadiazolyl, 3-

(1,2,5)oxadiazolyl, 4-(1,2,5)oxadiazolyl, 2-(1,3,4)oxadiazolyl, 5-(1,3,4)oxadiazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, *N*-substituted 2-pyrrolyl, *N*-substituted 3-pyrrolyl, *N*-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, *N*-substituted 3-pyrazolyl, *N*-substituted 4-pyrazolyl, *N*-substituted 5-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl. V is -O-, and T is a C_{1-3} straight chain alkylene substituted at the carbon adjacent to R^Y with fluoro, methyl, gem dimethyl, gem difluoro fluoromethyl, spiro cyclopropyl, spiro cyclobutyl, optionally *N*-substituted spiro azetidinyl, optionally *N*-substituted spiro aziridinyl, optionally *N*-substituted sprio pyrrolidinyl, optionally *N*-substituted spiro piperidinyl, amine, methylamine, dimethylamine, or hydroxyl.

[0094] Still more preferably R^Y is -C(O)OR^5, -C(O)N(R^5)$_2$, -OH, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl R^5 is –H, methyl, or ethyl R^1 in Structural Formula **(I-A)-(III-A)** is a phenyl ring optionally substituted by at the *para* position by V-T-R^Y or V-T-M-R^Y.

[0095] In another preferred embodiment, the present invention is a compound represented by Structural Formula **(V-A)**:



(V-A)

[0096] All variables in Structural Formula **(V-A)** are as described for Structural Formula **(I-A)**. Preferably R^9 in Structural Formula **(V-A)** 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, piperidinyl, or 1,2,5-thiadiazolidine S, S-dioxide In other embodiments, R^9 in Structural Formula **(V-A)** 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. R^9 is preferably *meta* or *para* to the carbon atom bonded

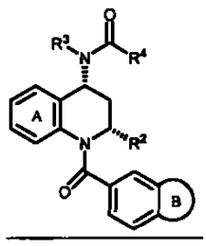
to the carbonyl, more preferably *para* V is preferably a covalent bond or –O-, more preferably a covalent bond

[0097] More preferably, R^9 in Structural Formula **(V-A)** is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted by alkyl, halide, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR^o$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR^o$ or -$N(R^{12})_2$, n is an integer from 1 to 4, and each R^{12} is independently -H, alkyl, haloalkyl, or hydroxyalkyl, and all of the other variables are as described in the previous paragraph. Alternatively, for those groups represented by R^9 which have a substitutable ring nitrogen, the group is *N*-substituted with T^2-R^{Y1}, which is defined below, and optionally substituted at one or more substitutable ring carbon atoms with one or more groups listed above in this paragraph

[0098] More preferably, R^9 in Structural Formula **(V-A)** is *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-substituted 2-piperazinyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, or -$C(O)N(R^{12})_2$, and wherein the *N*-substituents are alkyl, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR^o$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR^o$ or -$C(O)N(R^{12})_2$ For these groups represented by R^9 which have a substitutable ring N, one preferred *N*-substituent is T^2-R^{Y1}, which is defined below.

[0099] Even more preferably, R^9 in Structural Formula **(V-A)** is *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, or *N*-substituted 2-piperazinyl, and is optionally substituted by at any substitutable carbon atom by chloride, fluoride, bromide, methyl, ethyl, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$C(O)R^{12}$ or $C(O)NH_2$, and wherein the *N*-substituents are methyl, ethyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR^o$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR^o$, or -$C(O)NH_2$, and each R^{12} is independently -H, methyl, or ethyl For these groups represented by R^9 which have a substitutable ring N, one preferred *N*-substituent is T^2-R^{Y1}, which is defined below

[00100] In another preferred embodiment, the present invention is a compound represented by Structural Formula **(VI-A):**



(VI-A)

[00101] B is an optionally substituted monocyclic non-aromatic heterocyclic ring represented by R^{10}, or a monocyclic aromatic ring (preferably heteroaromatic) represented by R^{13}; all other variables in Structural Formula **(VI-A)** are as described for Structural Formula **(I-A).**

[00102] Preferably, R^{10} in Structural Formula **(VI-A)** is oxazolidinyl, oxazolidinonyl, dioxolanyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dithiolanyl, pyrrolidinyl, piperazinyl, piperidinyl, piperidinyl, tetrahydrothienyl S,S dioxide, thiomorpholinyl S,S dioxide, tetrahydrothiopyranyl S,S dioxide, each of which are optionally substituted R^{13} is pyrazolyl, triazolyl, imidazolyl, furanyl, pyrrolyl, thienyl, cyclopentadienyl, and thienyl S,S dioxide, each of which are optionally substituted All other variables in Structural Formula **(VI-A)** are as described in the previous paragraph.

[00103] Other examples of suitable values for R^{10} include tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}-$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}-$, $-C(O)N(R^{12})_2$, and other examples of suitable values for R^{13} include triazolyl, imidazolyl, furanyl, pyrrolyl, thienyl, each of which is optionally substituted at any substitutable ring carbon atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)OR^{12}-$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl haloalkyl,

hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -R^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, S(O)$_2$N(R^{12})$_2$, -C(O)N(R^{12})$_2$ Each R^{12} is independently H, alkyl, haloalkyl, or hydroxyalkyl.

[00104] Still other examples of suitable values for R^{10} include tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, -R^{12}C(O)OR^{12}-, -C(O)N(R^{12})$_2$, -NR^{12}C(O)R^{12}, -NR^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, -S(O)$_2$COR^{12}, -S(O)$_2$N(R^{12})$_2$, -S(O)$_2$OR^{12}, -S(O)OR^{12}, -OR^{12}, -SR^{12}, -CN, -NR^{12}C(O)N(R^{12})$_2$, -OC(O)N(R^{12})$_2$, or -N(R^{12})$_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -R^{12}C(O)OR^{12}-, -C(O)N(R^{12})$_2$, and other examples of suitable values for R^{13} include triazolyl, imidazolyl, furanyl, pyrrolyl, thienyl, each of which is optionally substituted at any substitutable ring carbon atom with alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, -C(O)OR^{12}-, -C(O)N(R^{12})$_2$, -NR^{12}C(O)R^{12}, -NR^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, -S(O)$_2$COR^{12}, -S(O)$_2$N(R^{12})$_2$, -S(O)$_2$OR^{12}, -S(O)OR^{12}, -OR^{12}, -SR^{12}, -CN, -NR^{12}C(O)N(R^{12})$_2$, -OC(O)N(R^{12})$_2$, or -N(R^{12})$_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -R^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, S(O)$_2$N(R^{12})$_2$, -C(O)N(R^{12})$_2$. Each R^{12} is independently H, alkyl, haloalkyl, or hydroxyalkyl

[00105] Even more preferably, in Structural Formula **(VI-A)** R^{10} is dioxolanyl, tetrahydrofuranyl, morpholinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, or -C(O)N(R^{12})$_2$, or each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, or -C(O)N(R^{12})$_2$. R^{13} is triazolyl, imidazolyl, or pyrrolyl each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, or -C(O)N(R^{12})$_2$, and each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, C(O)OR^{12}, -C(O)R^{12}, -R^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, S(O)$_2$N(R^{12})$_2$, -C(O)N(R^{12})$_2$.

[00106] Still more preferably, in Structural Formula **(VI-A)** R^{10} is morpholinyl and is optionally *N*-substituted by methyl, ethyl, -C(O)OR^{12}, C(O)NH$_2$ or -C(O)R^{12}, R^{13} is triazolyl and is optionally *N*-substituted by methyl, ethyl, -C(O)OR^{12}, C(O)NH$_2$ or -C(O)R^{12}, and each R^{12} is independently -H, methyl, or ethyl.

[00107] In another preferred embodiment, in Structural Formula **(VI-A)** Ring B a monocyclic non-aromatic heterocycle or a monocyclic heteroaryl group comprising a ring nitrogen atom that is substituted with T^2-R^{Y1} These monocyclic non-aromatic and heteroaryl groups are optionally further substituted. Preferably, the monocyclic non-aromatic heterocyclic ring is represented by R^{10}, Preferably, the monocyclic heteroaromatic ring is represented by R^{13} Examples of suitable values for R^{10} include oxazolidinyl, oxazolidinonyl, thiazolidinyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl, each of which is *N*-substituted with T^2-R^{Y1}

and optionally further substituted at any one or more ring carbon atoms by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$

[00108] Other examples of suitable values for R^{10} include oxazolidinyl, oxazolidinonyl, thiazolidinyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl, each of which is *N*-substituted with T^2-R^{Y1} and optionally further substituted at any one or more ring carbon atoms by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-N(R^{12})_2$.

[00109] Examples of suitable values for R^{13} include pyrazolyl, triazolyl, imidazolyl, or pyrrolyl, each of which is *N*-substituted with T^2-R^{Y1} and optionally further substituted at any one or more ring carbon atoms with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$

[00110] Other examples of suitable values for R^{13} include pyrazolyl, triazolyl, imidazolyl, or pyrrolyl, each of which is *N*-substituted with T^2-R^{Y1} and optionally further substituted at any one or more ring carbon atoms with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-N(R^{12})_2$ Each R^{12} is independently H, alkyl, haloalkyl, or hydroxyalkyl. All other variables are as described above for Structural Formula **(VI-A)**.

[00111] Preferably, T^2 in Structural Formula **(VI-A)** 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, amine, alkylamine, dialkylamine, or hydroxyl. R^{Y1} is $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-N(R^5)_2$, an optionally substituted non-aromatic heterocyclic group represented by R^7, or an optionally substituted heteroaryl group represented by R^8 R^7 is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahyrothiophene,

morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl. R^8 is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl.

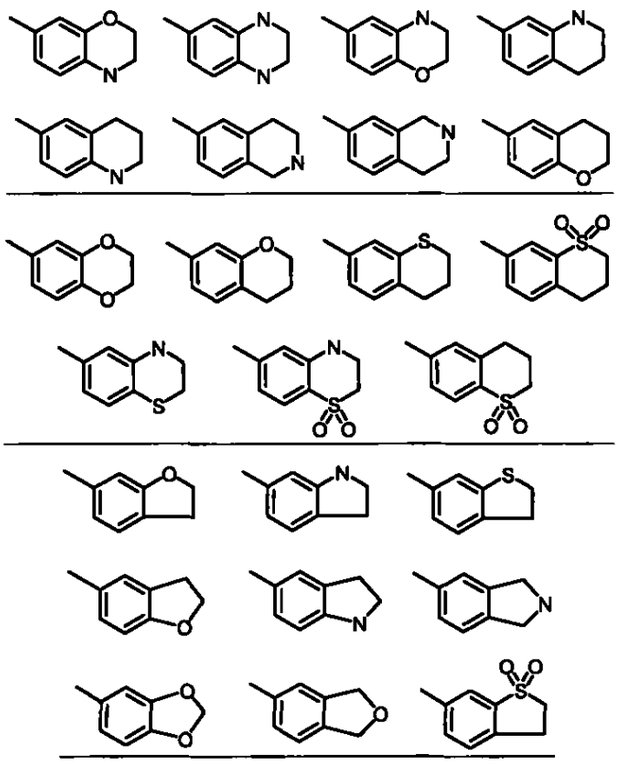
[00112] Other examples of suitable values for R^{10} include morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-N(R^{12})_2$. Other examples of suitable values for R^{13} include triazolyl, imidazolyl, or pyrrolyl, each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable ring carbon atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, or $-N(R^{12})_2$. R^{Y1} is $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, an optionally substituted non-aromatic heterocyclic group represented by R^7 or an optionally substituted heteroaryl group represented by R^8 Each R^5 is independently H or alkyl, or $N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group R^7 is piperidinonyl, morpholinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl R^8 is tetrazolyl, oxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, or imidazolyl. T^2 is a C_{1-5} straight chain alkylene optionally substituted at the carbon atom adjacent to R^Y with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, amine, dialkylamine, or hydroxyl.

[00113] Preferably, other examples of suitable values for R^{10} include morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$. Other examples of suitable values for R^{13} include imidazolyl, or pyrrolyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, or $-C(O)N(R^{12})_2$, and each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, $C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$ R^{Y1} is $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, *N*-substituted 2-imidazolidinyl, *N'*-substituted *N*-imidazolidinyl, *N*-substituted 4-imidazolidinyl, *N*-substituted 5-imidazolidinyl, *N*-imidazolidinonyl, 4-imidazolidinonyl, 5-imidazolidinonyl, *N*-

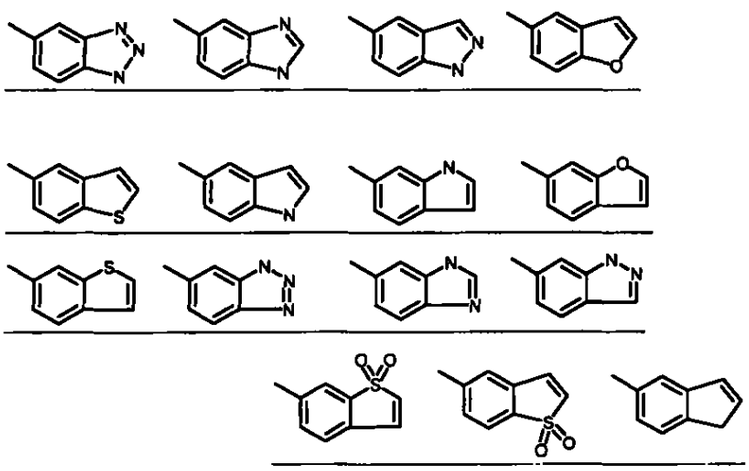
substituted 4-imidazolidinonyl, *N*-substituted 5-imidazolidinonyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-pyrrolidin-2-onyl,, 3-pyrrolidin-2-onyl, 4-pyrrolidin-2-onyl, 5-pyrrolidin-2-onyl, *N*-substituted 3-pyrrolidin-2-only, *N*-substituted 4-pyrrolidin-2-only, *N*-substituted 5-pyrrolidin-2-onyl, *N*-pyrrolidin-3-onyl, 2-pyrrolidin-3-onyl, 4-pyrrolidin-3-onyl, 5-pyrrolidin-3-onyl, *N*-substituted 2-pyrrolidin-3-onyl *N*-substituted 4-pyrrolidin-3-onyl, *N*-substituted 5-pyrrolidin-3-onyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperidin-2-onyl, 3-piperidin-2-onyl, 4-piperidin-2-onyl, 5-piperidin-2-onyl, 6-piperidin-2-onyl, *N*-substituted 3-piperidin-2-onyl, *N*-substituted 4-piperidin-2-onyl, *N*-substituted 5-piperidin-2-onyl, *N*-substituted 6-piperidin-2-onyl, *N*-piperidin-3-onyl, 2-piperidin-3-onyl, 4-piperidin-3-onyl, 5-piperidin-3-onyl, 6-piperidin-3-onyl, *N*-substituted 2-piperidin-3-onyl, *N*-substituted 4-piperidin-3-onyl, *N*-substituted 5-piperidin-3-onyl, *N*-substituted 6-piperidin-3-onyl, *N*-piperidin-4-onyl, 2-piperidin-4-onyl, 3-piperidin-4-onyl, 5-piperidin-4-onyl, 6-piperidin-4-onyl, *N*-substituted 2-piperidin-4-onyl, *N*-substituted 3-piperidin-4-onyl, *N*-substituted 5-piperidin-4-onyl, *N*-substituted 6-piperidin-4-onyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-substituted 2-piperazinyl, furanyl, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, 4-(1,2,3)oxadiazolyl, 5-(1,2,3)oxadiazolyl, 3-(1,2,4)oxadiazolyl, 5-(1,2,4)oxadiazolyl, 3-(1,2,5)oxadiazolyl, 4-(1,2,5)oxadiazolyl, 2-(1,3,4)oxadiazolyl, 5-(1,3,4)oxadiazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, *N*-substituted 2-pyrrolyl, *N*-substituted 3-pyrrolyl, *N*-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, *N*-substituted 3-pyrazolyl, *N*-substituted 4-pyrazolyl, *N*-substituted 5-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl. T^2 is a C_{1-3} straight chain alkylene substituted with fluoro, methyl, gem dimethyl, gem difluoro fluoromethyl, spiro cyclopropyl, spiro cyclobutyl, optionally *N*-substituted spiro azetidinyl, optionally *N*-substituted spiro aziridinyl, optionally *N*-substituted spiro pyrrolidinyl, optionally *N*-substituted spiro piperidinyl, amine, methylamine, dimethylamine, or hydroxyl

[00114] More preferably, other examples of suitable values for R^{10} include morpholinyl, *N*-substituted with T^2-R^{Y1} and further optionally substituted at the carbon alpha to the nitrogen atom with methyl or gem dimethyl. Other examples of suitable values for R^{13} include imidazolyl *N*-substituted with T^2-R^{Y1} and further optionally substituted at the carbon alpha to the nitrogen atom with methyl or gem dimethyl. R^{Y1} is -C(O)OR^5, -C(O)$N(R^5)_2$, -OH, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl

[00115] In one embodiment, in Structural Formula **(VI-A)** R^1 is an optionally substituted phenyl ring fused to the group represented by R^{10} as represented by the following Structural Formulas



[00116] In one embodiment in Structural Formula **(VI-A)** R^1 is an optionally substituted phenyl ring fused to the group represented by R^{13} as represented by the following Structural Formulas:



[00117] The Structural Formulas shown above for the fused bicyclic rings can be further optionally substituted at one or more substitutable carbon atoms or nitrogen atoms. Examples of suitable substituents as described above for the groups represented by R^{10} and R^{13}. In a more specific embodiment, any one of the fused bicyclic ring systems shown above that have substitutable nitrogen atoms are *N*-substituted with T^2-R^{Y1}. T^2-R^{Y1} is as described above.

As described above, Ring A (preferably phenyl ring A) in Structural Formulas **(I-A)-(VI-A)** is optionally substituted (preferably at the six and seven positions) with one or more groups represented by R^{14}; in Structural Formulas **(I-A)-(V-A)** R^1 is an aromatic group (preferably a phenyl ring) optionally substituted by 1-2 independently selected groups represented by R^Z; and in Structural Formulas **(I-A)-(VI-A)** R^3 is an aromatic group (preferably e g., a phenyl ring) optionally substituted with one or more groups represented by R^{11} Suitable values for R^{14}, R^Z, and R^{11} are ones that do not substantially decrease the ability of the compound of the invention to inhibit CRTH2. Examples of suitable substituents are halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$ Additional values for R^{11} include 3,4-methylene-dioxy and 3,4-ethylene-dioxy In other embodiments, suitable substituents for R^{11} also include halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, $-(CH_2)_{1-4}CO_2R^\circ$, $-O(CH_2)_{1-4}CO_2R^\circ$, $-(CH_2)_{1-4}CON(R^\circ)_2$, $-O(CH_2)_{1-4}CON(R^\circ)_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^\circ$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^\circ$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^\circ)_2$, $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^\circ)_2$, or $-C(=NH)-N(R')_2$.

[00118] Each R' is independently hydrogen, alkyl, $-C(O)OR^\circ$, $S(O)_2R^\circ$, or $-C(O)R^\circ$ Each R° is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group and aromatic group represented by R° is optionally substituted with one or more independently selected groups represented by $R^\#$ $R^\#$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$. R^+ is –H, a C_1-C_3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine, or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated

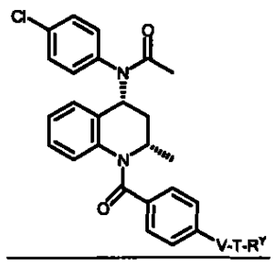
[00119] Preferred values for R^Z and R^{11} are halogen, haloalkyl, $-R^\circ$, $-OR^\circ$, -O(haloalkyl), $-CO_2R^\circ$, $-C(O)R^\circ$, $-NR'SO_2R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, and $-OC(O)N(R^\circ)_2$. 3,4-methylene-dioxy and 3,4-ethylene-dioxy, and $-N(R')_2$ are also preferred values for R^{11}. Each R° is independently hydrogen, haloalkyl or an alkyl group, each R' is independently H or alkyl

[00120] Preferably, R^3 is a phenyl ring optionally substituted at the *meta* or *para* positions with one or more groups represented by R^{11} More preferred values for R^{11} and R^Z are halogen, haloalkyl, -R^o, -OR^o, and –O(haloalkyl). -$NR'SO_2R^o$ and –$N(R')_2$ are also preferred values for R^{11}

[00121] More preferably, R^3 is a phenyl ring optionally substituted at the *para* position with R^{11}. R^1 is a phenyl ring optionally substituted at the *meta* position by R^Z Even more preferred values for R^Z and R^{11} are chloride, fluoride, bromide, -OR^o, or R^o. -$NR'SO_2R^o$ and –$N(R')_2$ are also preferred values for R^{11} Each R^o is independently hydrogen, haloalkyl or a C_{1-3} alkyl group Each R' is independently hydrogen or a C_{1-3} alkyl group

[00122] R^{14} is an optional substituent, preferably at the six an seven positions on phenyl ring A, preferred values are halogen R^o, -OR^o, -CO_2R^o, -$C(O)R^o$, -$C(O)N(R^o)_2$, -CN, -$OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, $NHC(O)N(R^o)_2$, $(CH_2)_nOH$, $O(CH_2)_nOH$, $(CH_2)_nC(O)N(R^o)_2$, or $O(CH_2)_nC(O)N(R^o)_2$ R^o is hydrogen, haloalkyl or a C_{1-3} alkyl group

[00123] Another embodiment of the present invention, is a compound represented by Structural Formula **(X-A)**:



(X-A)

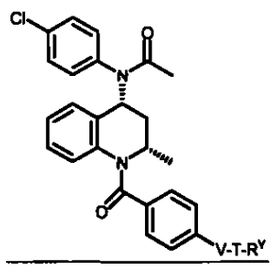
V is a covalent bond or –O-

T is an unsubstituted straight chained C_{1-10} alkylene.

R^Y is -$C(O)OR^5$, -$C(O)R^5$, -$OC(O)R^5$, -$C(O)N(R^5)_2$, -$NR^5C(O)R^5$, -$NR^5C(O)OR^5$, -$S(O)_2R^5$, -$S(O)_2COR^5$, -$S(O)_2N(R^5)_2$, -$NR^5S(O)_2$, -$NR^5S(O)_2R^5$, $S(O)_2OR^5$, -$S(O)OR^5$, -SR^5, -$C(O)NR^5S(O)_2R^5$, -CN, -$NR^5C(O)N(R^5)_2$, -$OC(O)N(R^5)_2$, -$N(R^5)_2$, -OR^5, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group

[00124] In some embodiments, the compound of Structural Formula **(X-A)**, excludes compounds where T-R^Y is–CH_2R^{20}, -$CH_2CH_2R^{21}$, or -$(CH_2)_3R^{22}$ R^{20} is -COOH, –$C(O)NH_2$, –$C(O)NHCH_3$, $C(O)N(CH_3)_2$, 5-tetrazolyl, 4-pyridinyl, *N*-ethyl-4-piperidinyl, or C(O)*N*-morpholinyl. R^{21} is -COOH, *N*-morpholinyl, $C(O)NH_2$, *N*-pyrrolidin-2-onyl, *N*-imidazolyl, or *N*-pyrrolidinyl. R^{22} is –COOH, $C(O)N(CH_2CH_3)_2$, $C(O)NH(CH_2CH_3)$, $C(O)NH_2$, $C(O)NHS(O)_2CH_3$, C(O)NHOH, $C(O)OCH_2CH_3$, NH_2, $C(O)CH_3$, CN, $NHS(O)_2CF_3$, C(O)*N*-pyrrolidinyl, *N*-pyrrolidinyl, 5-tetrazolyl, 5-(1,2,4)oxadiazolyl, *N*-morpholinyl, or *N*-imidazolyl.

[00125] In other embodiments, compounds of Structural Formula **(X-A)** (or a pharmaceutically acceptable salt thereof) are provided.



(X-A)

or a pharmaceutically acceptable salt thereof, wherein:

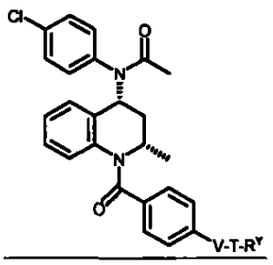
V is a covalent bond or –O-;

T is an straight chained C_{1-10} alkylene substituted with alkyl, gem dialkyl, haloalkyl, spiro cycloalkyl, or an optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group,

R^Y is R^Y is -C(O)OR^5, -C(O)R^5, -OC(O)R^5, -C(O)N(R^5)$_2$, -NR^{5}C(O)R^5, -NR^{5}C(O)OR^5, -S(O)$_2$R^5, -S(O)$_2$COR^5, -S(O)$_2$N(R^5)$_2$, -NR^{5}S(O)$_2$, -NR^{5}S(O)$_2$R^5, S(O)$_2$OR^5, -S(O)OR^5, -SR^5, -C(O)NR^{5}S(O)$_2$R^5, -CN, -NR^{5}C(O)N(R^5)$_2$, -OC(O)N(R^5)$_2$, -N(R^5)$_2$, -OR^5, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group, and

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, -C(O)OCH$_2$C$_6$H$_5$, S(O)$_2$CH$_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, C(O)NH$_2$, benzyl, pyrrolidinyl, morpholinyl, or -N(R^5)$_2$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group

[00126] In yet other embodiments, compounds of Structural Formula **(X-A)** (or a pharmaceutically acceptable salt thereof) are provided:



(X-A)

wherein·

V is–O-,

T is an straight chained C_{1-10} alkylene optionally 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, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is R^Y is -C(O)OR^5, -C(O)R^5, -OC(O)R^5, -C(O)$N(R^5)_2$, -NR^5C(O)R^5, -NR^5C(O)OR^5, -$S(O)_2R^5$, -$S(O)_2COR^5$, -$S(O)_2N(R^5)_2$, -$NR^5S(O)_2$, -$NR^5S(O)_2R^5$, $S(O)_2OR^5$, -S(O)OR^5, -SR^5, -C(O)$NR^5S(O)_2R^5$, -CN, -NR^5C(O)$N(R^5)_2$, -OC(O)$N(R^5)_2$, -$N(R^5)_2$, -OR^5, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group, and

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, -C(O)$OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or -$N(R^5)_2$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group

[00127] Compounds of general formula **I-A** (and subsets thereof as described directly above in section 2) include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed above and 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

[00128] The term "alkylene" as used herein means a straight chained hydrocarbon which is completely saturated An alkylene group is typically C_{1-10}, more typically C_{1-6}. more preferably from C_{1-5} and more preferably from C_{1-3} A "substituted alkylene" is an alkylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents are as described below for a substituted alkyl group. Preferred substituents for the alkylene group represented by T are fluoro, methyl, gem dimethyl, gem difluoro fluoromethyl, spiro cyclopropyl, spiro cyclobutyl, optionally *N*-substituted spiro azetidinyl, optionally *N*-substituted spiro aziridinyl, optionally *N*-substituted spiro pyrrolidinyl, optionally *N*-substituted spiro piperidinyl, amine, methylamine, dimethylamine, or hydroxyl. A "substitutable alkylene carbon atom" is an alkylene carbon atom that is bonded to one or more hydrogen atoms. The hydrogen atoms can therefore optionally be replaced with the substituent.

[00129] The terms "alkyl", "hydroxyalkyl", "carboxyalkyl", "haloalkyl", "alkylamine", "dialkylamine", used alone or as part of a larger moiety include both straight and branched saturated chains containing one to ten carbon atoms, preferably one to six, more preferably one to five, and even more preferably one to three.

[00130] The term "allyl" as used herein has the formula $-CH_2CH=CH_2$, and may be optionally substituted at any substitutable carbon atom A "substitutable allyl carbon atom" is an allyl carbon atom that is bonded to one or more hydrogen atoms The hydrogen atom can therefore optionally be replaced with the substituent Suitable substituents are as described for alkyl group.

[00131] The terms "gem dialkyl", and "gem dihalo" includes compounds where two alkyl substituents or two halo substituents, respectively, are attached to the same carbon atom, e g., $-C(CH_3)_2-$ or $C(F)_2-$.

[00132] A "spiro cycloalkyl" or "spiro non-aromatic heterocyclic" group is a cycloalkyl or non-aromatic heterocyclic group which shares one ring carbon atom with a carbon atom in an alkylene group or alkyl group

[00133] The terms "non-aromatic carbocyclic" or "cycloaliphatic" shall include cyclic C_{3-10} hydrocarbons which are completely saturated or which contain one or more units of unsaturation, but which are not aromatic Cycloaliphatic groups are typically C_{3-10}, more typically C_{3-7}.

[00134] "Alkoxy" means (alkyl)-O-, "haloalkoxy", means (halide)-O-; "alkoxyalkylene" means (alkyl)-O-(alkylene) such as methoxymethylene (CH_3OCH_2); "hydroxyalkyl" means hydroxy substituted alkyl group, acylated means "-C(O)-(alkyl)".

[00135] The term "heteroatom" means nitrogen, oxygen, or sulfur and includes any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen Also the term "nitrogen" includes a substitutable nitrogen of a heterocyclic ring 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-2H-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)

[00136] The term "aromatic group", includes carbocyclic aromatic ring groups and heteroaryl ring groups The term "aromatic group" may be used interchangeably with the terms "aryl", "aryl ring" or "aromatic ring"

[00137] Carbocyclic aromatic ring groups have only carbon ring atoms and include monocyclic aromatic rings such as phenyl and fused polycyclic aromatic ring systems in which two or more carbocyclic aromatic rings are fused to one another. Examples include 1-naphthyl, 2-naphthyl, 1-anthracyl and 2-anthracyl. Also included within the scope of the term "carbocyclic aromatic ring", as it is used herein, is a group in which an aromatic ring is fused to one or more non-aromatic rings (aliphatic or heterocyclic), such as in an indanyl, phthalimidyl, naphthimidyl, phenantridinyl, or tetrahydronaphthyl, where the radical or point of attachment is on the aromatic ring

[00138] The term "heteroaryl" or "heteroaromatic", refers to heteroaromatic ring groups having five to fourteen members, including monocyclic heteroaromatic rings and polycyclic aromatic rings in which a monocyclic aromatic ring is fused to one or more other carbocyclic or heteroaromatic aromatic rings Examples of heteroaryl rings include 2-furanyl, 3-furanyl, N-imidazolyl, 2-

imidazolyl, 4-imidazolyl, 5-imidazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, oxadiazolyl, 2-oxadiazolyl, 5-oxadiazolyl, 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl, 3-pyridazinyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-triazolyl, 5-triazolyl, tetrazolyl, 2-thienyl, 3-thienyl, carbazolyl benzimidazolyl, benzothienyl, benzofuranyl, indolyl, quinolinyl, benzotriazolyl, benzothiazolyl, benzooxazolyl, benzimidazolyl, isoquinolinyl, indolyl, isoindolyl, acridinyl, or benzoisazolyl

[00139] Also included within the scope of the term "heteroaryl", as it is used herein, is a group in which a heteroaryl ring is fused to one or more cycloaliphatic or non-aromatic heterocyclic groups where the radical or point of attachment is on the heteroaromatic ring. Examples include tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido [3, 4-d] pyrimidinyl The term "heteroaryl" may be interchangeably with the term "heteroaryl ring" or the term "heteroaromatic"

[00140] The term "non-aromatic heterocyclic group", or "non-aromatic heterocyclic ring" refers to non-aromatic ring systems typically having three to fourteen members, preferably three to six, in which one or more ring carbons, preferably one to four, are each replaced by a heteroatom such as N, O, or S. Examples of non-aromatic heterocyclic rings include 3-tetrahydrofuranyl, 2-tetrahydropyranyl, 3-tetrahydropyranyl, 4-tetrahydropyranyl, [1,3]-dioxalanyl, [1,3]-dithiolanyl, [1,3]-dioxanyl, 2-tetrahydrothiophenyl, 3-tetrahydrothiophenyl, 2-morpholinyl, 3-morpholinyl, *N*-morpholinyl, 2-thiomorpholinyl, 3-thiomorpholinyl, 4-thiomorpholinyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrorolidinyl, *N*-piperazinyl, 2-piperazinyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, piperidinonyl, 4-thiazolidinyl, diazolonyl, *N*-substituted diazolonyl, oxazolidinyl, oxazolidinyl, tetrahydrothienyl, imidazolidinyl, imidazolidinonyl, pyrrolidinonyl, isothiazolidinyl S,S, dioxide, piperidinyl, 1-pthalimidinyl, 3-1H-benzimidazol-2-one, benzoxanyl, benzopyrrolidinyl, benzopiperidinyl, benzoxolanyl, benzothiolanyl, and benzothianyl.

[00141] A "substituted aromatic group" is an aromatic group with a substituent at one or more substitutable ring carbon atoms or ring nitrogen atoms. Each substituent is independently selected Examples of suitable substituents on an unsaturated carbon atom or substitutable carbon atom of an aromatic group are as described above for R^Z, R^{11}, and R^{14}

[00142] A "substitutable ring carbon atom" in an aromatic ring (including the aromatic groups represented by Ring A, phenyl ring A, R^1 and R^3) is a ring carbon atom that is bonded to a hydrogen atom. The hydrogen atom can therefore optionally be replaced with the substituent. The term "substitutable ring carbon atom" in an aromatic ring therefore excludes ring carbon atoms that are fused with other rings or that are depicted as already being bonded to a substituent.

[00143] An alkyl group or a non-aromatic carbocycle or heterocycle may contain one or more substituents on any substitutable carbon atom A "substitutable alkyl carbon atom" is an alkyl carbon atom that is bonded to one or more hydrogen atoms. The hydrogen atoms can therefore optionally be replaced with the substituent. Examples of suitable substituents on the saturated carbon of an alkyl

group or a non-aromatic heterocycle include those listed above for the unsaturated carbon of an aromatic group and, at the internal carbon atoms of an alkyl group or on ring carbon atoms of a non-aromatic heterocyclic group, the following =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alkyl), =NNHSO$_2$ (alkyl), or =NR* Each R* is independently selected from hydrogen, an unsubstituted alkyl group or a substituted alkyl group. Examples of substituents on the alkyl group represented by R* include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylaminocarbonyloxy, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl

[00144] Suitable substituents on the substitutable nitrogen of a heteroaryl or non-aromatic heterocyclic group include –R^{12}, -N(R^{12})$_2$, -C(O)R^{12}, -CO$_2$R^{12}, -C(O)C(O)R^{12}, -C(O)CH$_2$ C(O)R^{12}, -SO$_2$ R^{12}, -SO$_2$N(R^{12})$_2$, -C(=S)N(R^{12})$_2$, -C(=NH)-N(R^{12})$_2$, and -NR^{12}SO$_2$R^{12}; wherein R^{12} is hydrogen, an alkyl group, a substituted alkyl group, phenyl (Ph), substituted Ph, -O(Ph), substituted -O(Ph), CH$_2$(Ph), or an unsubstituted heteroaryl or non-aromatic heterocyclic ring. Examples of substituents on the alkyl group or the phenyl ring represented by R^{12} include amino, alkylamino, dialkylamino, aminocarbonyl, halogen, alkyl, alkylaminocarbonyl, dialkylaminocarbonyloxy, alkoxy, nitro, cyano, carboxy, alkoxycarbonyl, alkylcarbonyl, hydroxy, haloalkoxy, or haloalkyl. A "substitutable ring nitrogen atom" in a heteroaryl or nitrogen-containing non-aromatic heterocyclic group is a ring nitrogen atom that is bonded to a hydrogen atom. The hydrogen atom can therefore optionally be replaced with the substituent. The term "substitutable ring nitrogen atom" therefore excludes ring nitrogen atoms that are depicted as already being bonded to a substituent, and ring nitrogen atoms that are ring atoms in two fused rings (as in, e g., indolizine) and ring nitrogen atoms that have three covalent bonds to other ring atoms (as e g., pyridine).

[00145] In certain instances compounds of the present invention may associated in isolated form with solvent or water, as in a "solvate" or "hydrate" References to the disclosed compounds or structural formulas depicting the disclosed compounds are meant to include such solvates and hydrates

[00146] *3 Uses, Formulation and Administration*

[00147] As discussed above, the present invention provides compounds that are useful as inhibitors of CRTH2, and thus the present compounds are useful for treating (therapeutically or prophylactically) disorders with an inflammatory component and allergic conditions. They can also be used to inhibit inflammatory disorders and allergic conditions mediated by Th2 cells, eosinophils and basophils.

[00148] 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

[00149] 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

[00150] 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 $N^+(C_{1-4}alkyl)_4$ 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

[00151] 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 a 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.

[00152] 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 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

[00153] 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.

[00154] 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, 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.

[00155] 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].

[00156] 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.

[00157] Diseases characterized by repurfusion 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.

[00158] Other diseases and conditions with an inflammatory component believed to be mediated by CRTH2 include mastitis (mammary gland), vaginitis, cholecystitis, cholangitis or pericholangitis (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 amendable 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.

[00159] 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.

[00160] 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.

[00161] 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), bucally, 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

[00162] 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

[00163] 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

[00164] 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.

[00165] 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 microencapsule 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.

[00166] 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

[00167] 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, polyvinylpyrrolidinone, 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.

[00168] 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 polethylene glycols and the like

[00169] 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 a 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

[00170] 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

[00171] 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".

[00172] 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.*, adrenocorticotropic hormone (ACTH)), cytokines (*e g* , interferons (*e g* , IFNβ-1a, IFNδ-1b)) and the like

[00173] 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

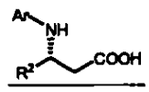
[00174] The compounds of this invention or pharmaceutically acceptable compositions thereof may also be incorporated into compositions for coating implantable medical devices, such as prostheses, artificial valves, vascular grafts, stents and catheters. Accordingly, the present invention, in another 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.

[00175] 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.

[00176] 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

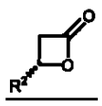
[00177] *4 General Synthetic Methods*

[00178] Aother embodiment of the present invention is a method of preparing an amino acid compound represented by Structural Formula **(XI-A):**



(XI-A)

[00179] The method comprises the step of reacting Ar-NH_2 with a lactone represented by Structural Formula **(XXII-A):**



(XII-A).

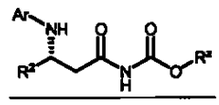
[00180] Ar is an optionally substituted monocyclic aromatic group and R^2 is C_1-C_3 alkyl. Preferably, Ar is an optionally substituted phenyl group and R^2 is methyl or ethyl Suitable

substituents for Ar are as described above for Ring A or Phenyl Ring A, provided, however, that functional groups which can interfere with the reaction are protected. Functional groups which require protection will be readily apparent to the skilled artisan and include amines, alcohols, carboxylic acids, and the like Examples of preferred substituents include halo, cyano, R^o, $-OR^{30}$, $-CO_2R^{31}$, $-C(O)R^o$, $-C(O)N(R^x)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)NR^x_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)N(R^x)_2$, $O(CH_2)_nC(O)N(R^x)_2$, n is an integer from 1-4, R^o is independently hydrogen, C_{1-3} haloalkyl or a C_{1-3} alkyl group; one R^x is –H or C_1-C_3 alkyl and the other is an amine protecting group, R^{30} is an alcohol protecting group; and R^{31} is a carboxylic acid protecting group Suitable protecting groups are well know in the art and are disclosed in, for example, in Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991) The entire teachings of Greene and Wits are incorporated herein by reference More commonly, Ar is a phenyl group

[00181] Also encompassed within the present invention is the corresponding reaction with the enantiomer of the amino acid compound represented by Structural Formula **(XII-A)**, thereby forming the enantiomer of the compound represented by Structural Formula **(XI-A)**.

[00182] The reaction of the aryl amine and cyclic lactone above can be carried out in solvents in which both reagents are soluble. Examples include protic solvents (e.g., water and methanol) and polar aprotic solvents (dimethylformamide, dimethyl sulfoxide,, hexamethylphosphoramide and the like). An excess of one reagent relative to the other can be used (e g , up to a ten fold excess), however equimolar amounts are more typical. The reaction is typically carried out at the boiling point of the solvent being used, but can also commonly carried out at temperatures ranging from ambient temperature to temperatures as high as 200° C Temperatures from 70° C to 90° C are most commonly used.

[00183] Another embodiment is a method of preparing an intermediate compound represented by Structural Formula **(XIII-A)** from the amino acid compound represented by Structural Formula **(XI-A)**·



(XIII-A).

[00184] The method comprises the step of amidating the carboxylic acid group of the amino acid compound with $NH_2C(O)OR^z$. The group $-C(O)OR^z$ is an amine protecting group that taken together with $-NH_2$ forms a carbamate Thus, R^z is a substituted or unsubstituted alkyl, allyl or aryl group. Substituents that can be present on the alkyl, allyl or aryl group represented by R^z are those which do not interfere in the reactions being carried and are readily recognizable to the skilled artisan. Examples include alkyl, halogen and alkoxy Thus, suitable values for R^z are well known to the

skilled artisan and are described, for example, in Green and Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991) Specific examples include, but are not limited to, benzyl, methyl, ethyl, allyl, 2,2,2,-trichloromethyl, 2,2,2-trichloro-*tert*-butyl, *tert*-butyl or fluorenylmethyl

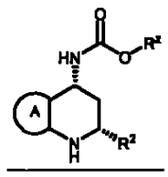
[00185] The term "amidating a carboxylic acid with $NH_2C(O)OR^z$ refers to converting a carboxylic acid (–COOH) to the amide $–C(O)NHC(O)OR^z$ in one or more reaction steps Many methods for converting a carboxylic acid to an amide are known in the art. Typically, the carboxylic acid is first converted into a group that is more readily displaced by an amine or amide than -OH. Thus, -OH is converted into a better leaving group. A "leaving group" is a group which can readily be displaced by a nucleophile In the present invention, the amino acid compound can be converted directly to the intermediate compound by activating the carboxylic acid of the amino acid compound and then reacting with $NH_2C(O)OR^z$. Alternatively, the carboxylic can be first be converted to carboxamide ($-C(O)NH_2$) by activating the carboxylic acid group of the amino acid compound and then reacting with NH_3 or a functional equivalent thereof (e.g., NH_4Cl) and then protecting the resulting carboxamide When $NH_2C(O)OR^z$ is used as a nucleophile, the amidation is preferably carried out in the presence of at least one equivalent of a non-nucleophilic base such as an alkoxide (lithium *ter*-butoxide, potassium *tert*-butoxide, lithium isopropoxide and potassium isopropoxide) or amide base (e g , lithium or potassium isopropylamide or hexamethylpiperidide)

[00186] In one example, -OH of the carboxylic acid is converted into a better leaving group by replacing it with a halogen, typically with chloride The carboxylic acid is thereby converted into an acid halide, e.g., an acid chloride Reagents suitable for preparing acid chlorides from carboxylic acids are well known in the art and include thionyl chloride, oxalyl chloride, phosphorus trichloride and phosphorus pentachloride Typically, each carboxylic acid group is reacted with about one equivalent or a slight excess of thionyl chloride, oxalyl chloride, phosphorus trichloride and phosphorus pentachloride in an inert solvent such as an ethereal solvent (e g., diethyl ether, tetrahydrofuran or 1,4-dioxane), a halogenated solvent (e g , methylene chloride or 1,2-dichloroethane) or aromatic solvent (e g , benzene or toluene). When oxalyl chloride is used, a tertiary amine is often added to accelerate the reaction in quantities ranging from a catalytic amount to about one equivalent relative to oxalyl chloride

[00187] Alternatively, the carboxylic acid is first converted into an "activated ester" An ester -COOR is said to be "activated" when -OR is readily displaced by an amine or amide than -OH. -OR is more easily displaced as R becomes more electron withdrawing. Some activated esters are sufficiently stable that they can be isolated, e.g., esters wherein R is phenyl or substituted phenyl. For example, diphenylmalonate can be prepared from malonyl chloride and phenol, both commercially available from Aldrich Chemical Co., Milwaukee, WI., by procedures described above Other activated esters are more reactive and are generally prepared and used *in situ*

[00188] Formation of an activated ester *in situ* requires a "coupling agent", also referred to as a "carboxylic acid activating agent", which is a reagent that replaces the hydroxyl group of a carboxyl acid with a group which is susceptible to nucleophilic displacement. Examples of coupling agents include 1,1'-carbonyldiimidazole (CDI), isobutyl chloroformate, dimethylaminopropylethyl-carbodiimide (EDC), dicyclohexyl carbodiimide (DCC) When amidating by *in situ* generation of an activated ester, an excess of either the carboxylic acid or amine can be used (typically a 50% excess, more typically about a 10-15% excess). However, it is more common when carrying out the present invention to use equimolar amounts of both reagents. Generally, from about 1.0 equivalent to about 10 equivalents of coupling agent are used relative to each carboxylic acid group, preferably from about 1 0 equivalent to about 1 5 equivalents. When DCC is used, a weak acid such as 1-hydroxybenzotriazole (HOBt) is often added to accelerate the reaction. Typically, about between one to about 1 5 equivalents of HOBt relative to DCC is used, preferably between about one to about 1 2 equivalents The reaction is generally carried out in inert, aprotic solvents, for example, halogenated solvents such as methylene chloride, dichloroethane and chloroform, ethereal solvents such as tetrahydrofuran, 1,4-dioxane and diethyl ether and dimethylformamide Suitable reaction temperature generally range from between about 0° to about 100°, but the reaction is preferably carried out at ambient temperature.

[00189] Yet another embodiment of the present invention is a method of preparing a product compound represented by Structural Formula **(XIV-A):**



(XIV-A).

[00190] The method comprises the step of reducing the amide carbonyl of the intermediate compound to form a second intermediate and then cyclizing the second intermediate to form the product compound. The variables in Structural Formula **(XIV-A)** are as described above for Structural Formulas **(XI-A)**-(XIII-A). The "amide carbonyl" is understood to be the carbonyl between the methylene carbon and nitrogen atom and not the carbonyl that is bonded to both a nitrogen and oxygen atom

[00191] To carry out the reduction step, a reducing agent is used which can reduces the amide carbonyl but not the carbamate group. Sodium borohydride together with a Lewis Acid such as magnesium chloride or calcium chloride is one common example. The reduction step is typically carried out in an alcoholic solvent such as methanol or ethanol An excess of sodium borohydride and Lewis Acid of up to 50% can be used, but typically from 0 5 to 1.0 equivalents of sodium borohydride and 0 5 to 2.0 equivalents of Lewis Acid are used.

[00192] The cyclization step is carried out in dilute aqueous or alcoholic acid, using, for example, 0.1 N to 10 N HCl, H_2SO_4, H_3PO_4 or a sulfonic acid such as methane sulfonic acid, toluene sulfonic acid or phenyl sulfonic acid. More typically, between 0.8 N and 1 2 N acid is used Commonly, an organic acid such acetic acid, benzoic acid, citric acid, and the like is also be present, for example between 0.5 equivalents to 10 equivalents. Typically, a co-solvent immiscible in water or alcohol is used. Common co-solvents include halogentated solvents such as dichloromethane or chloroform and ethereal solvents such as tetrahydrofuran and diethyl ether

[00193] Another embodiment of the present invention is a method of preparing the product compound represented by Structural Formula **(XIV-A)** from the cyclic lactone represented by Structural Formula **(XII-A)**. The method comprises combining the three reaction steps described above Alternatively, the enantiomer of the compound represented by Structural Formula **(XIV-A)** is prepared using the same three reaction steps, provided, however, that the enantiomer of the starting lactone represented by Structural Formula **(XII-A)** is used.

[00194] Yet another embodiment of the present invention is a compound represented by any one of Structural Formulas **(XI-A)-(XIV-A).**

[00195] The invention is illustrated by the following examples which are not intended to be limiting in any way.

EXEMPLIFICATION

[00196] 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/54mm 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 (Phenomenex C18 column, 5 micron, 50x4 6 mm) equipped with a Gilson 215 Liquid Handler Standard LC/MS conditions is as follows

Formic acid-Standard conditions:

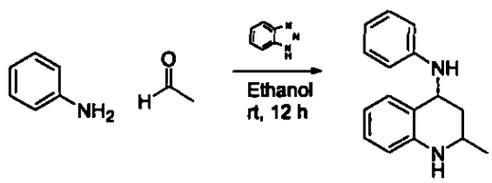
% C (Water)	95 0
% D (Acetonitrile)	5 0
% Formic Acid	0 1
Flow (ml/min)	3.500
Stop Time (mins)	4.4
Min Pressure (bar)	0
Max Pressure (bar)	400
Oven Temperature Left(°C)	25.0
Oven Temperature Right(°C)	25.0

HP1100 LC Pump Gradient Timetable

The gradient Timetable contains 5 entries which are ·

Time	A%	B%	C%	D%	Flow	Pressure
0.00	0 0	0 0	95.0	5 0	3.500	400
3.50	0.0	0 0	0 0	100.0	3.500	400
4.30	0.0	0.0	0 0	100.0	3.500	400
4.40	0 0	0.0	95.0	5.0	4.000	400
5.00	0 0	0.0	95 0	5.0	4.000	400

Scheme 1



1 = *trans*
2 = *cis*

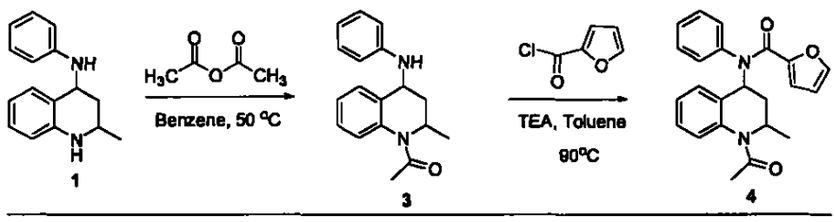
[00197] (±)-*Cis*- and (±)-*trans*-(2-ethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (1) & (2): A 250 mL flask under nitrogen atmosphere was charged with aniline (1.0 g, 10.7 mmol, 1.0 equiv), acetaldehyde (0.599 mL, 10.7 mmol), benzotriazole (0.255 g, 2.1 mmol, 0.2 equiv) and dry toluene (100 mL) (Caution· an exotherm was observed). The precipitated benzotriazole/aldehyde adduct was observed immediately. The solution was allowed to stir at room temperature for 12h. The

precipitate that forms after stirring over night was filtered and washed with minimal diethyl ether, to afford the *cis*-isomer exclusively The *trans*-isomer could be obtained by concentration of the filtrate. The residue was purified by Biotage flash system (95% hexane/5% diethyl ether) to yield the *cis* and *trans* isomers as a mixture. The resulting oily residue was then trituated with hexane to separate the cis isomer as a white solid and the filtrate was concentrated to give the *trans* isomer.

(±)-*Cis*-isomer - ^{1}H-NMR ($CDCl_3$) δ. 1.24 (d, 3H), 1 52 (q, 1H), 2.38 (dddd, 1H), 3.63 (m, 1H), 3.75 (bs, 2H, -NH), 4.83 (dd, 1H), 6 51 (d, 1H), 6 68 (m, 4H), 7 05 (m, 1H), 7.19-7.26 (m, 2H), 7 39 (d, 1H).

(±)-*Trans*-isomer - ^{1}H-NMR ($CDCl_3$) δ 1 22 (d, 3H), 1.56 (m, 1H), 2 20 (dt, 1H), 3 4 (m, 1H), 3.89 (bs, 2H, -NH), 4.55 (dt, 1H), 6 56 (dd, 1H), 6 66-6.75 (m, 4H), 7.08 (m, 1H), 7.19-7.26 (m, 3H)

Scheme 2



[00198] ***Cis*-(±)-1-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (3)**

[00199] A 30 mL flask under nitrogen atmosphere was charged with (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (0.520 g, 2 2 mmol, 1 0 equiv), and acetic anhydride (0.209 mL, 2 2 mmol, 1.0 equiv) and dry toluene (31 mL) The solution was heated to 50 °C for 15h. The reaction mixture was evaporated *in vacuo* The residue was purified by Biotage flash system (70% hexane/30% ethyl acetate) to yield the 2-acetyl *cis* isomers 67 % yield.

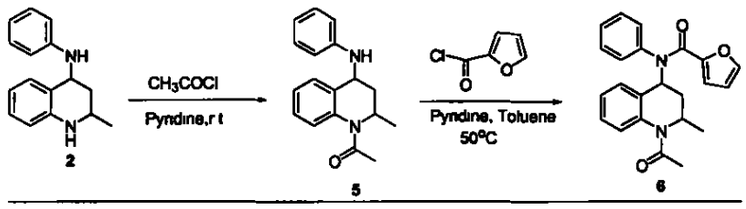
^{1}H-NMR ($CDCl_3$) δ. 1.17 (d, 3H), 1.25 (q, 1H), 2 19 (s, 3H), 2.22(bs, 1H), 2 65 (m, 1H), 4 21 (dd, 1H), 4.96 (m, 1H), 6 65 (d, 2H), 6.75 (t, 1H), 7 12-7.33 (m, 6H)

[00200] ***Cis*-(±)-furan-2-carboxylic acid (1-acetyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amide (4)**

[00201] A round bottom flask under nitrogen atmosphere was charged with *cis*-1-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (0 163 g, 0 58 mmol, 1.0 equiv) and 2-furoyl chloride (0.285 mL, 2.9 mmol, 5 0 equ), pyridine (1 0 equiv.) and dry toluene (3 mL) The solution was heated to 90 °C for 15h The reaction mixture was evaporated *in vacuo*. The residue was purified by Biotage flash system (50% hexane/50% ethyl acetate) to yield the *cis* isomer 40 % yield

^{1}H-NMR ($CDCl_3$) δ: 1.08 (d, 3H), 1 63 (m, 1H), 2.14 (s, 3H), 2 2 (bs, 1H), 4 77 (m, 1H), 5 75 (bs, 1H), 6 23 (dd, 1H), 7 12-7 45 (m, 10H)

Scheme 3



[00202] (±)-*Trans*-1-(2-Methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (5)

[00203] A 30 mL flask under nitrogen atmosphere was charged with (±)-*trans*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (0 260 g, 1 1 mmol, 1 0 equiv) and acetyl chloride (0.075 mL, 1.0 mmol, 0 95 equ) in pyridine (5 mL) The solution was allowed to stir at room temperature for 6 h. The reaction mixture was evaporated *in vacuo*. The residue was purified by Biotage flash system (70% hexane/30% ethyl acetate to 60% hexane/40% ethyl acetate to 50% hexane/50% ethyl acetate) to yield the 2-acetyl *trans* isomers 35 % yield.

^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, 3H), 1 76 (m, 1H), 2.17(s, 3H), 2 52 (dd, 1H), 4.60(t, 1H), 4.93 (m, 1H), 6 67 (d, 2H), 6.71 (t, 1H), 7 13-7.36 (m ,6H), 7 41 (d, 1H).

[00204] (±)-*Trans*-furan-2-carboxylic acid (1-acetyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amide (6)

[00205] A round bottom flask under nitrogen atmosphere was charged with (±)-*trans*-1-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (0 110 g, 0 39 mmol, 1 0 equiv) and 2-furoyl chloride (0.193 mL, 1.9 mmol, 5.0 equ), pyridine (1 0 equ) and dry toluene (5 mL). The solution was heated to 50 °C for 5h The reaction mixture was evaporated *in vacuo*. The residue was purified by Biotage flash system (30% hexane/70 % ethyl acetate to 50% hexane/50% ethyl acetate) to yield the *trans* isomer 34 % yield

^{1}H-NMR ($CDCl_3$) δ: 1 11(d, 3H), 1 76 (s, 3H), 2.07 (dd, 1H), 2.37 (m, 1H), 5.00 (m, 1H), 5 48 (d, 1H),6.14 (dd, 1H), 6 29 (t, 1H), 6 90 (m, 1H), 6.99 (m, 1H), 7 22-7.32 (m, 6H), 7 34 (d, 1H), 7.54 (dd, 1H).

[00206] (±)-*Cis*-N-(1-Acetyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-4-fluoro-N-phenyl-benzamide (7)

[00207] A 30 mL flask under nitrogen atmosphere was charged with (±)-cis- (2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (0 520 g, 2 2 mmol, 1.0 equiv) and acetic anhydride (0.209 mL, 2.2 mmol, 1 0 eq) and dry toluene (31 mL) The solution was heated to 50 °C for 15h. The reaction mixture was evaporated *in vacuo* The residue was purified by Biotage flash system (70% hexane/30% ethyl acetate) to yield the 2-acetyl *cis* isomers 67 % yield

^{1}H-NMR ($CDCl_3$) δ 1.17 (d, 3H), 1.25 (q, 1H), 2 19 (s, 3H), 2.22(bs, 1H), 2.65 (m, 1H), 4.21 (dd, 1H), 4 96 (m, 1H), 6.65 (d, 2H), 6 75 (t, 1H), 7 12-7 33 (m, 6H)

[00208] A round bottom flask under nitrogen atmosphere was charged with (±)-*cis*-1-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (1.0 equiv) and 2-fluorobenzoyl chloride (5.0 equ), pyridine (1.0 equ) and dry toluene (3 mL). The solution was heated to 90 °C for 15h The reaction mixture was evaporated *in vacuo*. The residue was purified by Biotage flash system (50% hexane/50% ethyl acetate) to yield the *cis* isomer 40 % yield.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.2 (1H, m), 2 1 (3H, s), 2 1 (1H, m), 4.8 (1H, m), 5 4 (1H, m), 6 8 (2H, m), 6 9-7.4 (9H, m), 7.5 (1H, m).

MS m/z· 403 (M+1).

[00209] (±)-*Trans*-N-(1-Acetyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-4-fluoro-N-phenyl-benzamide (8)

[00210] A 30 mL flask under nitrogen atmosphere was charged with (±)-*trans*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (0 260 g, 1.1 mmol, 1.0 equiv) and acetyl chloride (0 075 mL, 1 0 mmol, 0.95 equ) in pyridine (5 mL). The solution was allowed to stir at room temperature for 6 h. The reaction mixture was evaporated *in vacuo*. The residue was purified by Biotage flash system (70% hexane/30% ethyl acetate to 60% hexane/40% ethyl acetate to 50% hexane/50% ethyl acetate) to yield the 2-acetyl *trans* isomers 35 % yield.

^{1}H-NMR ($CDCl_3$) δ: 1.19 (d, 3H), 1 76 (m, 1H), 2 17(s, 3H), 2 52 (dd, 1H), 4 60(t, 1H), 4.93 (m, 1H), 6 67 (d, 2H), 6.71 (t, 1H), 7.13-7.36 (m ,6H), 7.41 (d, 1H)

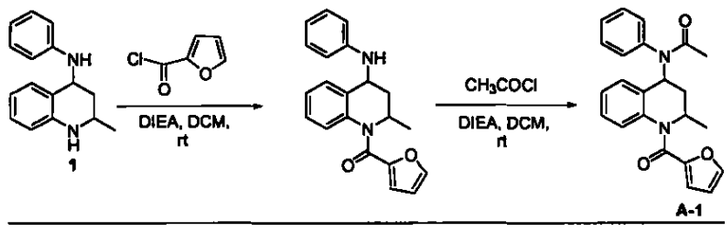
[00211] A round bottom flask under nitrogen atmosphere was charged with (±)-*trans*-1-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-ethanone (1 0 equiv) and 4-fluorobenzoyl chloride (5 0 equ), pyridine (1.0 equ.) and dry toluene (5 mL). The solution was heated to 50 °C for 5h. The reaction mixture was evaporated *in vacuo* The residue was purified by Biotage flash system (30% hexane/70 % ethyl acetate to 50% hexane/50% ethyl acetate) to yield the *trans* isomer 34 % yield.

^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, d), 1 9 (3H, s), 2 0 (1H, m), 2.3 (1H, m), 5.0 (1H, m), 6 2 (1H, m), 6 6-6.8 (4H, m), 7.1 (3H, m), 7 3 (4H, m), 7 6 (1H, m).

MS m/z: 403 (M+1)

General Procedure A

Scheme 4



[00212] (±)-*Cis*-N-[1-(furan-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-1)

[00213] To a solution of (±)-*cis*-(2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (430 mg, 1.83 mmol) in dichloromethane (18 mL) at room temperature was added diisopropylethylamine (318 uL, 1.83 mmol) followed by 2-furoyl chloride. It was allowed to let stir at room temperature for 12h. The mixture was poured into water and extracted with dichloromethane The extracts were washed with 1 M(aq) NaOH and brine, dried over magnesium sulfate, filtered and concentrated The crude residue was purified by silica gel chromatography (80% hexanes/20% ethyl acetate) to afford the amide (500 mg, 83 %).

[00214] To a solution of (±)-*cis*-furan-2-yl-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-methanone (360 mg, 1.0 mmol) in methylene chloride (5 mL) was added diisopropylethylamine (1 9 mL, 10 mmol) followed by acetyl chloride (388 uL, 5 mmol). The mixture was stirred at room temperature over night The mixture was poured into water and extracted with dichloromethane The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (50% hexanes/50% ethyl acetate) to afford the amide (230 mg, 57 %).

^{1}H-NMR ($CDCl_3$) δ: 1.12 (d, 3H), 1.25 (t, 1H), 2 01 (s, 3H), 2 32 (m, 1H), 4.12 (sextet, 1H), 5.49 (bs, 1H), 6 22 (m, 2H), 6.84(d, 1H), 7.10 (t, 1H), 7.28-7.31 (m, 4H), 7. 38 (m, 4H)

MS m/z 375 (M+1)

[00215] (±)-*Cis*-2-methoxy-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-2)

[00216] (±)-*Cis*-2-methoxy-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride and methoxyacetyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1 14 (d, 3H), 1.25 (t, 1H), 2 33 (m, 1H), 3 39 (s, 3H), 3.60(s, 3H), 3.85(d, 1H), 3 98 (d, 1H), 4 79 (sextet, 1H), 5 62 (bs, 1H), 6 53 (d, 1H), 6 72 (s, 1H), 6.81(d, 1H), 6.92 (t, 1H), 7.08 (t, 1H), 7.16 (t, 1H), 7 29 (m, 2H), 7. 35-7.42 (m, 3H).

MS m/z: 445 (M+1)

[00217] (±)-*Cis*-4-chloro-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-benzamide (A-3)

[00218] (±)-*Cis*-4-Chloro-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-benzamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride and 4-chlorobenzoyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1.24 (d, 3H), 1 26 (m, 1H), 2.29 (m, 1H), 3.60 (s, 3H), 4.84 (sextet, 1H), 5.92 (bs, 1H), 6.58 (d, 1H), 6 78(d, 2H), 6.82 (s, 1H), 6 95 (t, 1H), 7 08 (t, 2H), 7 16-7 25 (m, 7H), 7.34 (d, 2H), 7.53 (d, 1H)

MS m/z 511.0 (M+1).

[00219] (±)-*Cis*-N-[1-(3-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide (A-4)

[00220] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride and isobutyryl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 9H), 1.23 (t, 1H), 2.28 (m, 1H), 2.65 (sextet, 1H), 3.65 (s, 3H), 4 77 (sextet, 1H), 5.63 (bs, 1H), 6.51 (d, 1H), 6.67(d, 1H), 6.78 (d, 1H), 6.86 (m, 2H), 7 01 (t, 1H), 7 14 (t, 1H), 7 24-7.37 (m, 6H)

MS m/z 443 0 (M+1)

[00221] (±)-*Cis*-N-[2-Methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-5)

[00222] (±)-*Cis*-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 2-thiophene carbonyl chloride for 2-furoyl chloride

[00223] (±)-*Cis*-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90%

hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)- N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (**A-11** & **A-10**, respectively).
^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H), 1 25 (m, 1H), 2.02 (s, 3H), 2.31 (m, 1H), 4 73 (sextet, 1H), 5 53 (bs, 1H), 6.68 (dd, 1H), 6 77 (t, 1H), 6 88 (d, 1H), 7 06 (t, 1H), 7 25-7 32 (m, 4H), 7.39 (m, 4H)
MS *m/z*· 391 0 (*M*+1)

[00224] (±)-*Cis*-N-[1-(4-tert-butyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-6)

[00225] (±)-*Cis*-N-[1-(4-tert-butyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-*tert*-butylbenzoyl chloride for 2-furoyl chloride.

[00226] (±)-*Cis*-N-[1-(4-tert-butyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-[1-(4-tert-butyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (**A-8** & **A-9**, respectively)
^{1}H-NMR ($CDCl_3$) δ: 1 14 (d, 3H), 1 16 (m, 1H), 1.23 (s, 9H), 2.04 (s, 3H), 2.33 (m, 1H), 4.78 (sextet, 1H), 5 62 (bs, 1H), 6.53 (d, 1H), 6 91 (t, 1H), 7.15-7.40 (m, 11H).
MS m/z: 441 (M+1).

[00227] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-7)

[00228] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride.

[00229] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (**A-52** & **A-44**, respectively).
^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.25 (m, 1H), 2 03 (s, 3H), 2.32 (m, 1H), 4.78 (sextet, 1H), 5.62 (bs, 1H), 6.47 (d, 1H), 6 83-6.95 (m, 3H), 7 16-7.40 (m, 9H)
MS m/z 403 (M+1)

[00230] (±)-*Cis*-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-12)

[00231] (±)-*Cis*-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 5-methyl-2-thiophenecarbonyl chloride for 2-furoyl chloride.

[00232] (±)-*Cis*-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)- *cis*-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide **(A-59 & A-60,** respectively)

^{1}H-NMR ($CDCl_3$) δ 1.07 (m, 1H), 1.12 (d, 3H), 2 01 (s, 3H), 2 31 (m, 1H), 2 39 (s, 3H), 4.69 (sextet, 1H), 5 50 (bs, 1H), 6.44 (s, 1H), 6.51 (d, 1H), 6.94 (d, 1H), 7.09 (t, 1H), 7.21-7.30 (m, 3H), 7 39-7 41 (m, 4H)

MS m/z· 405 (M+1)

[00233] (±)-*Cis*-N-[2-methyl-1-(4-methyl-2-pyrazin-2-yl-thiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-13)

[00234] (±)-*Cis*-N-[2-ethyl-1-(4-methyl-2-pyrazin-2-yl-thiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-methyl-2-(2-pyrazinyl)-1,3-thiazole-5-carbonyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ. 1 18 (d, 3H), 1.77 (bs, 1H), 2.03 (s, 3H), 2.10 (s, 3H), 2 32 (m, 1H), 4 79 (sextet, 1H), 5 50 (bs, 1H), 6 74 (d, 1H), 7.03 (t, 1H), 7.26-7.41 (m, 7H), 8.55 (d, 1H), 9.32 (s, 1H)

MS *m/z*: 484 (M+1).

[00235] (±)-*Cis*-N-[2-methyl-1-(3-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-14)

[00236] (±)-*Cis*-N-[2-methyl-1-(3-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-methyl-2-thiophenecarbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 13 (d, 3H), 1 16 (m, 1H), 1.80 (s, 3H), 2.00 (s, 3H), 2 29 (m, 1H), 4.73 (sextet, 1H), 5.49 (bs, 1H), 6.56 (d, 1H), 6.66 (d, 1H), 6.97 (t, 1H), 7 16 (d, 2H), 7 25 (d, 2H), 7 32 (d, 1H), 7 38 (bs, 3H).

MS m/z· 405 (M+1)

[00237] (±)-*Cis*-N-[2-methyl-1-(5-phenyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-15)

[00238] (±)-*Cis*-N-[2-methyl-1-(5-phenyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 5-phenyl-2-thiophenecarbonyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 15 (d, 3H), 1.17 (m, 1H), 2 03 (s, 3H), 2.31 (m, 1H), 4 73 (sextet, 1H), 5.55 (bs, 1H), 6 59 (s, 1H), 6 95 (d, 2H), 6 99 (s, 1H), 7.10 (t, 1H), 7.26-7 44 (m, 9H), 7.53 (d, 2H).
MS m/z 467 (M+1)

[00239] **(±)-*Cis*-N-[2-methyl-1-(4-methyl-2-phenyl-thiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-16)**

[00240] (±)-*Cis*-N-[2-methyl-1-(4-methyl-2-phenyl-thiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-methyl-2-phenyl-1,3-thiazole-5-carbonyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, 3H), 1 18 (m, 1H), 2.03 (s, 3H), 2.14 (s, 3H), 2.32 (m, 1H), 4 74 (sextet, 1H), 5 53 (bs, 1H), 6 77 (d, 2H), 7.04 (t, 1H), 7 24-7 28 (m, 3H), 7 38-7.40 (m, 7H), 7.83 (d, 2H).
MS m/z 482 (M+1)

[00241] **(±)-*Cis*-N-[2-methyl-1-(4-methyl-[1,2,3]thiadiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-17)**

[00242] (±)-*Cis*-N-[2-methyl-1-(4-methyl-[1,2,3]thiadiazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-methyl-[1,2,3]thiadiazole-5-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 17 (d, 3H), 1 21 (m, 1H), 2.01 (s, 3H), 2.36 (s, 3H), 2.24 (m, 1H), 4.81 (sextet, 1H), 5.48 (bs, 1H), 6 52 (d, 1H), 6.98 (t, 1H), 7.22-7 26 (m, 3H), 7.37-7.42 (m, 4H).
MS m/z 407 (M+1).

[00243] **(±)-*Cis*-N-[1-(5-isopropyl-thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-19)**

[00244] (±)-*Cis*-N-[1-(5-isopropyl-thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 5-isopropylthiophene carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1.11 (d, 3H), 1 15 (m, 1H), 1 19-1 25 (m, 6H), 2 01 (s, 3H), 2.30 (m, 1H), 2 70 (m, 1H), 4.69 (sextet, 1H), 5.51 (bs, 1H), 6.45 (s, 1H), 6.55 (s, 1H), 6 87-6.95 (m, 1H), 7 04-7 08 (m, 1H), 7.27 (s, 3H), 7.38 (s, 4H)
MS m/z 433 (M+1).

[00245] (±)-*Cis*-N-[2-methyl-1-(3,4,5-trifluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-20)

[00246] (±)-*Cis*-N-[2-methyl-1-(3,4,5-trifluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3,4,5-trifluorobenzoyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1.12 (d, 3H), 1 21 (m, 1H), 2 03 (s, 3H), 2.31 (m, 1H), 4.71 (sextet, 1H), 5.55 (bs, 1H), 6.50 (d, 1H), 6 82 (t, 1H), 6.99 (t, 1H), 7.06 (t, 1H), 7 24-7.27 (m, 3H), 7 39 (m, 3H), 7 46 (d, 1H)

MS m/z. 439 (M+1).

[00247] (±)-*Cis*-N-[1-(4-fluoro-3-methyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-21)

[00248] (±)-*Cis*-N-[1-(4-fluoro-3-methyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-fluoro-3-methyl benzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1 12 (d, 3H), 1 22 (m, 1H), 2.04 (s, 3H), 2.15 (s, 3H), 2.29 (m, 1H), 4 75 (sextet, 1H), 5 60 (bs, 1H), 6 50 (d, 1H), 6.73 (t, 1H), 6 86 (s, 1H), 6.93 (t, 1H), 7.15-7.39 (m, 8H).

MS m/z 417 (M+1)

[00249] (±)-*Cis*-N-[1-(4-fluoro-3-trifluoromethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-22)

[00250] (±)-*Cis*-N-[1-(4-fluoro-3-trifluoromethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-fluoro-3-(trifluoromethyl)-benzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H), 1.24 (m, 1H), 2 04 (s, 3H), 2.33 (m, 1H), 4.75 (sextet, 1H), 5 58 (bs, 1H), 6 46 (d, 1H), 6.87-6.96 (m, 3H), 7.10-7 41 (m, 6H), 7 49 (d, 1H), 7.74 (d, 1H)

MS m/z 471 (M+1).

[00251] (±)-*Cis*-N-[1-(3-chloro-4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-23)

[00252] (±)-*Cis*-N-[1-(3-chloro-4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-chloro-4-fluorobenzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1 13 (d, 3H), 1.24 (m, 1H), 2 04 (s, 3H), 2 31 (m, 1H), 4.76 (sextet, 1H), 5 59 (bs, 1H), 6.50 (d, 1H), 6 85 (d, 2H), 6.96 (t, 1H), 7 21 (t, 1H), 7.27 (m, 2H), 7 39 (m, 4H), 7 50 (d, 1H)
MS m/z· 437 (M+1)

[00253] (±)-*Cis*-N-[2-methyl-1-(2,4,6-trifluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-24)

[00254] (±)-*Cis*-N-[2-methyl-1-(2,4,6-trifluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 2,4,6-trifluorobenzoyl chloride for 2-furoyl chloride.
^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H), 1 21 (m, 1H), 2 05 (s, 3H), 2 29 (m, 1H), 4.86 (sextet, 1H), 5.45 (bs, 1H), 6 35 (t, 1H), 6.70 (d, 2H), 6.95 (t, 1H), 7 2 -7 5 (m, 7H)
MS m/z 439 (M+1)

[00255] (±)-*Cis*-N-[1-(4-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-25)

[00256] (±)-*Cis*-N-[1-(4-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-chlorobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR ($CDCl_3$) δ· 1.09 (t, 3H), 1.12 (d, 3H), 1 22 (m, 1H), 2 23 (m, 3H), 4.73 (sextet, 1H), 5.58 (bs, 1H), 6 46 (d, 1H), 6.78 (d, 1H), 6 88 (t, 1H), 6 98 (t, 1H), 7.15 (t, 1H), 7.18-7.44 (m, 8H)
MS m/z 433 (M+1)

[00257] (±)-*Cis*-N-[2-methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-26)

[00258] (±)-*Cis*-N-[2-methyl-1-(4-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-(trifluoromethoxy)benzoyl chloride for 2-furoyl chloride
^{1}H-NMR ($CDCl_3$) δ 1.16 (d, 3H), 1 24 (m, 1H), 2 28 (m, 3H), 4.78 (sextet, 1H), 5.61 (bs, 1H), 6.46 (d, 1H), 6.91 (t, 1H), 6.92 (t, 1H), 7 02 (d, 2H), 7.18 (t, 1H), 7.23-7.27 (m, 4H), 7.33 (d, 1H), 7 39 (s, 3H)
MS m/z. 469 (M+1).

[00259] (±)-*Cis*-N-[2-methyl-1-(3-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-27)

[00260] (±)-*Cis*-N-[2-methyl-1-(3-trifluoromethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-(trifluoromethoxy)benzoyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 14 (t, 3H), 1.15 (d, 3H), 1 25 (m, 1H), 2 25 (m, 3H), 4.78 (sextet, 1H), 5.59 (bs, 1H), 6 46 (d, 1H), 6.91 (t, 1H), 6 95 (d, 1H), 7.12 -7.27 (m, 6H), 7 34 (d, 1H), 7.39 (s, 3H).

MS m/z. 469 (M+1)

[00261] (±)-*Cis*-N-[2-methyl-1-(3-phenyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-28)

[00262] (±)-*Cis*-N-[2-methyl-1-(3-phenyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 3-phenyl-5-isoxazole carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (t, 3H), 1 19 (d, 3H), 1 61 (m, 1H), 2.24 (m, 3H), 4 78 (sextet, 1H), 5.49 (bs, 1H), 6.34 (bs, 1H), 6.85 (d, 1H), 7 10 (t, 1H), 7.26 (s, 3H), 7.32 (t, 1H), 7 40 (m, 6H), 7.67 (s, 2H)

MS m/z 466 (M+1).

[00263] (±)-*Cis*-N-{2-methyl-1-[4-(5-methyl-tetrazol-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-29)

[00264] (±)-*Cis*-N-{2-methyl-1-[4-(5-methyl-tetrazol-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made following general procedure A, substituting 4-(5-methyl-1H-tetrazole-1-yl)-benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 16 (t, 3H), 1.17 (d, 3H), 1.24 (m, 1H), 2.26 (m, 3H), 2.55 (s, 3H), 4 82 (sextet, 1H), 5.64 (bs, 1H), 6 50 (d, 1H), 6.94 (t, 1H), 7 21-7.41 (m, 11H)

MS m/z 481 (M+1).

[00265] (±)-*Cis*-N-{1-[3-(4-chloro-phenyl)-isoxazole-5-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-30)

[00266] (±)-*Cis*-N-{1-[3-(4-chloro-phenyl)-isoxazole-5-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made following general procedure A substituting 3-(4-chlorophenyl)-5-isoxazole carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 21 (m, 6H), 1 24 (m, 1H), 2.23 (m, 3H), 4.76 (sextet, 1H), 5.48 (bs, 1H), 6.28 (s, 1H), 6.84 (d, 1H), 7.07 (m, 2H), 7 26-7 67 (m, 7H), 7.78 (d, 1H), 8.03 (t, 2H)

MS m/z: 500 (M+1)

[00267] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-hydroxy-N-phenyl-acetamide (A-31)

[00268] (±)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-hydroxy-N-phenyl-acetamide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and acetoxyacetyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1 13 (d, 3H), 1 22 (m, 1H), 2 39 (m, 1H), 3.42 (s, 1H), 3.85 (d, 1H), 4 04 (d, 1H), 4.77 (sextet, 1H), 5.54 (bs, 1H), 6.49 (d, 1H), 6 85 (t, 2H), 6 94 (t, 1H), 7.18-7.27 (m, 5H), 7.33 (d, 1H), 7.43 (s, 3H).

MS m/z 419 (M+1).

[00269] (±)-*Cis*-N-[1-(1H-indole-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-32)

[00270] (±)-*Cis*-N-[1-(1H-indole-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting indole-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.25 (t, 3H), 1.26 (d, 3H), 1.27 (m, 1H), 2 36 (m, 3H), 4.86 (sextet, 1H), 5 62 (bs, 1H), 5 95 (s, 1H), 7.11 (t, 1H), 7 18 (t, 2H), 7.29 (t, 1H), 7.37 (m, 4H), 7.44-7.55 (m, 5H).

MS m/z. 438 (M+1).

[00271] (±)-*Cis*-N-[2-methyl-1-(4-pyrazol-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-33)

[00272] (±)-*Cis*-N-[2-methyl-1-(4-pyrazol-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-(1H-pyrazol-1-yl)-benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1.03 (t, 3H), 1.11 (d, 3H), 1 20 (m, 1H), 2 19 (m, 3H), 4 73 (sextet, 1H), 5 62 (bs, 1H), 6 39 (s, 1H), 6.48 (d, 1H), 6.86 (t, 1H), 7.10-7.34 (m, 9H), 7.48 (d, 2H), 7.65 (s, 1H), 7.81 (s, 1H)

MS m/z: 465 (M+1).

[00273] (±)-*Cis*-N-[1-(benzofuran-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-34)

[00274] (±)-*Cis*-N-[1-(benzofuran-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 2-benzofuran carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.04 (t, 3H), 1 07 (d, 3H), 1.18 (m, 1H), 2 19 (m, 3H), 4 69 (sextet, 1H), 5 54 (bs, 1H), 6.41 (d, 1H), 6.70-7 39 (m, 12H), 7 43 (d, 1H).
MS m/z 439 (M+1)

[00275] (±)-*Cis*-N-[1-(3-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-35)

[00276] (±)-*Cis*-N-[1-(3-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was following general procedure A made substituting 3-chlorobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR ($CDCl_3$) δ· 1.09 (t, 3H), 1 12 (d, 3H), 1.22 (m, 1H), 2 23 (m, 3H), 4 73 (sextet, 1H), 5.58 (bs, 1H), 6 46 (d, 1H), 6.78 (d, 1H), 6 88 (t, 1H), 6 98 (t, 1H), 7.15 (t, 1H), 7 18-7.44 (m, 8H).

MS m/z 433 (M+1).

[00277] (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester (A-36)

[00278] (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester was made from (±)-N-[1-(4-Hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (±)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl propionamide (0.147 g) was dissolved in DMF (5 mL) at room temperature. Sodium hydride (60 % in oil, 0.021g) was added and the mixture allowed to stir 30 min Ethyl 4-bromoacetate (0 065 g) was added and the reaction was allowed to stir over night. Ethanol was added and the reaction was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (80/20 hexanes/ethyl acetate – 50/50 hexanes ethyl acetate gradient) to afford the product (130 mg, 73 %)
^{1}H-NMR ($CDCl_3$) δ· 1 08-1.16 (m, 9H), 1 21 (t, 1H), 2.24 (m, 3H), 4.09 (q, 2H), 4 53 (s, 2H), 4.74 (sextet, 1H), 5.59 (bs, 1H), 6.48 (d, 1H), 6.67 (d, 2H), 6 89 (t, 1H), 7 11-7 37 (m, 9H)
MS m/z. 500 (M+1)

[00279] (±)-*Cis*-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-37)

[00280] (±)-*Cis*-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide substituting 3-chlorobenzoyl chloride. (±)-*Cis*-N-[1-(4-

methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was (0.548 g, 0.001 mol) was dissolved in dichloromethane and a solution of BBr_3 (1 0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for 4h or until no starting material remained The reaction was carefully washed with sat $NaHCO_3$ and brine The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure The phenol was concentrated and the residue was purified by Biotage flash chromatography using 100 % EtOAc to give a white solid, 68 % yield

^{1}H-NMR ($CDCl_3$) δ 1.09 (d, 3H), 1.11 (t, 3H), 1.19 (m, 1H), 2 26 (m, 3H), 4.74 (sextet, 1H), 5 54 (bs, 1H), 6 46 (d, 1H), 6.53 (d, 1H), 6 96 (t, 1H), 7.14-7 40 (m, 9H).

MS m/z 415 (M+1)

[00281] (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-38)

[00282] (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-methoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1.12 (d, 3H), 1 15 (t, 3H), 1.17 (m, 1H), 2.23 (m, 3H), 3.74 (s, 3H), 4 74 (sextet, 1H), 5 61 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6.92 (d, 1H), 7 17 (d, 2H), 7.25-7.34 (m, 4H), 7.39 (bs, 3H)

MS m/z: 429 (M+1)

[00283] (±)-*Cis*-{4-[2-Methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid (A-39)

[00284] (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid was made from (±)-*cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester. (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester was dissolved in ethanol (5 mL) and 0.5 mL of 1N NaOH was added at room temperature. The reaction was allowed to stir for 4h The ethanol was removed *in vacuo* and the aqueous solution was acidified with 1N HCl to give a white precipitate which was filtered to give the desired product in 88 % yield.

^{1}H-NMR ($CDCl_3$) δ. 1.12 (d, 3H), 1.16 (t, 3H), 1.15 (m, 1H), 2.28 (m, 3H), 4.52 (s, 2H), 4.74 (sextet, 1H), 5 63 (bs, 1H), 6 50 (d, 1H), 6 68 (d, 2H), 6.91 (t, 1H), 7.16 (t, 1H), 7 18 (d, 2H), 7 26-7 32 (m, 4H), 7.40 (bs, 2H).

MS m/z 473.0 (M+1)

[00285] (±)-*Cis*-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-40)

[00286] (±)-*Cis*-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide. (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was dissolved in DMF (5 mL) at room temperature. Sodium hydride (60 % in oil, 0.061g) was added and the mixture allowed to stir 30 min 4-(2-chloroethyl)morpholine hydrochloride (0.143 g) was added and the reaction was allowed to stir over night. Ethanol was added and the reaction was concentrated *in vacuo*. The residue was partition between ethyl acetate and water, then extracted 3x with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (2/98 methanol/dichloromethane – 5/95 methanol/dichloromethane gradient) to afford the product (200 mg)
^{1}H-NMR ($CDCl_3$) δ: 1 09 (d, 3H), 1 12 (m, 4H), 1.22 (s, 4H), 2.23 (m, 3H), 2.50 (s, 4H), 2.70 (m, 2H), 4.01 (t, 2H), 4.70 (sextet, 1H), 5.59 (bs, 1H), 6 49 (d, 1H), 6.64 (d, 2H), 6.89 (t, 1H), 7.13 (d, 2H), 7.23-7 36 (m, 7H).
MS m/z 528.1 (M+1)

[00287] (±)-*Cis*-N-[1-(4-carbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-41)

[00288] (±)-*Cis*-N-[1-(4-carbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide. (±)-*Cis*-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (0 120 g) was dissolved in DMF (5 mL) at room temperature. Sodium hydride (60 % in oil, 0 70 g) was added and the mixture allowed to stir 30 min 2-Bromoacetamide (0.320 g) was added and the reaction was allowed to stir over night Ethanol was added and the reaction was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted 3x with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (2/98 methanol/dichloromethane – 10/90 methanol/dichloromethane gradient) to afford the product (20 mg, 15%).
^{1}H-NMR ($CDCl_3$) δ: 1.12 (d, 3H), 1.14 (t, 3H), 1.24 (t, 1H), 2.25 (m, 3H), 4.42 (s, 2H), 4.73 (sextet, 1H), 5.61 (bs, 1H), 5.79 (s, 1H), 6.49 (d, 2H), 6.70 (d, 2H), 6.92 (t, 1H), 7 14-7.39 (m, 8H).
MS m/z 472.0 (M+1)

[00289] (±)-*Cis*-N-{1-[4-(2-hydroxy-2-methyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-42)

[00290] (±)-*Cis*-N-{1-[4-(2-hydroxy-2-methyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made from (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester. (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester (0.170 g) was dissolved in THF and cooled to 0 °C Methylmagnesium bromide (3 0M sol in diethyl ether, 0 5 mL) was added and the reaction was allowed to stir at 0 °C for 30 min The reaction was quenched with a saturated solution of ammonium chloride and diluted with ethyl acetate. The organics were seperated and washed with brine, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50/50 hexanes/ethyl acetate – 75/25 hexanes ethyl acetate gradient) to afford the product (132 mg, 80 %).

^{1}H-NMR ($CDCl_3$) δ: 1 10 (d, 3H), 1.14 (t, 3H), 1 23 (t, 1H), 1.29 (s, 6H), 2.24 (m, 3H), 3.70 (s, 2H), 4.74 (sextet, 1H), 5.61 (bs, 1H), 6 50 (d, 1H), 6.66 (d, 2H), 6.91 (t, 1H), 7.13 (t, 1H), 7.14 (d, 2H), 7 25 (d, 1H), 7 32 (d, 1H), 7 37 (bs, 4H).

MS m/z 487.1 (M+1)

[00291] (±)-*Cis*-N-[1-(4-dimethylcarbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-43)

[00292] (±)-*Cis*-N-[1-(4-dimethylcarbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid (±)-*Cis*-{-4-[2-Methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid (0.146 g) was dissolved in THF (2 mL) at room temperature. HOBt (0.063 g), EDCI (0 071 g), and dimethylamine (2 0M solution in THF, 0 162 mL) was added along with 2 drops of DMF and stirred at room temperature for 11 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (100% ethyl acetate) to afford the product (84 mg, 54%)

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3 H), 1 13 (t, 3 H), 1 22 (t, 1 H), 2 23 (m, 3 H), 2.94 (s, 3 H), 3.00 (s, 3 H), 4.60 (s, 2 H), 4 71 (sextet, 1 H), 5.58 (bs, 1 H), 6.49 (d, 1 H), 6 70 (d, 2 H), 6.89 (t, 1 H), 7.13 (d, 1 H), 7.24 (d, 2 H), 7 30 (d, 1 H), 7 37 (bs, 7 H).

MS m/z 500.1 (M+1).

[00293] (±)-*Cis*-N-[1-(3-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-45)

[00294] (±)-*Cis*-N-[1-(3-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 3-dimethylaminobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1 11 – 1.24 (m, 7 H), 2 12 – 2.40 (m, 3 H), 2.83 (s, 6 H), 4.80 (ddd, 1 H), 5 59 (br s, 1 H), 6.49 (d, 1 H), 6 55 – 6.69 (m, 3 H), 6 92 (dd, 1 H), 7 00 (ddd, 1 H), 7.15 (ddd, 1 H), 7.23 – 7 34 (m, 3 H), 7.35 – 7 44 (m, 3 H).
MS m/z 442 (M + 1)

[00295] (±)-*Cis*-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-46)

[00296] (±)-*Cis*-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-dimethylaminobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.09 – 1 28 (m, 7 H), 2.12 – 2 39 (m, 3 H), 2 93 (s, 6 H), 4.73 (ddd, 1 H), 5 61 (br s, 1 H), 6 47 (d, 2 H), 6 62 (d, 1 H), 6.96 (dd, 1 H), 7 12 – 7 20 (m, 3 H), 7.26 – 7.36 (m, 3 H), 7.38 – 7 46 (m, 3 H).
MS m/z 442 (M + 1).

[00297] (±)-*Cis*-N-[2-methyl-1-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-47)

[00298] (±)-*Cis*-[2-ethyl-1-(pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 3-pyridinyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR (300 MHz, $CDCl_3$) δ· 1 08 – 1 32 (m, 7 H), 2 16 – 2.44 (m, 3 H), 4 84 (ddd, 1 H), 5.62 (br s, 1 H), 6 53 (d, 1 H), 6.97 (dd, 1 H), 7.11 (dd, 1 H), 7 20 – 7 51 (m, 8H), 8 55 (dd, 1 H), 8 68 (br s, 1 H).
MS m/z. 400 (M + 1)

[00299] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-4-methoxy-N-phenyl-butyramide (A-48)

[00300] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-4-methoxy-N-phenyl-butyramide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and 4-methoxy-butyryl chloride for acetyl chloride

^{1}H-NMR (300 MHz, $CDCl_3$) δ. 1.08 – 1.20 (m, 4 H), 1 86 – 2 02 (m, 2 H), 2 21 – 2.41 (m, 3 H), 3.26 (m, 3 H), 3.28 – 3 44 (m, 2 H), 4 76 (ddd, 1 H), 5 64 (br s, 1 H), 6 43 (d, 1 H), 6.83 – 6 96 (m, 3 H), 7.17 – 7.34 (m, 5 H), 7.36 – 7.51 (m, 4 H)
MS m/z: 461 (M + 1).

[00301] (±)-*Cis*-2-(acetyl-methyl-amino)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-49)

[00302] (±)-*Cis*-2-(acetyl-methyl-amino)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and (acetyl-methyl-amino)-acetyl chloride for acetyl chloride.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.10 – 1.18 (m, 4 H), 2.13 (s, 3 H), 2 27 – 2.43 (m, 1 H), 3.14 (m, 3 H), 3.77 (d, 1 H), 4.03 (d, 1 H), 4 76 (ddd, 1 H), 5 55 (br s, 1 H), 6 45 (d, 1 H), 6.81 – 6 95 (m, 3 H), 7.15 – 7 26 (m, 3 H), 7.31 – 7.49 (m, 5 H), 7 54 (d, 1 H).

MS m/z = 474 (M + 1).

[00303] (±)-*Cis*-cyclohexanecarboxylic acid [1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenylamide (A-54)

[00304] (±)-*Cis*-cyclohexanecarboxylic acid [1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenylamide was made following general procedure A substituting 3-methoxybenzoyl chloride for 2-furoyl chloride and cyclohexane carbonyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ· 0.8 (8 H, m), 1 5-1.8 (5 H, m), 2.0-2.4 (3 H, m), 3.7 (3 H, d), 4.8 (1 H, m), 5 6 (1 H, d), 6.2-6.6 (2 H, m), 6 6-7.5 (11 H, m)

MS m/z 483 (M+1).

[00305] (±)-*Cis*-isoxazole-5-carboxylic acid [1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenyl-amid (A-55)

[00306] (±)-*Cis*-isoxazole-5-carboxylic acid [1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenyl-amide was made following general procedure A substituting 3-methoxybenzoyl chloride for 2-furoyl chloride and isoxazole-5-carbonyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 2 (3 H, d),1 2 (1 H, m), 2.4 (1 H, m), 3.6 (3 H, s), 4.9 (1 H, m), 5 8 (1 H, m), 6.4 (1 H, d), 6 7-7 7 (12 H, m), 8.2 (1 H, s), 8 4 (1 H, m)

MS m/z· 468 (M+1)

[00307] (±)-*Cis*-N-[1-(furan-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-56)

[00308] (±)-*Cis*-N-[1-(furan-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 3- furoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1.1 (3 H, d),1 2 (1 H, m), 2 0 (3 H, s), 2.2 (1 H, m), 4 7 (1 H, m), 5 5 (1 H, m), 5 9 (1 H, s), 6 9 (1 H, d), 7 1 (2 H, m) 7 2-7 4 (7 H, m).
MS m/z 375 (M+1).

[00309] (±)-*Cis*-N-[1-(3-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-61)

[00310] (±)-*Cis*-N-[1-(3-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 3-fluorobenzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.1 (3 H, d), 1.1 (1 H, m), 2.0 (3 H, s), 2.3 (1 H, m), 4 7 (1 H, m), 5.6 (1 H, m), 6 4 (1 H, d), 6 8 (1 H, d), 6.9-7.4 (11 H, m).
MS m/z: 403 (M+1)

[00311] (±)-*Cis*-N-[1-(3,4-difluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-62)

[00312] (±)-*Cis*-N-[1-(3,4-difluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 3,4-difluorobenzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1.1 (3 H, d), 1.1 (1 H, m), 2.0 (3 H, s), 2.3 (1 H, m), 4.7 (1 H, m), 5 6 (1 H, m), 6 5 (1 H, d), 6 8-7 0 (4 H, d), 7.3-7 5 (7 H, m).
MS m/z· 421 (M+1).

[00313] (±)-*Cis*-N-[1-(benzo[b]thiophene-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-63)

[00314] (±)-*Cis*-N-[1-(benzo[b]thiophene-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting benzo[b]thiophene-3-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.2 (3 H, d), 1.3 (1 H, m), 2 0 (3 H, s), 2.3 (1 H, m), 4 9 (1 H, m), 5 7 (1 H, m), 6.5 (1 H, d), 6 8 (1 H, m), 7.1-7 5 (10 H, m), 7.8 (1 H, d), 8.0 (1 H, d).
MS m/z· 442 (M+2).

[00315] (±)-Cis-N-[1-(3,5-dimethyl-thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-64)

[00316] (±)-*Cis*-N-[1-(3,5-dimethyl-thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 3,5-dimethyl-thiophene-2-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.1 (3 H, d), 1 1 (1 H, m), 1.7 (3 H, s), 2 0 (3 H, d), 2.0 (1 H, m), 2.3 (3 H, s), 4 7 (1 H, m), 5 5 (1 H, m), 6.2 (1 H, s), 6 7 (1 H, d), 7 0 (1 H, t),7.1-7.4 (7 H, m)

MS m/z· 419 (M+1)

[00317] (±)-Cis-N-[1-(3-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide (A-65)

[00318] (±)-*Cis*-N-[1-(3-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide was made following general procedure A substituting 3-fluorobenzoyl chloride for 2-furoyl chloride and isopropyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.0-1 2 (10 H, m), 2.3 (1 H, m), 2.7 (1 H, m), 4 8 (1 H, m), 5.6 (1 H, m), 6.5 (1 H, m), 6.8-7 6 (12 H, m).

MS m/z: 431 (M+1).

[00319] (±)-Cis-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide (A-66)

[00320] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-isobutyramide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and isopropyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.0-1.2 (10 H, m), 2 3 (1 H, m), 2.6 (1 H, m), 4 8 (1 H, m), 5.6 (1 H, m), 6 5 (1 H, d), 6.8-7.0 (3 H, m), 7.1-7.4 (9 H, m).

MS m/z· 431 (M+1)

[00321] (±)-*Cis*-N-[1-(2,4-dimethyl-thiazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-67)

[00322] (±)-*Cis*-N-[1-(2,4-dimethyl-thiazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A substituting 2,4-dimethyl-thiazole-5-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1 2 (3 H, d), 1.2 (1 H, m), 2.0 (3 H, s), 2 2 (3 H, s), 2.3 (1 H, m), 2.6 (3 H, s), 4 7 (1 H, m), 5 4 (1 H, m), 6 8 (1 H, d), 7.1 (2 H, m), 7 2-7.5 (6 H, m)

MS m/z 420 (M+1).

[00323] (±)-*Cis*-N-[1-(furan-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-68)

[00324] (±)-*Cis*-N-[1-(furan-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 0-1.2 (7 H, m), 2 2-2.4 (3 H, m), 4 7 (1 H, m), 5 4 (1 H, m), 6 2 (2 H, m), 6 8 (1 H, d), 7.0-7.4 (9 H, m)

MS m/z: 389 (M+1).

[00325] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-butyramide (A-69)

[00326] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-butyramide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and butyryl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 0 8 (3 H, t), 1.2 (3 H, d), 1 2 (1 H, m), 1 5 (2 H, m), 2 0 (3 H, m), 4 7 (1 H, m), 5.4 (1 H, m), 6 5 (1 H, d), 6.6-6 8 (4 H, m), 6.9-7 3 (8 H, m).

MS m/z 432 (M+2).

[00327] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-phenoxy-N-phenyl-acetamide (A-72)

[00328] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-phenoxy-N-phenyl-acetamide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and 1-chloro-3-phenoxy-propan-2-one for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 1 (3 H, d), 1 1 (1 H, m), 2.3 (1 H, m), 4.5 (2 H, s), 4.7 (1 H, m), 5.7 (1 H, m), 6 4 (1 H, d), 6 7-6.9 (7 H, m), 7.1-7.4 (9 H, m), 10.0 (1 H, m).

MS m/z 496 (M+2).

[00329] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-3,N-diphenyl-propionamide (A-73)

[00330] (±)-*Cis*-N-[1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-3,N-diphenyl-propionamide was made following general procedure A substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and 3-phenylpropionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.2 (3 H, d), 1.2 (1 H, m), 2.2 (1 H, m), 2 7 (2 H, t), 3.1 (2 H, t), 4 7 (1 H, m), 5.7 (1 H, m), 6.6 (1 H, d), 6.8-7.6 (17 H, m).

MS m/z 494 (M+2)

[00331] **(±)-*Cis*-N-[1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-75)**

[00332] (±)-*Cis*-N-[1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting benzo[b]thiophene-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.2 (7 H, m), 2 1-2 3 (3 H, m), 4.8 (1 H, m), 5.6 (1 H, m), 6.9 (1 H, d), 7 0 (2 H, m), 7 2-7 5 (9 H, m), 7.6 (1 H, d), 7.8 (1 H, d)

MS m/z 456 (M+2).

[00333] **(±)-*Cis*-N-[1-(4-cyano-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-76)**

[00334] (±)-*Cis*-N-[1-(4-cyano-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-cyanobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.3 (7 H, m), 2.2-2 4 (3 H, m), 4 8 (1 H, m), 5 6 (1 H, m), 6.4 (1 H, d), 6.9 (1 H, t), 7 2-7.6 (11 H, m)

MS m/z: 424 (M+1).

[00335] **(±)-*Cis*-N-[1-(3-fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-77)**

[00336] (±)-*Cis*-N-[1-(3-fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 3-fluoro-4-methoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 1-1.2 (7 H, m), 2 1-2.3 (3 H, m), 3.8 (3 H, s), 4.8 (1 H, m), 5 6 (1 H, m), 6 5 (1 H, d), 6.7 (1 H, t), 6.8 (1 H, d), 6.9 (1 H, t), 7 2-7.5 (8 H, m)

MS m/z: 447 (M+1)

[00337] **(±)-*Cis*-N-[1-(4-methoxy-3-methyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-78)**

[00338] (±)-*Cis*-N-[1-(4-methoxy-3-methyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 3-methyl-4-methoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 0.9-1.1 (7 H, m), 1 8-2 2 (6 H, m), 3 8 (3 H, s), 4 8 (1 H, m), 5.6 (1 H, m), 6.5 (2 H, m), 6 7-7 8 (10 H, m)

MS m/z· 443 (M+1).

[00339] (±)-*Cis*-N-[1-(4-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-79)

[00340] (±)-*Cis*-N-[1-(4-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-ethoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1-1 3 (7 H, m), 1.4 (3 H, t), 2 2-2.4 (3 H, m), 4.0 (2 H, q), 4.8 (1 H, m), 5 6 (1 H, m), 6.5 (1 H, d), 6.9 (2 H, d), 6.9 (1 H, t), 7 2-7 6 (9 H, m)

MS m/z. 443 (M+1)

[00341] (±)-*Cis*-N-[2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-80)

[00342] (±)-*Cis*-N-[2-methyl-1-(4-trifluoromethyl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-trifluoromethylbenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.3 (7 H, m), 2 2-2 4 (3 H, m), 4 8 (1 H, m), 5 6 (1 H, m), 6 4 (1 H, d), 6 9 (1 H, t), 7 2-7.6 (11 H, m).

MS m/z: 319 (M-147).

[00343] (±)-*Cis*-N-[1-(4-benzyl-morpholine-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-81)

[00344] (±)-*Cis*-N-[1-(4-benzyl-morpholine-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-benzyl-morpholine-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.2 (7 H, m), 2.1-2 3 (4 H, m), 2 6 (3 H, m), 3.5 (2 H, m), 3.9 (1 H, m), 4 2 (1 H, m), 4 7 (1 H, m), 5.2 (1 H, m), 7.1-7 5 (14 H, m)

MS m/z 498 (M+1)

[00345] (±)-*Cis*-N-[1-(4-ethyl-morpholine-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-82)

[00346] (±)-*Cis*-N-[1-(4-Ethyl-morpholine-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-ethyl-morpholine-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 1-1.2 (10 H, m), 2 1-2 4 (6 H, m), 2.6 (2 H, m), 3.6 (1 H, t), 3 9 (1 H, m), 4 2 (1 H, m), 4 7 (1 H, m), 5 2 (1 H, m), 7 2-7.5 (14 H, m)
MS m/z 436 (M+1)

[00347] (±)-*Cis*-N-[2-methyl-1-(4-phenoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-83)

[00348] (±)-*Cis*-N-[2-methyl-1-(4-phenoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-phenoxy benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ· 1 0-1.2 (7 H, m), 2 2-2.4 (3 H, m), 4 7 (1 H, m), 5 6 (1 H, m), 6.5 (1 H, d), 6 5 (1 H, d), 6.8 (2 H, d), 7.0-7.4 (15 H, m).
MS m/z 491 (M+1)

[00349] (±)-*Cis*-N-[1-(4-fluoro-3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-84)

[00350] (±)-*Cis*-N-[1-(4-fluoro-3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-fluoro-3-methoxy benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride ^{1}H-NMR ($CDCl_3$) δ 1 0-1.2 (7 H, m), 2.2-2 4 (3 H, m), 3 6 (3 H, s), 4.7 (1 H, m), 5.6 (1 H, m), 6.4 (1 H, d), 6 7-6.9 (4 H, m), 7 1-7.4 (7 H, m) MS m/z: 447 (M+1).

[00351] (±)-*Cis*-N-[1-(4-methoxy-3-trifluoromethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-85)

[00352] (±)-*Cis*-N-[1-(4-methoxy-3-trifluoromethyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 4-methoxy-3-trifluoromethyl benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 0-1 2 (7 H, m), 2 2-2 4 (3 H, m), 3 8 (3 H, s), 4 7 (1 H, m), 5 6 (1 H, m), 6.5 (1 H, d), 6.7 (1 H, d), 7.0 (2 H, m), 7.2-7.4 (7 H, m), 7.8 (1 H, s)
MS m/z. 497 (M+1)

[00353] (±)-*Cis*-N-[1-(2,3-dihydro-benzofuran-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-86)

[00354] (±)-*Cis*-N-[1-(2,3-dihydro-benzofuran-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A substituting 2,3-dihydro-benzofuran-5-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ 1.1-1 2 (7 H, m), 2.1-2.3 (3 H, m), 4 5 (2 H, t), 4 8 (1 H, m), 5 6 (1 H, m), 6.5 (2 H, m), 6 9 (2 H, m), 7.1-7.4 (7 H, m).
MS m/z 441 (M+1).

[00355] **(±)-*Cis*-N-{2-methyl-1-[4-(3-methyl-ureido)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-acetamide (A-87)**

[00356] (±)-*Cis*-N-{2-methyl-1-[4-(3-methyl-ureido)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-acetamide was made from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-nitrobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride. The resulting nitro analog was reduced with Pd/C (10%) in ethanol in a Parr shaker at 35 psi. (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (150 mg, 0 376mmol) was dissolved in 10 ml toluene and 64 mg methylisocyanate (1 13mmol) was added The resulting reaction mixture was stirred at room temperature for 2 hours, then was heated to 50 °C overnight The mixture was concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with methanol-dichloromethane (1:19) to give the title compound (87 mg, 51%).
^{1}H-NMR ($CDCl_3$) δ. 1 1 (3 H, d), 1 1 (1 H, m), 2.0 (3 H, s), 2.3 (1 H, m), 2 7 (3 H, s), 4 7 (1 H, m), 5 1 (2 H, m), 5.6 (1 H, m), 6.5 (1 H, d), 6 9-7.0 (6 H, m), 7.2 (1 H, t), 7.2-7.4 (5 H, m)
MS m/z 457 (M+1)

[00357] **(±)-*Cis*-N-[1-(4-diethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-88)**

[00358] (±)-*Cis*-N-[1-(4-diethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide. (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was dissolved in methylene chloride and ethyl iodide (1 5 equiv.) was added followed by K_2CO_3 The reaction was allowed to stir at room temperature for 12h The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with methanol-dichloromethane (1:19) to give the title compound.

^{1}H-NMR ($CDCl_3$) δ 1 0-1 2 (10 H, m), 2.0 (3 H, s), 2 4 (1 H, m), 3.3 (4 H, q), 4.7 (1 H, m), 5 6 (1 H, m), 6 4 (2 H, d), 6.6 (1 H, d), 6 9 (1 H, t), 7 0-7 4 (9 H, m) .
MS m/z 456 (M+1).

[00359] (±)-*Cis*-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-acetic acid (A-89)

[00360] (±)-*Cis*-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-acetic acid was made from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide. (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was dissolved in dimethylformamide and bromoacetic acid ethyl ester was added followed by K_2CO_3 The reaction was allowed to heat to 90 °C for 12h. The reaction mixture was filtered and concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with methanol-dichloromethane (2:18) to give the ester. The ester was hydrolyzed using NaOH (aqueous) in methanol and water to give the title compound
^{1}H-NMR ($CDCl_3$) δ 1 1 (3 H, d), 1 1 (1 H, m), 2.0 (3 H, s), 2 3 (1 H, m), 3 6 (1 H, s), 4.7 (3 H, b), 5.6 (1 H, m), 6.3 (1 H, m), 6 6 (1 H, d), 6 8-7 4 (11 H, m).
MS m/z· 458 (M+1).

[00361] (±)-*Cis*-{N-[1-(4-methanesulfonylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-90)

[00362] (±)-*Cis*-{N-[1-(4-methanesulfonylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide. (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (50 mg, 0 12mmol) was dissolved in 5 ml DMF and methanesulfonic anhydride (21 mg, 0 12mmol) was added. The resulting reaction mixture was heated to 45 °C and stirred for 1 hour. The mixture was concentrated under vacuum The residue was purified by silica gel chromatography, eluting with methanol-dichloromethane (1.9) to give the title compound (15 mg, 25%)
^{1}H-NMR ($CDCl_3$) δ 1 1-1 2 (7 H, m), 2 1-2 3 (3 H, m), 3.0 (3 H, s), 4.7 (1 H, m), 5 6 (1 H, m), 6 5 (1 H, d), 6 7 (2 H, d), 6 9 (1 H, t), 7.1 (2 H, m), 7 2-7.4 (7 H, m)
MS m/z· 491 (M).

[00363] (±)-*Cis*-N-[6-Fluoro-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-fluoro-phenyl)-propionamide (A-91)

[00364] (±)-*Cis*-N-[6-fluoro-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-fluoro-phenyl)-propionamide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride, (±)-*cis*-(6-fluoro-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(4-fluoro-phenyl)-amine for (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine and propionyl chloride for acetyl chloride (±)-*Cis*-(6-fluoro-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(4-fluoro-phenyl)-amine was synthesized following the reactions detailed in scheme 1, substituting 4-fluoroaniline for aniline

^{1}H-NMR ($CDCl_3$) δ. 1 1-1.2 (6H,m), 2 2-2.4 (4H, m), 4 8 (1H, dd), 5.4-5.6 (1H, br), 6.4 (1H, dd), 6.6 (1H, td), 6 8-7.0 (2H, m), 7.0-7 4 (6H, m)
MS m/z: 453 (M + 1).

[00365] (±)-*Cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-bromo-phenyl)-propionamide (A-92)

[00366] (±)-*Cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-bromo-phenyl)-propionamide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride, (±)-*cis*-(6-bromo-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(4-bromo-phenyl)-amine for (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine and propionyl chloride for acetyl chloride (±)-*cis*-(6-bromo-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(4-bromo-phenyl)-amine was synthesized following the reactions detailed in scheme 1, substituting 4-bromoaniline for aniline
^{1}H-NMR ($CDCl_3$) δ: 1.1-1.2 (6H,m), 1.6 (1H, m), 2 2-2.4 (3H, m), 4 8 (1H, m), 5.4-5 6 (1H, br), 6 4 (1H, d), 6.8 (2H, m), 7.0-7 4 (6H, M), 7.8-7.9 (2H, m)
MS m/z. 573 (M + 1).

[00367] (±)-*Cis*-N-[1-(3-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-93)

[00368] (±)-*Cis*-N-[1-(3-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-ethoxybenzoyl chloride for 2-furoyl chloride.
^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H,m), 1 4 (4H, m), 2.1 (3H, s), 2.4 (1H, m), 4 0 (2H, m), 4.9 (1H, m), 5.6 (1H, br), 6 6 (1H, d), 6 9 (2H, m), 7.0 (1H, m), 7.2 (1H, m), 7.3 (1H, m), 7 4 -7.5 (7H, m)
MS m/z 429 (M+1).

[00369] (±)-*Cis*-N-[1-(4-isopropoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-94)

[00370] (±)-*Cis*-N-[1-(4-isopropoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-isopropoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ· 0.9-1.2 (12H,m), 1 4(1H, m), 2.0 (3H, m), 4.3 (1H, m), 4.5 (1H, m), 5 4 (1H, br), 6.3 (1H, d), 6.4 (2H, d), 6.7 (1H, m), 6 9-7 2 (9H, m).

MS m/z· 457 (M+1).

[00371] (±)-*Cis*-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-95)

[00372] (±)-*Cis*-N-[1-(1-Isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 1-isopropyl-1H-benzotriazole-5-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 3 (7H,m), 1.8 (6H, m), 2.4 (3H, m), 5 0 (1H, m), 5.1 (1H, m), 5 7 (1H, br), 6.6 (1H, d), 7.0 (1H, m), 7.2-7 5 (9H, m), 8.3 (1H, s).

MS m/z 482 (M+1).

[00373] (±)-*Cis*-N-[1-(3-Ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-96)

[00374] (±)-*Cis*-N-[1-(3-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 3-ethoxybenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.^{1}H-NMR ($CDCl_3$) δ 1 2 (6H,m), 1.5 (4H, m), 2.4 (3H, m), 4 0 (2H, m), 4 9 (1H, m), 5 7 (1H, br), 6.6 (1H, d), 6 8 (1H, d), 6 9 (1H, m), 7.1 (2H, m), 7.2 (1H, m), 7 3-7 6 (7H, m).

MS m/z 443 (M+1).

[00375] (±)-*Cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester (A-97)

[00376] (±)-*Cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester was made following general procedure A, substituting 4-(4-chlorocarbonyl-phenyl)-piperidine-1-carboxylic acid ethyl ester for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.1-1 3 (10H, m), 1 5 (2H, m), 1 7 (2H, m), 2 3 (3H, m), 2.6 (1H, m), 2.8 (2H, t), 4 1 (2H, m), 4 2 (2H, m), 4.8 (1H, m), 5 6 (1H, br), 6 5 (1H, d), 6.9 (1H, m), 7 2 (2H, m), 7 3-7 4 (9H, m)

MS m/z: 554 (M+1).

[00377] (±)-*Cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-98)

[00378] (±)-*Cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was prepared from (±)-*cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester. (±)-*Cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester (96 mg, 0 17 mmol) was dissolved in acetonitrile (2 mL) Iodotrimetylsilane (74 uL, 0.51 mmol) was added and the reaction was allowed to stir at room temperature over night. Excess reagent was quenched by the addition of methanol (1 mL) and the mixture was concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The extracts were washed with 1 M sodium hydroxide, saturated aqueous sodium thiosulfate and brine, dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography (3 1 methylene chloride / methanol) (77 mg, 94 %)

^{1}H-NMR ($CDCl_3$) δ· 1 1 (6H,m), 1 3 (1H, t), 1.6 (2H, m), 1.7 (2H, d), 2.3 (3H, m), 2.6 (1H, m), 2 7 (2H, t), 3 2 (2H, d), 4.8 (1H, m), 5 6 (1H, br), 6.5 (1H, d), 6 9 (1H, m), 7 0 (2H, d), 7.2 (3H, m), 7 3-7 4 (6H, m).

MS m/z 482 (M+1).

[00379] (±)-*Cis*-N-[1-(4-Bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-99)

[00380] (±)-*Cis*-N-[1-(4-bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-bromobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1.2 (6H,m), 1 25 (1H, m), 2.3 (3H, m), 4.8 (1H, m), 5 6 (1H, br), 6 4 (1H, d), 6.9 (1H, m), 7.1 (2H, d), 7 2 (1H, m), 7.3-7 4 (8H, m).

MS m/z 477 (M+1).

[00381] (±)-*Cis*-N-{1-[4-(1-acetyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-100)

[00382] To a solution of (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (636 mg, 2.70 mmol) in dichloromethane (10 mL) at room temperature was added diisopropylethylamine (1.04 g, 1 44 mL, 2 98 mmol) followed by freshly prepared 4-(4-chlorocarbonyl-phenyl)-piperidine-1-carboxylic acid tert-butyl ester (2.98 mmol) The mixture was stirred at room temperature over night, poured into water and extracted with dichloromethane The extracts were washed with 1 M(aq) NaOH and brine, dried over magnesium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (100 % hexanes to 70/30 hexanes ethyl acetate gradient) to afford the pure amide (827 mg, 58 %).

[00383] The (±)-*cis*-4-[4-(2-methyl-4-phenylamino-3,4-dihydro-2H-quinoline-1-carbonyl)-phenyl]-piperidine-1-carboxylic acid tert-butyl ester (827 mg, 1.57 mmol) thus formed was dissolved in methylene chloride (50 mL). Trifluoroacetic acid (3 mL) was added and the mixture was stirred at rt 70 min. Solvent and excess acid were removed under reduced pressure. The crude residue was dissolved in ethyl acetate and neutralized with 1 M sodium hydroxide (to pH = 10 5). The aqueous phase was extracted twice with additional ethyl acetate. The extracts were combined and washed with brine, dried over sodium sulfate, filtered and concentrated to afford the crude diamine (676 mg, 100 %) as an oil

[00384] To a solution of the piperidine amine obtained above (676 mg, 1.59 mmol) in methylene chloride (25 mL) was added diisopropylethylamine (616 mg, 849 uL, 4 77 mmol), followed by acetyl chloride (162 mg, 156 uL, 2.06 mmol) The mixture was stirred at room temperature over night. The reaction mixture was poured into saturated aqueous sodium bicarbonate and extracted with additional methylene chloride The extracts were combined, washed with brine, dried over sodium sulfate, filtered, dried and concentrated to afford the piperidine acetamide (844 mg, > 100 %)

[00385] The crude piperidine acetamide obtained above (844 mg) was dissolved in methylene chloride (25 mL) to which was then added diisopropylethylamine (205 mg, 283 uL, 1 59 mmol) followed by propionyl chloride (4.42 g, 4.2 mL, 47.7 mmol) The resulting reaction mixture was stirred at room temperature 96 h and concentrated The resulting residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The extracts were washed with brine and dried over sodium sulfate, filtered, dried and concentrated. The crude residue was purified by silica gel chromatography (50/50 ethyl acetate/hexanes to 100% ethyl acetate gradient) to afford the product (437 mg, 52 %).

[00386] (±)-*Cis*-N-{1-[4-(1-acetyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-{1-[4-(1-acetyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (**A-51** & **A-50**, respectively)

^{1}H-NMR ($CDCl_3$) δ· 1 2 (7H, m), 1 6 (2H, m), 1.8 (2H, d), 2 1 (3H, s), 2 3 (3H, m), 2.6 (2H, m), 3.1 (1H, t), 3 9 (1H, m), 4 8 (2H, m), 5.6 (1H, br), 6.5 (1H, d), 6.9 (1H, m), 7.0 (2H, d), 7.1 (2H, d), 7.2-7.4 (7H, m)
MS m/z: 524 (M+1)

[00387] (±)-*Cis*-N-{1-[4-(1-ethyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-101)

[00388] (±)-*Cis*-N-{1-[4-(1-ethyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made from (±)-*cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide. (±)-*Cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl propionamide was dissolved in dichloromethane (3 mL) Acetaldehyde (18 uL, 0 33 mmol) was added in a single portion. The mixture was stirred at room temperature 30 minutes and then a solution sodium triacetoxyborohydride (35 mg, 0 165 mmol) in dichloromethane (1 mL) was slowly added, followed by 1 drop acetic acid The mixture was allowed to stir at room temperature over night and was quenched by aqueous sodium bicarbonate. The biphasic mixture was extracted three times with methylene chloride (20 mL); the combined extracts were washed with brine, dried over magnesium sulfate, filtered, concentrated and purified by HPLC to afford the product (35 mg, 62 %)
^{1}H-NMR ($CDCl_3$) δ: 1.0-1 2 (9H, m), 1.3 (1H, m), 1.8 (4H, br), 2 0 (2H, m), 2 3 (3H, m), 2.5 (2H, m), 3 1 (3H, m), 4.8 (1H, m), 5.6 (1H, br), 6 5 (1H, d), 6 9 (1H, m), 7.0 (2H, d), 7 1-7.4 (9H, m).
MS m/z 511 (M+2)

[00389] (±)-*Cis*-N-[2-Methyl-1-(4-nitro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-102)

[00390] (±)-*Cis*-N-[2-methyl-1-(4-nitro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-nitrobenzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR ($CDCl_3$) δ. 1 2 (7H,m), 2.3 (3H, m), 4.8 (1H, m), 5.6 (1H, br), 6 4 (1H, d), 6.9 (1H, m), 7.2-7.4(9H, m), 8.0 (2H, d)
MS m/z· 444 (M+1)

[00391] (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-103)

[00392] (±)-*Cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was prepared from (±)-*cis*-N-[2-methylmethyl-1-(4-nitro-benzoyl)-1,2,3,4-tetrahydro-

quinolin-4-yl]-N-phenyl-propionamide (±)-*Cis*-N-[2-methyl-1-(4-nitro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (200 mg, 0.45 mmol) was dissolved in ethanol (20 mL). Palladium on carbon (10 %) was carefully added and the resulting suspension was shaken under hydrogen gas (40 psi) over night. The suspension was filtered through Celite ® to remove solids, and the filter cake washed three times with ethanol Concentration of the solution afforded pure product (160 mg, 86 %).

^{1}H-NMR ($CDCl_3$) δ: 1.2 (7 H, m), 2.3 (3 H, m), 3 9 (2 H, br), 4 7 (1 H, m), 5 6 (1 H, br), 6.4 (2 H, d), 6 6 (1 H, d), 6.9 (1 H, m), 7.0 (2 H, d), 7.1 (1 H, m), 7.2-7 4 (6 H, m).

MS m/z 414 (M+1).

[00393] (±)-*Cis*-N-[2-methyl-1-(4-pyrrol-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-104)

[00394] (±)-*Cis*-N-[2-methyl-1-(4-pyrrol-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-pyrrol-1-yl-benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1.2 (6 H, m), 1.3 (1 H, m), 2.3 (3 H, m), 4.8 (1 H, m), 5.6 (1 H, br), 6.3 (2 H, s), 6 6 (1 H, d), 6 9 (1 H, m), 7.1 (2 H, s), 7 2-7.4(11 H, m)

MS m/z· 464 (M+1).

[00395] (±)-*Cis*-N-[1-(4-acetylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-105)

[00396] (±)-*Cis*-N-[1-(4-acetylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was prepared from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide To a solution of (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (100mg, 0.24mmol) in 2.5ml tetrahydrofuran was added acetyl chloride (44 µL, 0.63mmol) followed by triethylamine (88 µL ,0.63mmol) The reaction was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was purified by silica gel chromatography, eluting with hexane-ethyl acetate (3·1) to give the title compound (51 mg, 46%)

^{1}H-NMR ($CDCl_3$) δ 1 1 (7 H, m), 2 2 (3 H, s), 2 3 (3 H, m), 4.8 (1 H, m), 5.6 (1 H, br), 6.5 (1 H, d), 6 9 (1 H, m), 7.1 (2 H, d), 7.2 (1 H, d), 7.3-7.4 (8 H, m), 8.4 (1 H, br)

MS m/z. 456 (M+1)

[00397] (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-carbamic acid ethyl ester (A-106)

[00398] (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-carbamic acid ethyl ester was made from (±)-*cis*-N-[1-(4-aminoamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, following the method described above in the synthesis of (±)-*cis*-N-[1-(4-acetylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, substituting ethyl chloroformate for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (6 H,m), 1 3 (4 H,m), 2.3 (3 H, m), 4.2 (2 H, m), 4 8 (1 H, m), 5.6 (1 H, br), 6 5 (1 H, d), 6 7 (1 H, br), 6 9 (1 H, m), 7.1-7.4 (10 H, m).

MS m/z 486 (M+1).

[00399] **(±)-*Cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-107)**

[00400] (±)-*Cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide. (±)-*Cis*-N-[1-(4-bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (100 mg, 0.22 mmol) was combined with cesium carbonate (355 mg, 1.09 mmol), racemic BINAP (25 mg, 0 04 mmol), Pd_2dba_3 (36 mmol, 0 04 mmol) and 1-methyl piperazine and dissolved in toluene (10 mL). The reaction mixture was heated at 100 °C under argon overnight. The reaction was cooled to room temperature, filtered and the solids washed with ether. The filtrate was washed with water and brine, dried over magnesium sulfate, filtered and concentrated The crude product was purified by HPLC

^{1}H-NMR ($CDCl_3$) δ: 1.2 (6 H,m), 1 3 (1 H,m), 2 2 (3 H, m), 2.3 (3 H, s), 2.5 (4 H, m), 3 2 (4 H, m), 4 7 (1 H, m), 5 6 (1 H, bs), 6.6 (1 H, d), 6.7 (2 H, d), 7 0 (1 H, m), 7 2-7.4 (9 H, m)

MS m/z 498 (M+2)

[00401] **(±)-*Cis*-N-[2-methyl-1-(4-pyrimidin-2-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-108)**

[00402] (±)-*Cis*-N-[2-methyl-1-(4-pyrimidin-2-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-pyrimidin-2-yl-benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1.2 (7 H, m), 2 3 (3 H, m), 4.8 (1 H, m), 5.6 (1 H, br), 6.5 (1 H, d), 6 9 (1 H, m), 7 2-7 4 (10 H, m), 8.3 (2 H, d), 8.8 (2 H, d)

MS m/z. 478 (M+2).

[00403] **(±)-*Cis*-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-109)**

[00404] (±)-*Cis*-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 1 (6H, m), 1.3 (1H, t), 2 3 (3H, m), 2.8 (3H, s), 3 3 (2H, t), 4 2 (2H, t), 4.7 (1H, m), 5 6 (1H, br), 6.3 (1H, d), 6 5 (1H, d), 6.6 (1H, d), 6.9 (1H, s), 7.0 (1H. m), 7.1 (1H, m), 7.3-7 4 (7H, m)

MS m/z 471 (M+2).

[00405] (±)-*Cis*-N-[2-Methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-110)

[00406] (±)-*Cis*-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, following the procedure used to make (±)-*cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide substituting morpholine for 1-methyl piperazine.

[00407] (±)-*Cis*-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)- *cis*-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (**A-120** & **A-119**, respectively)

^{1}H-NMR ($CDCl_3$) δ 1 1 (7H, m), 2.3 (3H, m), 3 1 (4H, t), 3.8 (4H, t), 4.7 (1H, m), 5 6 (1H, br), 6.6 (1H, d), 6 7 (2H, d), 6.9 (1H, m), 7.2-7.4 (9H, m).

MS m/z 485 (M+2).

[00408] (±)-*Cis*-N-{1-[4-(2,5-dimethyl-pyrrol-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-111)

[00409] (±)-*Cis*-N-{1-[4-(2,5-dimethyl-pyrrol-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was prepared from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide A solution of (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (150 mg, 0.36 mmol), and propionic acid (0.5 ml) in dry benzene (20 ml) was heated at reflux under argon in a flask equipped with a Dean-Stark trap while stirring with the exclusion of light. The resulting solution was cooled to room temperature, and concentrated under vacuum. Recovered oil was purified by silica gel chromatography, eluting with hexane-ethyl acetate (3.1) to give the title compound (140 mg, 80%)

^{1}H-NMR ($CDCl_3$) δ: 1.2 (7H, m), 2 0 (6H, s), 2 3(3H, m), 4.8 (1H, m), 5 6 (1H, br), 5.9 (2H, s), 6.5 (1H, d), 6.9 (1H, m), 7.0 (1H, d), 7 2 (2H, m), 7 3-7.4 (8H, m).
MS m/z 493 (M+2).

[00410] (±)-*Cis*-N-{1-[4-(2-ethyl-butylamino)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-112)

[00411] (±)-*Cis*-N-{1-[4-(2-ethyl-butylamino)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was prepared from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide To a solution of (±)-*cis*-N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (75 mg, 0.145mmol) in dichloromethane (3 mL) was added 2-ethylbutyraldehyde (26uL, 0.2mmol) in one portion. The mixture was stirred at room temperature for a 0 5 h before a solution of sodium triacetoxyborohydride (74 mg, 0 348 mmol) 1 ml DCM was added slowly. A single drop of acetic acid was added and the reaction was allowed to stir at room temperature over night. Excess reagent was quenched by the addition of saturated aqueous sodium bicarbonate The resulting mixture was extracted three times with 20 mL dichloromethane The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. Crude product was purified by HPLC to afford the title compound (60 mg, 83%).
^{1}H-NMR ($CDCl_3$) δ: 0.9 (6H, m), 1.2 (7H,m), 1 4 (5H, m), 2 3 (3H, m), 3 0 (2H, d), 4.7 (1H, m), 5.6 (1H, br), 6.3 (2H, d), 6 6 (1H, d), 7.0 (1H, m), 7.1 (2H, d),7 2 (1H, m), 7 3-7.4 (6H, m).
MS m/z: 499 (M+2).

[00412] (±)-*Cis*-N-[2-Methyl-1-(4-propylamino-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-113)

[00413] (±)-*Cis*-N-[2-methyl-1-(4-propylamino-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was prepared from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide utilizing the reductive amination conditions described for the synthesis of (±)-*cis*-N-{1-[4-(2-ethyl-butylamino)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide Propionaldehyde was substituted for 2-ethylbutyraldehyde The reaction was poorly selective and afforded approximately equivalent amounts of mono- and di-alkylated products (i e., (±)-*cis*-N-[1-(4-dipropylamino-benzoyl) -2-methyl-1,2,3,4- tetrahydro- quinolin- 4- yl]-N-phenyl propionamidel see below).
^{1}H-NMR ($CDCl_3$) δ: 1 0 (3H, m), 1 1 (7H,m), 1.6 (2H, m), 2.3 (3H, m), 3.0 (2H, d), 4.0 (1H, br), 4 7 (1H, m), 5 6 (1H, br), 6 3 (2H, d), 6 6 (1H, d), 6 9 (1H, m), 7.06 (2H, d), 7.14 (1H, m), 7.3-7 4 (6H, m)
MS m/z 457 (M+2)

[00414] (±)-*Cis*-N-[1-(4-dipropylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-114)

[00415] (±)-*Cis*-N-[1-(4-Dipropylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was prepared as a by-product in the synthesis of (±)-*cis*-N-[2-methyl-1-(4-propylamino-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide described above

^{1}H-NMR ($CDCl_3$) δ: 1.0 (6H, t), 1.1 (6H,m), 1 4 (1H, m), 1 5 (4H, m), 2 3 (3H, m), 3.2 (4H, t), 4.7 (1H, m), 5.6 (1H, br), 6 4 (2H, d), 6 7 (1H, d), 7.0 (1H, m), 7 1-7.2 (3H, m), 7.3-7 4 (6H, m)

MS m/z 499 (M+2).

[00416] (±)-*Cis*-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-115)

[00417] (±)-*Cis*-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-bromo-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide following the procedure used to make (±)-*cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide substituting pyrollidine for 1-methylpiperazine.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (7H, m), 2 0 (4H, m), 2.3 (3H, m), 3.2 (4H, m), 4 7 (1H, m), 5.6 (1H, br), 6.3 (2H, d), 6 6 (1H, d), 6.9 (1H, m), 7 1-7.4 (9H, m)

MS m/z. 468 (M+1).

[00418] (±)-*Cis*-N-[2-methyl-1-(4-ureido-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-116)

[00419] (±)-*Cis*-N-[2-methyl-1-(4-ureido-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide. A mixture of (±)-*cis*-N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (100mg, 0 24mmol) and trimethylsilyl isocyanate (120µL, 30.72mmol) in dry DMF (0.5mL) was stirred at room temperature for 3 days and then concentrated under reduced pressure at 30 °C to dryness The residual syrup was stirred with ethyl acetate to which was added an additional 10mL of ethyl acetate with 10mL water. The pH was adjusted to 3.0 with 3 N HCl, and the separated aqueous layer was extracted with ethyl acetate The combined ethyl acetate extracts were washed with water and brine, dried over magnesium sulfate and concentrated *in vacuo*, yielding the product (10mg, 9% yield).

^{1}H-NMR ($CDCl_3$) δ 1.2 (7H, m), 2 3 (3H, m), 4.7 (1H, m), 5.1 (2H, br), 5.6 (1H, br), 6.5 (1H, d), 6 9 (5H, m), 7.2 (7H, m), 7 9 (1H, br)

MS m/z 457 (M+1).

[00420] (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester (A-117)

[00421] (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester was prepared from (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide A mixture of (±)-*cis*-N-[1-(4-amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (210 mg, 0.53 mmol), potassium carbonate (123 mg, 0.89 mmol), and methyl 2-bromopropionate (70 uL, 0 63mmol) in dry dimethylformamide (2 mL) was heated at 100°C for 6h, then cooled to room temperature and stirred with 20ml water until all of the salts dissolved The aqueous layer was separated and was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure. The resulting oil was purified by silica gel chromatography, eluting with (97.3 methylene chloride/methanol) to afford the title compound (220 mg, 87%)

^{1}H-NMR ($CDCl_3$) δ 1.2 (4H, m), 1 4 (3H, d), 2 0 (3H, s), 2 3 (1H, br), 3 7 (3H, s), 4.1 (1H, m), 4 7 (1H, m), 5 6 (1H, br), 6.3 (2H, d), 6 6 (1H, d), 6.9 (1H, m), 7.0 (2H, d), 7.3-7.4 (7H, m).
MS m/z 487 (M+2).

[00422] (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionamide (A-118)

[00423] (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionamide was prepared from (±)-*cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester.

[00424] To concentrated ammonium hydroxide (2 mL, 2 0 M) were added crude (±)-*cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester (180 mg, 0.37 mmol) and trace amount ammonium chloride, the mixture was heated at 100 °C for 6 h in a pressure reactor with good mixing. After cooling to 0 °C, the resulting precipitate was filtered and washed with ice-water and extracted with ether The combined extracts were washed with water and brine, dried over magnesium sulfate and concentrated under reduced pressure The crude product was purified by HPLC to give the title compound (10 mg, 6%)

^{1}H-NMR ($CDCl_3$) δ: 1 2 (4H, m), 1 5 (3H, d), 2.1 (3H, s), 2 3 (1H, br), 3 8 (1H, s), 4 4 (2H, br), 4 7 (1H, m), 5 6 (2H, m), 6 3 (2H, m), 6 6 (2H, d), 7 0 (1H, m), 7 1 (2H, d), 7 2 (1H, m), 7 3-7.4 (5H, m)
MS m/z 471 (M+1)

[00425] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-123)

[00426] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride

[00427] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)- *cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (**A-126** & **A-127**, respectively)

^{1}H-NMR ($CDCl_3$) δ 1 15 (3 H, d; overlapping 1 H, t), 2 05 (3 H, s), 2.33 (1 H, m), 3.60 (3 H,s), 4.80 (1 H, m), 5 65 (1 H, m), 6.55 (1 H, d), 6.75-6 85 (3 H, complex), 6 95 (1 H, t), 7 15 (1 H, t), 7.25 (1 H, t), 7.25-7.55 (6 H, m).

MS m/z: 415 (M +1).

[00428] (±)-*Trans*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-124)

[00429] (±)-*Trans*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride, and *trans*-(2-ethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine for *cis*-(2-ethyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine

[00430] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-128)

[00431] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride, and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ· 1.15 (3H, d, overlapping 3H, t, 1H, t), 2 20 (2H,q), 2.33 (1H, m), 3.65 (3H,s), 4.80 (1H, m), 5.60 (1H, m), 6.55 (1H, d), 6.75-6 85 (3H, complex), 6.95 (1H, t), 7.15 (1H, t), 7.20 (1H, t), 7 25-7.55 (6H, m) .

MS m/z 429 (M + 1)

[00432] (±)-*Cis*-N-[6-chloro-1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (A-129)

[00433] (±)-*Cis*-N-[6-chloro-1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide was made following general procedure A, substituting 3-methoxybenzoyl chloride for 2-furoyl chloride, and (±)-*cis*-(6-chloro-2-methyl-1,2,3,4-tetrahydro-

quinolin-4-yl)-(4-chloro-phenyl)-amine for (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-phenyl-amine (±)-*Cis*-(6-chloro-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-(4-chloro-phenyl)-amine was synthesized following the reactions detailed in scheme 1, substituting 4-chloroaniline for aniline.
^{1}H-NMR ($CDCl_3$) δ 1.15 (3H, d; overlapping 1H, t), 2.02 (3H, s), 2.35 (1H, m), 3.65(3H,s), 4.80 (1H, m), 5 60 (1H, m), 6.42 (1H, d), 6 65-6.95 (overlapping 1H, d; 1H,dd; 1H dd), 7.15 (1H, t), 7.20-7 30 (6H, m), 7.40 (1H, d)
MS m/z· 484(M + 1).

[00434] (±)-*Cis*-N-[2-methyl-1-(1-methyl-1H-pyrrole-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-130)

[00435] (±)-*Cis*-N-[2-methyl-1-(1-methyl-1H-pyrrole-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 1-methyl-1H-pyrrole-2-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 12 (3H, d, overlapping 1H, t), 2.00 (3H, s), 2.35 (1H, m), 3.80 (3H,s), 4.70 (1H, m), 5 50 (1H, m), 5.80 (1H, d), 6.55 (1H,d), 6 80 (1H, d), 7.00 (1H,t), 7 20-7.50 (6H, m)
MS m/z· 388 (M + 1).

[00436] (±)-*Cis*-N-[2-methyl-1-(2-methyl-pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-131)

[00437] (±)-*Cis*-N-[2-methyl-1-(2-methyl-pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 2-methyl-isonicotinoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ: 1 11-1 16 (3H, d; overlapping 3H, t, and 1H, t), 2 20-2 35 (overlapping 2H, q; and 1H, m), 2 47 (3H, s), 4.80 (1H, m), 5 60(1H, m), 6 48 (1H, d), 6.65 (1H,d), 6 85 (1H, t), 7 10-7 40 (8H, m), 8 30 (1H, d)
MS m/z 414 (M + 1).

[00438] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-3-methyl-N-phenyl-butyramide (A-132)

[00439] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-3-methyl-N-phenyl-butyramide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and 3-methyl-butyryl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 0.90 (2 x 3H, d), 1 15 (3H, d, overlapping 1H, t), 2.15 (1H, m), 2.20-2.35 (overlapping 2H, m; 1H, m), 4.80 (1H, m), 5 65 (1H, m), 6 50 (1H, d), 6.90 (4H, complex), 7.20-7 60 (8H, m)
MS m/z: 445 (M + 1).

[00440] (±)-*Cis*-N-[2-methyl-1-(6-methyl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-133)

[00441] (±)-*Cis*-N-[2-methyl-1-(6-methyl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 6-methyl-nicotinoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ. 1.11-1.16 (3H, d; overlapping 3H, t, and 1H, t), 2 20-2.40 (overlapping 2H, q; and 1H, m), 2.49 (3H, s), 4.80 (1H, m), 5.60(1H, m), 6.48 (1H, d), 6.80-7.00 (1H,d; 1H, t), 7.10-7.50 (9H, m), 8.60 (1H, d)
MS m/z: 414 (M + 1)

[00442] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-morpholin-4-yl-N-phenyl-acetamide (A-134)

[00443] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-2-morpholin-4-yl-N-phenyl-acetamide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and morpholinoacetyl chloride for acetyl chloride.

[00444] (±)-*Cis*-N-[1-(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-135)

[00445] (±)-*Cis*-N-[1-(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting (±)-*cis*-2,3-dihydro-benzo[1,4]dioxine-6-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ 1 10 (3H, d, overlapping 3H, t; 1H, t), 2.10 (2H, q, 1H, m), 4 10 (2x2H, m), 4.70 (1H, m), 5.65 (1H, m), 6 50-6.60 (2X1H, d), 7.20-7 40 (7H, m).
MS m/z: 457 (M + 1).

[00446] (±)-*Cis*-N-[2-methyl-1-(5-trifluoromethyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-136)

[00447] (±)-*Cis*-N-[2-methyl-1-(5-trifluoromethyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 5-

trifluoromethyl-thiophene-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ· 1 10-1.15 (3H, d, overlapping 3H, t; 1H, t), 2 15- 2.35 (2H, q, 1H, m), 4.70 (1H, m), 5.55 (1H, m), 6.45 (1H, d), 6.85 (1H, d), 7 00 - 7.20 (overlapping 1H,d; 1H, t), 7 20-7.60 (7H, m)

MS m/z 473 (M + 1).

[00448] (±)-*Cis*-N-[2-methyl-1-(6-trifluoromethyl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-137)

[00449] (±)-*Cis*-N-[2-methyl-1-(6-trifluoromethyl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 6-trifluoromethyl-nicotinoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 10 (3H, d; overlapping 3H, t; 1H, t), 2 00-2.40 (2H, q, 1H, m), 4 80 (1H, m), 5.65 (1H, m), 6 40 (1H, d), 7 00 (1H, d), 7.20-7.50 (9H, m), 8.70 (1H).

MS m/z· 468 (M + 1).

[00450] (±)-*Cis*-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-138)

[00451] (±)-*Cis*-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 3-methyl-isoxazole-5-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 10 (overlapping 3H, d, 3H,t; 1H, t), 2.10- 2 40 (overlapping 3H, s; 2H, q; 1H, m), 4.80 (1H, m), 5 50 (1H, m), 6.80 (1H, d), 7 10 (1H, t), 7.20-7.50 (9H, m)

MS m/z 404 (M + 1)

[00452] (±)-*Cis*-N-[2-methyl-1-(4-oxazol-5-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-139)

[00453] (±)-*Cis*-N-[2-Methyl-1-(4-oxazol-5-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 4-oxazol-5-yl-benzoyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 00-1.20 (overlapping 3H,t; 3H, d, 1H, t), 2.20-2.40 (2H, q; 1H, m), 4 80 (1H, m), 5 65 (1H, m), 6.55 (1H, d), 6 90 (1H, t), 7 20-7.60 (12H, m), 7.90 (1H, s).

MS m/z 466 (M + 1)

[00454] (±)-*Cis*-N-[1-(benzo[c]isoxazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-140)

[00455] (±)-*Cis*-N-[1-(benzo[c]isoxazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting benzo[c]isoxazole-3-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 14 (3H, t); 1.23 (3H, d), 2.20 (2H, q), 2 40 (1H, m), 4.80 (1H, m), 5.60 (1H, m), 6.60 (1H, d), 7.00 (3H, complex), 7 00-7 40 (8H, m), 7.55 (1H, d).

MS m/z· 440 (M + 1).

[00456] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-succinamic acid methyl ester (A-141)

[00457] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-succinamic acid methyl ester was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and 3-chlorocarbonyl-propionic acid methyl ester for acetyl chloride.

[00458] (±)-*Cis*-N-{1-[5-(4-chloro-phenyl)-furan-2-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-142)

[00459] (±)-*Cis*-N-{1-[5-(4-chloro-phenyl)-furan-2-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made following general procedure A, substituting 5-(4-chloro-phenyl)-furan-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.08-1.36(7H, m), 2 15-2.35 (3H, m), 4.72 (1H, q), 5 40-5 60 (1H, br), 6 53 (2H, d), 6 89 (1H, d), 7 04-7 09 (1H, m), 7 17-7.40 (10H, m)

MS m/z· 499 (M+1).

[00460] (±)-*Cis*-N-{1-[5-(2-chloro-4-trifluoromethyl-phenyl)-furan-2-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-143)

[00461] (±)-*Cis*-N-{1-[5-(2-chloro-4-trifluoromethyl-phenyl)-furan-2-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made following general procedure A, substituting 5-(2-chloro-4-trifluoromethyl-phenyl)-furan-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ. 1.08-1 36(7H, m), 2.15-2 35 (3H, m), 4 72 (1H, q), 5.40-5 60 (1H, br), 6.78-6.87 (2H, m), 7.05-7.49 (11H, m).

MS m/z· 567 (M+1).

[00462] (±)-*Cis*-N-{2-methyl-1-[5-(4-nitro-phenyl)-furan-2-carbonyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-144)

[00463] (±)-*Cis*-N-{2-methyl-1-[5-(4-nitro-phenyl)-furan-2-carbonyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide propionamide was made following general procedure A, substituting 5-(4-nitro-phenyl)-furan-2-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ. 1.13-1 22(7H, m), 2.20-2 36 (3H, m), 4.70 (1H, q), 5.40-5 60 (1H, br), 6.70 (2H, d), 6.87 (1H, d), 7 03 (1H, t), 7 25-7.47 (8H, m), 8 15 (2H, d)

MS m/z. 510 (M+1).

[00464] (±)-*Cis*-N-[2-methyl-1-(5-methyl-isoxazole-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-145)

[00465] (±)-*Cis*--N-[2-methyl-1-(5-methyl-isoxazole-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 5-methyl-isoxazole-3-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.27(7H, m), 2 13-2.35 (6H, m), 4.78 (1H, q), 5 40-5.60 (1H, br), 6.84-6.86 (1H, d), 7 05 (1H, t), 7.22-7 38 (7H, m).

MS m/z: 404 (M+1).

[00466] (±)-*Cis*-N-[2-methyl-1-(2-methyl-thiophene-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-146)

[00467] (±)-*Cis*-N-[2-methyl-1-(2-methyl-thiophene-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide was made following general procedure A, substituting 2-methyl-thiophene-3-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 01-1 27(7H, m), 2 13-2.39 (6H, m), 4 62-4.78 (1H,m), 5.40-5.60 (1H, br), 6.31-6 45 (2H, m), 6.60-6.83 (2H, m), 7.02-7.38 (6H, m).

MS m/z· 420 (M+1).

[00468] (±)-*Cis*-but-3-enoic acid [1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenyl-amide (A-147)

[00469] (±)-*Cis*-but-3-enoic acid [1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-phenyl-amide was made following general procedure A, substituting 4-fluorobenzoyl chloride for 2-furoyl chloride and but-3-enoyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 0.98-1 17(4H, m), 2.13-2 29 (1H, m), 2 98-3 15 (2H, m), 4 60-4.78 (1H, m), 4.98-5 20 (2H, m), 5 40-5 60 (1H, m), 5.70-5.91 (1H, m), 6.40 (1H, d), 6 75-7.46 (11H, m)

MS m/z 429 (M+1)

[00470] (±)-*Cis*-N-{1-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazole-5-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide (A-148)

[00471] (±)-*Cis*-N-{1-[3-(4-fluoro-phenyl)-[1,2,4]oxadiazole-5-carbonyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide was made following general procedure A, substituting 3-(4-fluoro-phenyl)-[1,2,4]oxadiazole-5-carbonyl chloride for 2-furoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 14 (3H, t), 1 23-1 25 (4H, m), 2.17-2 39 (3H, m), 4 78-4 80 (1H, m), 5 40-5.60 (1H, br), 7 03-7.09 (3H, m), 7 10-7.22 (4H, m), 7.24-7.40 (4H, m), 7.97-8 02 (2H, m).

MS m/z 485 (M+1).

[00472] (±)-*Cis*-N-(1-benzoyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide (A-150)

[00473] (±)-*Cis*-N-(1-benzoyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide was made following general procedure A, substituting benzoyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d), 1.58-1 69 (1H, m), 2.03 (3H, s), 2.22-2 37 (1H, m), 4.72-4 86 (1H, m), 5.62 (1H, br s), 6.49 (1H, d), 6 88 (1H, t), 7 13-7.46 (12H, m).

MS m/z 385 (M+1).

[00474] (±)-*Cis*-N-[1-(4-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-151)

[00475] (±)-*Cis*-N-[1-(4-chloro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-chlorobenzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ. 1 14 (3H, d), 1 61 (1H, br s), 2.03 (3H, s), 2 24-2 36 (1H, m), 4 71-4.83 (1H, m), 5 51-5.69 (1H, m), 6 48 (1H, d), 6 93 (1H, t), 7 12-7.28 (7H, m), 7 35-7.40 (4H, m)

MS m/z. 419 (M)

[00476] (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-152)

[00477] (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 4-methoxybenzoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 12 (3H, d), 1.65 (1H, br s), 2.03 (3H, s), 2 24-2.37 (1H, m), 3.74 (3H, s), 4.66-4 84 (1H, m), 5 53-5 70 (1H, m), 6 50-6 54 (1H, d), 6.68 (2H, d), 6 89-6 96 (1H, m), 7 05-7.55 (9H, m).
MS m/z. 415 (M+1)

[00478] (±)-*Cis*-N-[2-methyl-1-(2-methyl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-153)

[00479] (±)-*Cis*-N-[2-methyl-1-(2-methyl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 2-toluoyl chloride for 2-furoyl chloride.
^{1}H-NMR ($CDCl_3$) δ 1.11 (3H, d), 1 60-1 64 (1H, m), 1 97 (3H, s), 2.03-2 3 (4H, m), 4.77-4 89 (1H, m), 5.41-5.58 (1H, m), 6.38-6 44 (1H, m), 6.79 (1H, t), 6 91-7.14 (4H, m), 7.16-7.28 (4H, m), 7 28-7 41 (3H, m).
MS m/z 399 (M+1)

[00480] (±)-*Cis*-N-[1-(3,5-dimethyl-isoxazole-4-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-154)

[00481] (±)-*Cis*-N-[1-(3,5-dimethyl-isoxazole-4-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 3,5-dimethyl-isoxazole-4-carbonyl chloride for 2-furoyl chloride.
^{1}H-NMR ($CDCl_3$) δ. 1 13 (3H, d), 1.57-181 (3H, m), 1.96-2 03 (5H, m), 2 15-2 63 (3H, m), 4.66-4.81 (1H, m), 5.41-5.50(1H, m), 6.12 (1H, d), 7.03-7.15 (1H, m), 7.24-7.48 (7H, m)
MS m/z: 404 (M+1)

[00482] (±)-*Cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-155)

[00483] (±)-*Cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting isoxazole-5-carbonyl chloride for 2-furoyl chloride.

[00484] (±)-*Cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)- *cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (**A-70** & **A-71**, respectively)
^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d), 1.64 (1H, s), 1.96 (3H, s), 2.21-2 31 (1H, m), 4.63-4 75 (1H, m), 5 34-5.44 (1H, s), 5 98 (1H, s), 6.70 (1H, d), 7.04 (1H, t), 7.21-7 35 (7H, m), 8 04-8.08 (1H, m).

MS m/z 376 (M+1).

[00485] (±)-*Cis*-N-(1-cyclohexanecarbonyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide (A-157)

[00486] (±)-*Cis*-N-(1-cyclohexanecarbonyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide was made following general procedure A, substituting cyclohexanecarbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d), 1.13-1 27 (3H, m), 1.31-1.47 (2H, m), 1 58-1 89 (7H, m), 1 99 (3H, s), 2 14-2.24 (1H, m), 2.62-2.71 (1H, m), 4.70-4 78 (1H, m), 5.24-5 29 (1H, m), 7 07-7 10 (1H, m), 7 21-7.24 (2H, m), 7 28-7.33 (2H, m), 7.34-7 42 (4H, m).

MS m/z. 391 (M+1)

[00487] (±)-*Cis*-N-[2-methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-158)

[00488] (±)-*Cis*-N-[2-methyl-1-(pyridine-4-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting isonicotinoyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 16 (3H, d), 2.04 (3H, s), 2 25-2.35 (1H, m), 4.75-4.83 (1H, m), 5.56-5.67 (1H, m), 6.45-6.48 (1H, m), 6.92 (1H, t), 7.08 (2H, d), 7.19-7.27 (3H, m), 7.34-7.42 (4H, m), 8.49 (2H, d)

MS m/z 386 (M+1).

[00489] (±)-*Cis*-N-[1-(2,5-dimethyl-2H-pyrazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-159)

[00490] (±)-*Cis*-N-[1-(2,5-dimethyl-2H-pyrazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting 2,5-dimethyl-2H-pyrazole-3-carbonyl chloride for 2-furoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, d), 2.02 (3H, m), 2.07 (3H, m), 2.23-2.32 (2H, m), 4.68-4.76 (1H, m), 5.50 (1H, s), 6.66 (1H, d), 7.04 (1H, t), 7 21-7.28 (4H, m), 7.34-7.48 (4H, m).

MS m/z: 404 (M+1).

[00491] (±)-*Cis*-N-[2-methyl-1-(pyridine-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-160)

[00492] (±)-*Cis*-N-[2-methyl-1-(pyridine-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure A, substituting pyridine-2-carbonyl chloride for 2-furoyl chloride.

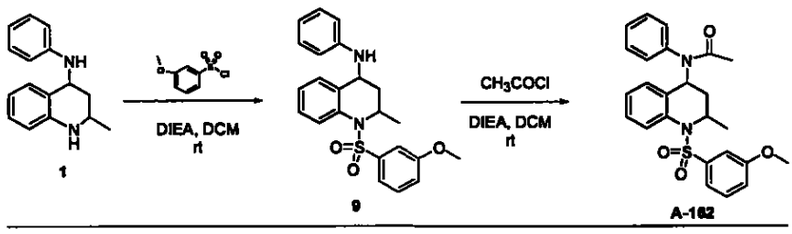
^{1}H-NMR ($CDCl_3$) δ 1.17 (3H, d), 1.93-2.03 (1H, m), 2.02 (3H, s), 2 32 (1H, br s), 4 78-4 86 (1H, m), 5 60-5 61 (1H, m), 6.51 (1H, d), 6 86 (1H, t), 6 99 (1H, d), 7 14-7.50 (9H, m), 8 53 (1H, d).
MS m/z 385 (M+1).

[00493] (±)-*Cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (A-161)

[00494] (±)-*Cis*-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide following general procedure A, substituting isoxazole-5-carbonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ. 0 95-1.20 (5H, m), 2 10-2.30 (4H, m), 4.69-4.74(1H, m), 5 30-5.43 (1H, m), 5.96 (1H, s), 6.75 (1H, d), 7 75 (1H, t), 7.25-7 38 (8H, m), 8.06 (1H, s).
MS m/z· 390 (M+1).

Scheme 5

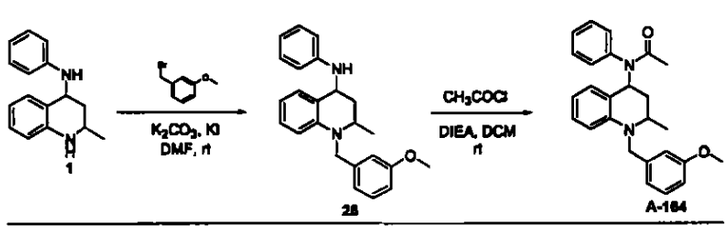


[00495] (±)-*Cis*-N-[1-(3-Methoxy-benzenesulfonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-162)

[00496] (±)-*Cis*-N-[1-(3-methoxy-benzenesulfonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was synthesized using general procedure A, substituting 3-methoxy-benzenesulfonyl chloride for 2-furoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 4 (3H, d), 1.4 (1H, m), 1 9 (3H, s), 2 0 (1H, m), 3 6 (3H, s), 4.1 (1H, m), 6 4 (1H, m), 6 9-7 4 (12H, m), 7 7 (1H, d)
MS m/z 451 (M+1).

Scheme 6



[00497] (±)-*Cis*-N-[1-(3-Methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (A-164)

[00498] (±)-*Cis*-N-[1-(3-methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was synthesized by dissolving (±)-*cis*-(2-methyl-1,2,3,4-tetrahydroquinol-4-yl) aniline in dimethylformamide and adding potassium carbonate (1.0-10 0 equiv.),and the 1-bromomethyl-3-methoxy-benzene (1.1-3 0 equiv), catalytic potassium iodide and was stirred at room temperature for 18 hours The reaction mixture was filtered for removal of inorganic salts and concentrated. The crude mixture was purified by flash chromatography on silica gel using gradient elution hexane-ethyl acetate (5-20%) The corresponding aniline was then acylated as previously described in general procedure A to give (±)-*cis*-N-[1-(3-methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide

^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d; overlapping 1H, t), 1.90(1H,m; 2H, m), 2 00 (3H, s), 3.33 (1H, m), 3.60(3H,s), 4.30 (1H, m), 6.30 (1H, complex), 6 90 (1H, t), 6.90-7 40 (10H, m)
MS m/z 443 (M +1)

[00499] (±)-*Cis*-N-(1-Benzyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide (A-165)

[00500] (±)-*Cis*-N-(1-benzyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide was made following the procedure describing the synthesis of **A-164**, substituting benzyl bromide for 1-bromomethyl-3-methoxy-benzene

^{1}H-NMR (CDCl3) δ 1 15 (3H, d, overlapping 1H, t), 1.90(1H,m, 2H, m), 2 00 (3H, s), 3 33 (1H, m), 4.30 (1H, m), 6.30 (1H, m), 6.70 (1H, t), 6 90-7.40 (11H, m)
MS m/z: 413 (M +1).

[00501] (±)-*Cis*-N-(1-Ethyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide (A-166)

[00502] (±)-*Cis*-N-(1-Ethyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-acetamide was made following the procedure describing the synthesis of **A-164**, substituting ethyl bromide for 1-bromomethyl-3-methoxy-benzene.

^{1}H-NMR ($CDCl_3$) δ: 1.01 (3H, t), 1.15 (3H, d, overlapping 1H, t), 1.40 (1H, m), 1 90-2.00 (overlapping 3H, s, 1H, m), 3.20 (1H, m), 3 40 (1H, q), 3 60 (1H, m), 4 60 (1H, s), 6.20 (1H, br,m), 6 60- 6 80 (2H, m), 7.00-7 50 (7H, m)
MS m/z 309 (M +1)

[00503] (±)-*Cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-aceticacid methyl ester (A-167)

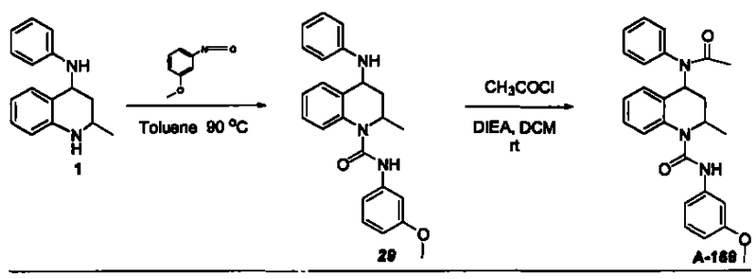
[00504] (±)-*Cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-aceticacid methyl ester was made following the procedure describing the synthesis of **A-164**, substituting bromo-acetic acid methyl ester for 1-bromomethyl-3-methoxy-benzene.

^{1}H-NMR (CDCl3) δ:: 1 20 (3H, d, overlapping 1H, t), 1 80(1H,m, 2.00 (3H, s), 3.40 (1H, m), 3.70(3H,s), 3.90(2H, s), 4 50 (1H, m), 6 10 (1H, t), 6.20 (1H,d), 6.75 (1H, m), 6.90-7 10 (3H, complex), 7 20-7.50 (3H, m)
MS m/z: 353 (M +1)

[00505] (±)-*Cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-acetic_acid (A-168)

[00506] (±)-*Cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-acetic acid was made from (±)-*cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-aceticacid methyl ester. To a solution of (±)-*cis*-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-acetic acid methyl ester was added 1.0 N aqueous sodium hydroxide and heated to 80°C for 1 hr. The reaction mixture was concentrated and aqueous mixture was acidified to pH 6.0 using hydrochloric acid (1N) followed by extraction with ethyl acetate twice. Organics were dried over sodium sulfate, filtered and concentrated to yield the desired product.
^{1}H-NMR (CDCl3) δ 1.20 (3H, d, overlapping 1H, t), 1 80(1H,m, 2.00 (3H, s), 3 40 (1H, m), 3.90(2H, s), 4 50 (1H, m), 6 10 (1H, t), 6.20 (1H,d), 6 75 (1H, m), 6.90-7 10 (3H, m), 7.20-7.50 (3H, m)
MS m/z 339(M +1)

Scheme 7



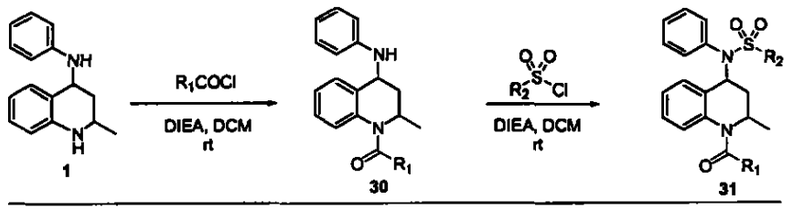
[00507] (±)-*Cis*-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylicacid (3-methoxy-phenyl)-amide (A-169)

[00508] (±)-*Cis*-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carboxylicacid (3-methoxy-phenyl)-amide was synthesized using general procedure A, substituting 3-methoxyphenylisocyanate for 2-furoyl chloride using the following procedure To a solution of (±)-*cis*-(3-methoxy-phenyl)-(2-methyl-4-anilino-3,4-dihydro-2H-quinolin-1-yl)-methanone (0 1 g, 0.42 mmol) in toluene was added 3-methoxyphenylisocyanate (0.056 mL, 0 4255 mmol) and the reaction mixture was heated to 90°C for 18 hours. Reaction was cooled to room temperature and concentrated. The crude mixture was purified by flash chromatography on silica gel using gradient elution hexane-ethyl acetate (80%/20%) to give 38% of the desired product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d),1.2 (1H, m), 2.0 (3H, s), 2 3 (1H, m), 3.8 (3H, s), 4.5 (1H, m), 5.4 (1H, m), 6 6 (1H, d), 6.8 (2H, m) 7 1-7.5 (11H, m).

MS m/z: 430 (M+1).

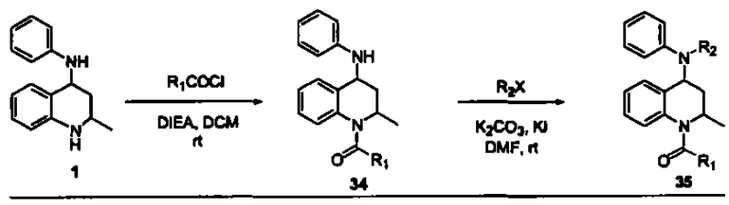
Scheme 8



[00509] **(±)-*Cis*-N-(1-alkyl/aroyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-phenyl-alkyl/aryl sulfonamide**

[00510] (±)-*Cis*-1-(2-Methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-alkanone or (±)-*cis*-(2-Methyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-aryl-methanone can be prepared from compound **1** using general procedure A, substituting the corresponding sulfonyl chloride for acetyl chloride

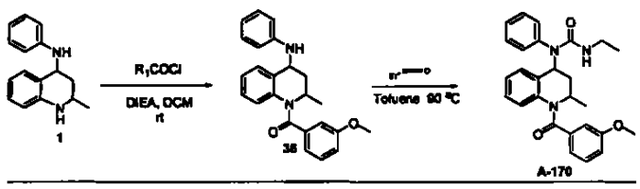
Scheme 9



[00511] **(±)-*Cis*-1-[4-(alkyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-alkanone or (±)-*Cis*-1-[4-(alkyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-aryl methanone**

[00512] (±)-*Cis*-1-[4-(alkyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-alkanone or (±)-*cis*-1-[4-(alkyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-aryl methanone may be prepared from compound **1** using general procedure A, substituting the corresponding alkyl chloride for acetyl chloride and using the alkylation procedure in the synthesis of **A-164** Representative examples of compound **35** are shown in the table below.

Scheme 10



[00513] **(±)-*Cis*-3-ethyl-1-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-1-phenyl-urea (A-170)**

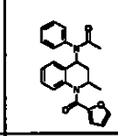
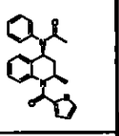
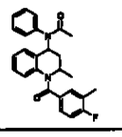
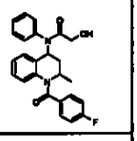
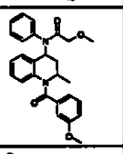
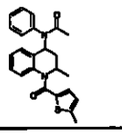
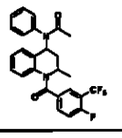
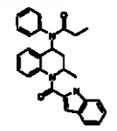
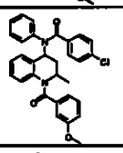
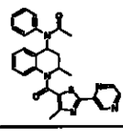
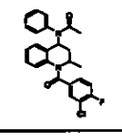
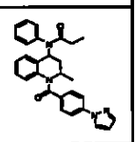
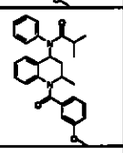
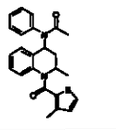
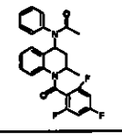
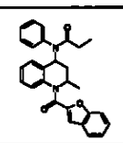
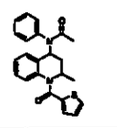
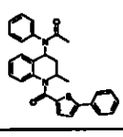
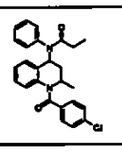
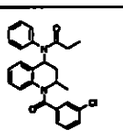
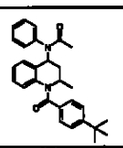
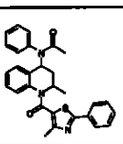
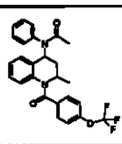
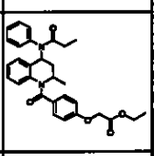
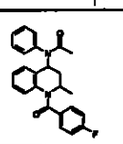
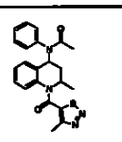
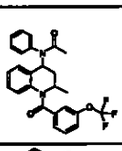
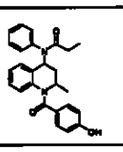
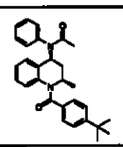
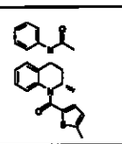
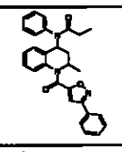
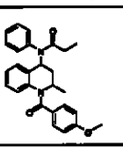
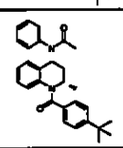
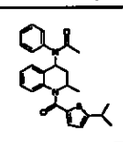
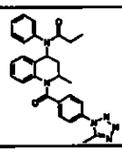
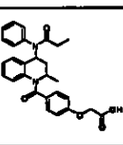
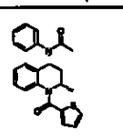
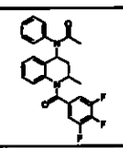
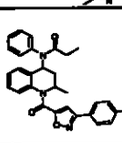
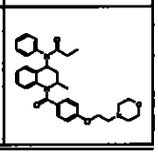
[00514] (±)-*Cis*-3-ethyl-1-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-1-phenyl-urea was synthesized using general procedure A, substituting ethyl isocyanate for acetyl chloride using the following procedure To a solution of (±)-*cis*-(3-methoxy-phenyl)-(2-methyl-4-anilino-3,4-dihydro-2H-quinolin-1-yl)-methanone in DMF was added ethyl isocyanate and reaction mixture was heated to 90°C for 18 hours The reaction was cooled to room temperature and concentrated. Crude mixture was purified by flash chromatography on silica gel using gradient elution hexane-ethyl acetate (5-20%).

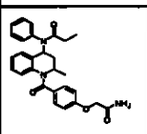
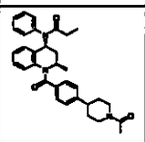
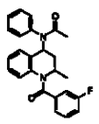
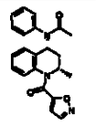
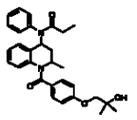
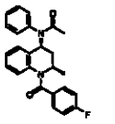
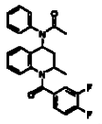
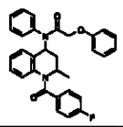
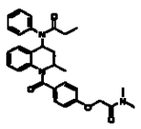
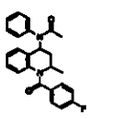
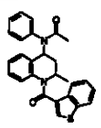
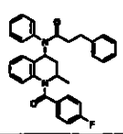
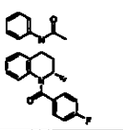
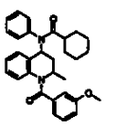
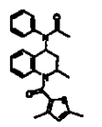
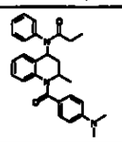
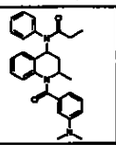
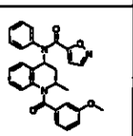
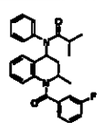
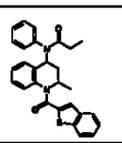
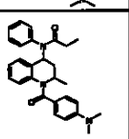
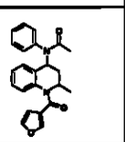
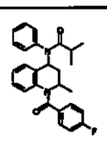
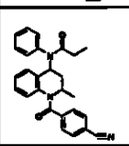
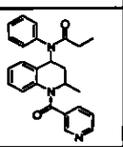
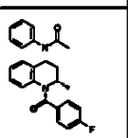
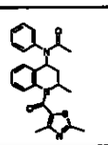
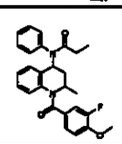
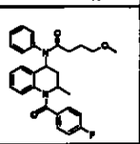
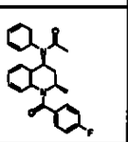
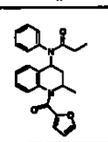
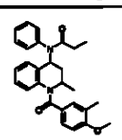
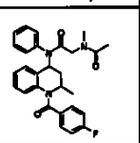
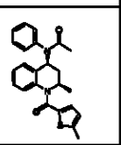
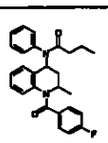
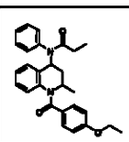
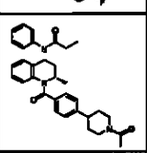
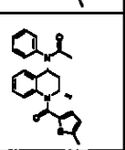
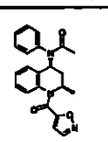
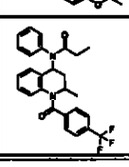
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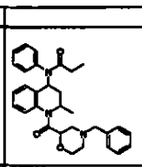
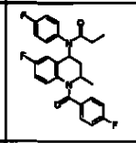
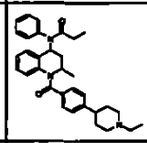
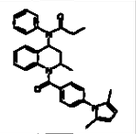
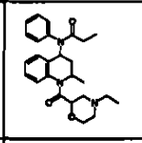
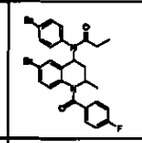
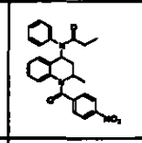
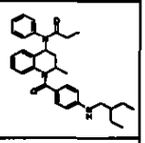
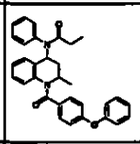
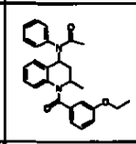
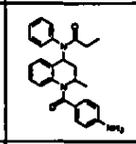
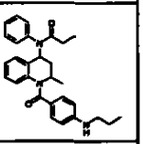
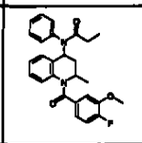
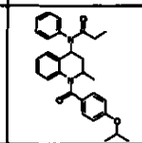
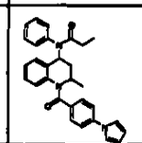
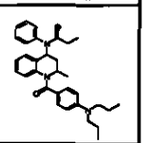
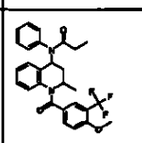
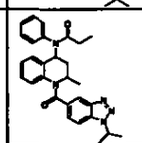
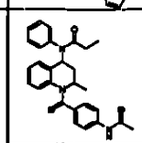
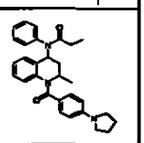
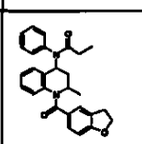
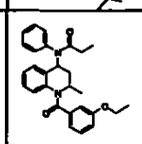
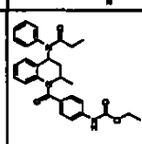
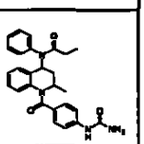
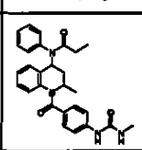
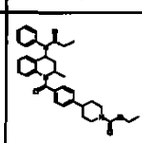
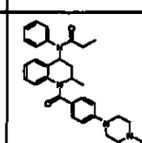
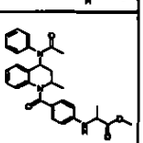
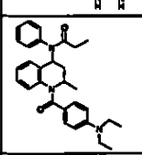
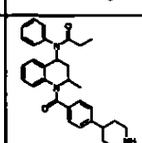
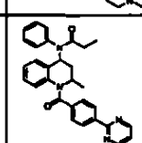
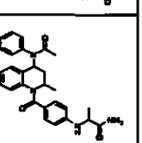
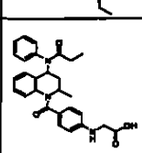
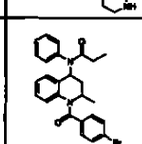
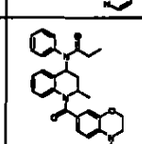
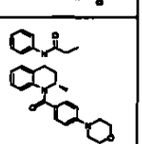
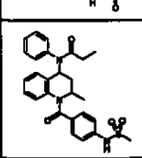
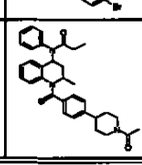
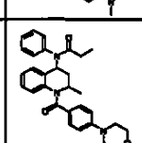
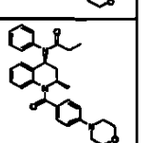
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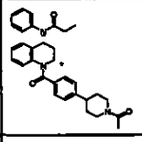
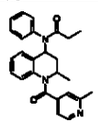
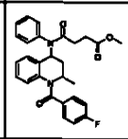
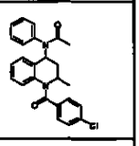
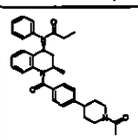
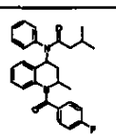
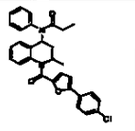
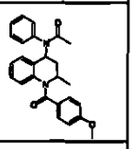
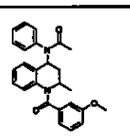
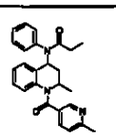
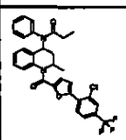
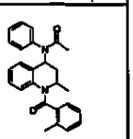
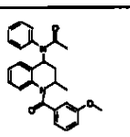
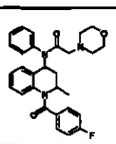
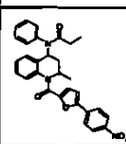
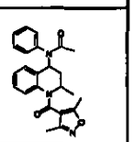
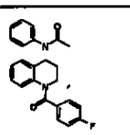
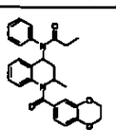
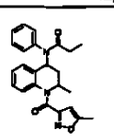
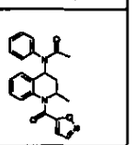
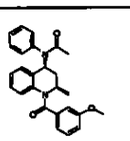
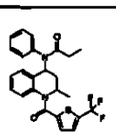
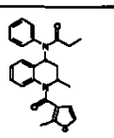
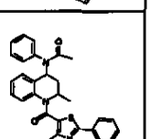
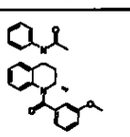
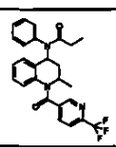
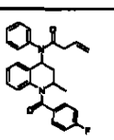
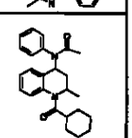
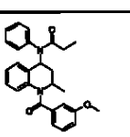
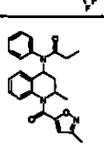
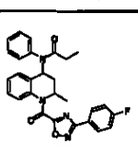
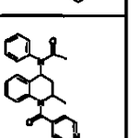
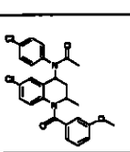
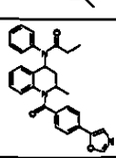
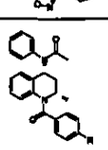
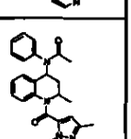
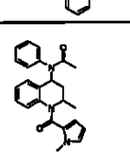
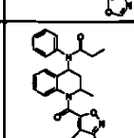
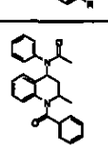
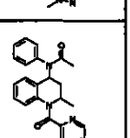
[00515] Compounds **A-163, A-171- A-232** can be prepared by the schemes set forth in Schemes 1- 10 and by the general procedures A and others described herein. Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

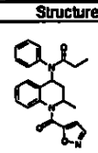
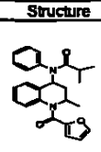
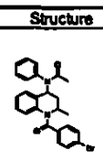
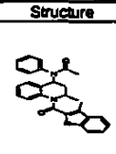
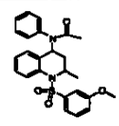
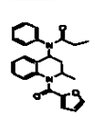
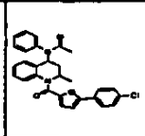
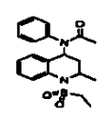
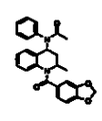
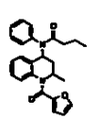
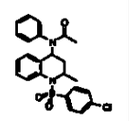
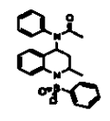
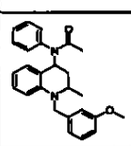
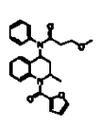
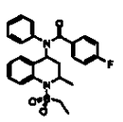
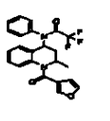
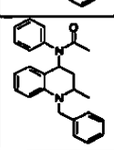
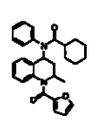
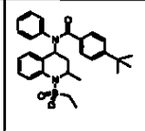
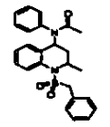
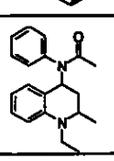
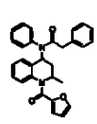
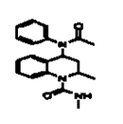
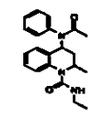
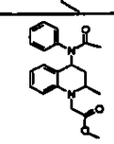
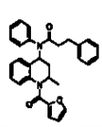
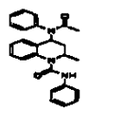
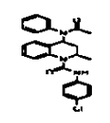
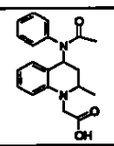
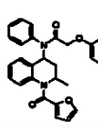
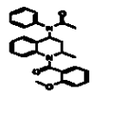
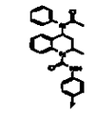
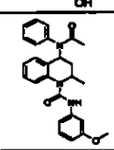
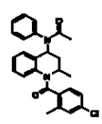
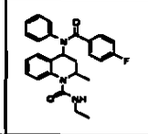
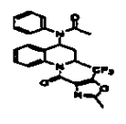
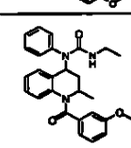
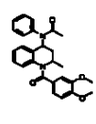
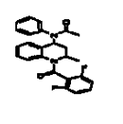
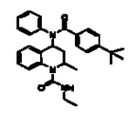
[00516] **Table 1: Compounds Derived from General Procedure A**

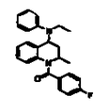
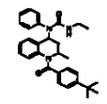
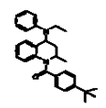
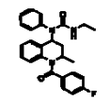
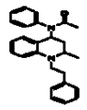
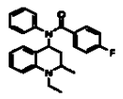
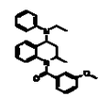
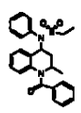
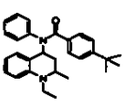
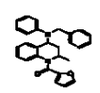
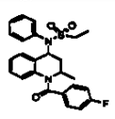
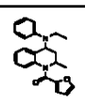
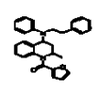
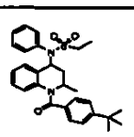
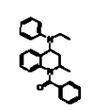
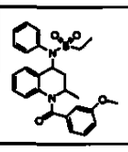
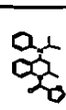
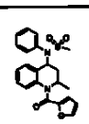
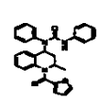
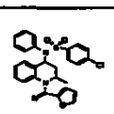
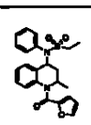
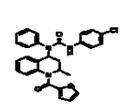
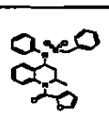
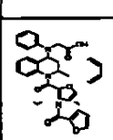
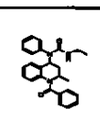
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A-10		A-20		A-30		A-40	

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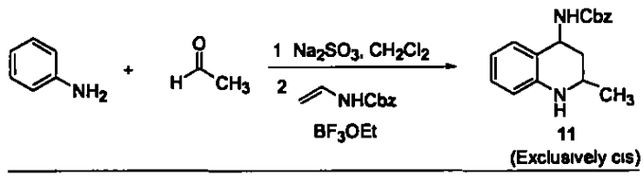
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Scheme 11



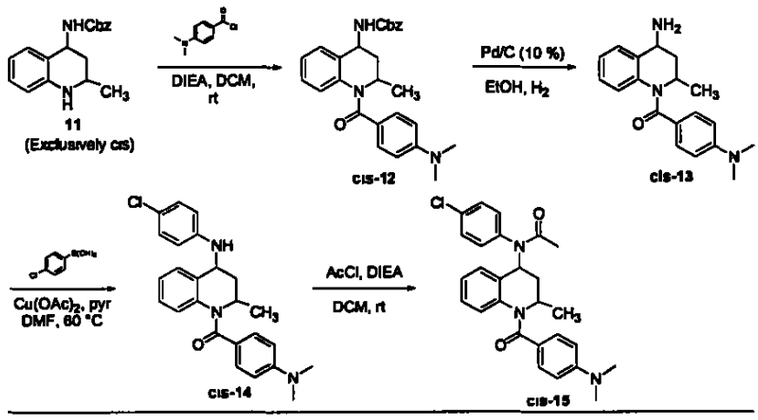
[00517] **(±)-*Cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (11)**

[00518] Aniline (3.64 mL, 39 97 mmol, 1 0 equ) was dissolved in methylene chloride (100 mL) and Na_2SO_4 (2 g) was added and cooled to -25 °C Acetaldehyde (2 23 mL, 39 97 mmol, 1.0 equ) was added to the solution and stirred for 1h at -25 °C. Sodium sulfate was filtered off and N-vinyl-carbamic acid benzyl ester (7 07g, 39 97 mmol, 1 0 equiv) was added to the filtrate at -25°C, followed by boron triflouride diethyl etherate (0.50 mL, 3.9 mmol, 0 1 equ). The reaction was allowed to stir at -25°C for 1h and then warmed to room temperature and stirred for 10h. The reaction was evaporated *in vacuo* and the residue was purified by Biotage flash system (20% ethyl acetate/80% hexane) to yield 4 0 g, 33 % of (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester as a white solid.

H^1 NMR (300 MHz, $CDCl_3$) δ 7.38 (m, 5H), 7 17 (d, 1H), 7 02 (t, 1H, C7-H), 6 68 (t, 1H), 6.47 (d, 1H), 5.17 (bs, 2H), 5.07 (m, 1H), 4.92 (d, 1H), 3.57 (m, 1H), 2 30 (m, 1H), 1 47 (q, 1H), 1.21 (d, 3H)

General Procedure B

Scheme 12



[00519] **(±)-*Cis*-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (12)**

[00520] To a solution of (±)-*cis*-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (500 mg, 1.68 mmol) in methylene chloride (20 mL) at room temperature was added

diisopropylethylamine (542 mg, 749 uL, 4 2 mmol) followed by 4-dimethylaminobenzoyl chloride and stirred at rrom temperature until no starting material was present. The mixture was poured into water and extracted with ethyl acetate. The extracts were washed with 1 M (aq) NaOH and brine, dried over sodium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (100% hexanes to 70% hexanes/30% ethyl acetate gradient) to afford the amide (665 mg, 89 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1 24 (d, 3 H), 1 36 (m, 1 H), 2 75 (ddd, 1 H), 2 91 (s, 6 H), 4.79 – 4 92 (m, 3 H), 5.22 (s, 2 H), 6 43 (d, 2 H), 6.65 (d, 1 H), 6 90 (dd, 1 H), 7 07 – 7.18 (m, 5 H), 7 2 – 7 48 (m, 4 H).

MS m/z 444 (M + 1).

[00521] **(±)-*Cis*-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-4-aminoquinoline (13)**

[00522] (±)-*Cis*-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic

acid benzyl ester (665 mg, 1 49 mmol) was dissolved in ethanol (30 mL) The resulting solution was evacuated and backfilled with argon. A catalytic amount of palladium on carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen from a balloon The reaction was then allowed to react at room temperature over night under a hydrogen atmosphere Reaction was complete after 18h. The mixture was carefully filtered and concentrated to 10% volume The resulting concentrated solution was filtered through an Acrodisc ® and concentrated to afford the crude amine (423 mg, 92 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1 19 – 1.40 (m, 4 H), 2.76 (ddd, 1 H), 2 95 (s, 6 H), 4.08 (dd, 1 H), 4.81 (m, 1 H), 6 42 (d, 2 H), 6.64 (d, 1 H), 6.99 (dd, 1 H), 7.08 – 7.23 (m, 5 H), 7.52 (d, 1 H).

MS m/z. 310 (M + 1)

[00523] **(±)-*Cis*-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-4-(*N*-4-chlorophenyl)aminoquinoline (14)**

[00524] To a solution of (±)-*cis*-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-4-aminoquinoline (423 mg, 1.36 mmol) in DMF (15 mL, dry) was added 4-chlorophenylboronic acid (425 mg, 2.72 mmol), pyridine (322 mg, 330 uL, 4 08 mmol) and copper(II)acetate (494 mg, 2.72 mmol). The heterogeneous green mixture was stirred open to air for 1 h and then warmed to 60 °C and stirred over night (14 h). The mixture was then cooled to rt, poured into rapidly stirred ethyl acetate (150 mL); solids were removed by filtration The extracts were washed several times with water and then once with brine The extracts were then dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel

chromatography (100 % hexanes to 50/50 hexanes/ethyl acetate gradient) to afford the aniline product (120 mg, 22 %) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (d, 3 H), 1.36 (ddd, 1 H), 2.82 (ddd, 1 H), 2.95 (s, 6 H), 4.90 (br s, 1 H), 4.41 (br d, 1 H), 4.87 (ddd, 1 H), 6 65 (d, 2 H), 6.62 – 6.76 (m, 3 H), 6.97 – 7.11 (m, 2 H), 7 17 – 7.29 (m, 5 H)

MS m/z· 420 (M + 1)

[00525] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (15)

[00526] To a solution of (±)-*cis*-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-4-(*N*-4-chlorophenyl)aminoquinoline (120 mg, 0 29 mmol) in methylene chloride (2 mL) was added diisopropylethylamine (37 mg, 0.051 mL, 0.29 mmol) followed by acetyl chloride (2 mL). The mixture was stirred at rt 4 h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aqueous sodium bicarbonate, brine and dried over sodium sulfate The drying agent was removed by filtration under reduced pressure, concentrated and purified by silica gel chromatography (100 % hexanes – 25/75 hexanes/ethyl acetate gradient) to afford pure (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (45 mg, 34 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.14 – 1.33 (m, 4 H), 2.13 (s, 3 H), 2.24 – 2.39 (m, 1 H), 2.94 (s, 6 H), 4.75 (ddd, 1 H), 5.61 (br s, 1 H), 6.44 (d, 2 H), 6 63 (d, 1 H), 6.96 (dd, 1 H), 7.07 – 7.36 (m, 6 H), 7 40 (d, 2 H).

MS m/z· 420 (M + 1)

[00527] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-o-tolyl-acetamide (B-1)

[00528] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-o-tolyl-acetamide was made following general procedure B, substituting 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride and 2-tolylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 3H), 1.26 (s, 1H), 1.58 (s, 3H), 1.97 (s, 3H), 2.08 (m, 1H), 3.63 (s, 3H), 4 80 (sextet, 1H), 5 55 (bs, 1H), 6.53 (d, 1H), 6.76 (s, 1H), 6.83 (t, 2H), 6 93 (t, 1H), 7 10 (t, 1H), 7.15-7 37 (m, 6H).

MS m/z 429 (M+1)

[00529] N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-2)

[00530] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride

[00531] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide **(B-9 & B-8,** respectively)

^{1}H-NMR ($CDCl_3$) δ: 1 17 (d, 3H), 1.25 (t, 1H), 2.03 (s, 3H), 2.29 (m, 1H), 3.62 (s, 3H), 4.80 (sextet, 1H), 5.60 (bs, 1H), 6.54 (d, 1H), 6 74(s, 1H), 6 80 (t, 1H), 6.93 (t, 1H), 7 08 (t, 1H), 7.14-7 30 (m, 5H), 7 38 (d, 2H).

MS m/z: 449 (M+1)

[00532] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-3)

[00533] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 2-thiophenecarbonyl chloride for 4-dimethylaminobenzoyl chloride.

[00534] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide **(B-7 & B-6,** respectively)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.11 – 1.24 (m, 4 H), 2 03 (s, 3 H), 2.22 – 2 35 (m, 1 H), 4 73 (ddd, 1 H), 5 52 (br s, 1 H), 6.69 (dd, 1 H), 6.67 (dd, 1 H), 6.89 (d, 1 H), 7.08 (dd, 1H), 7.21 (d, 2 H), 7 27 – 7 43 (m, 5 H).

MS m/z. 425 (M + 1)

[00535] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-isobutyramide (B-4)

[00536] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-isobutyramide was made following general procedure B, substituting 5-

methyl-2-thiophenecarbonyl chloride for 4-dimethylaminobenzoyl chloride and isobutyryl chloride for acetyl chloride.

[00537] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-isobutyramide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-Chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-isobutyramide (**B-11** & **B-10** respectively)

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 6H), 1 16 (d, 3H), 1 25 (m, 1H), 2 23 (m, 3H), 2.39 (s, 1H), 2.60 (septet, 1H), 4 66 (sextet, 1H), 5 50 (bs, 1H), 6.42 (s, 1H), 6.51 (s, 1H), 6 93 (d, 1H), 7 08 (t, 1H), 7 21 (d, 2H), 7.27 (d, 2H), 7 37 (bs, 2H)

MS m/z 468 (M+1)

[00538] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-fluoro-phenyl)-propionamide (B-5)

[00539] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-fluoro-phenyl)-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, 4-fluorophenylboronic acid for 4-chlorophenylboronic acid, and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.14 (t, 3H), 1.15 (d, 3H), 1 24 (m, 1H), 2.26 (m, 3H), 4.75 (sextet, 1H), 5.61 (bs, 1H), 6.46 (d, 1H), 6.87 (m, 3H), 7 10-7.26 (m, 8H).

MS m/z 435 (M+1)

[00540] (±)-*Cis*-N-(4-chloro-3-methyl-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-12)

[00541] (±)-*Cis*-N-(4-chloro-3-methyl-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, propionyl chloride for acetyl chloride and 4-chloro-3-tolylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.08 (t, 3H), 1.09 (d, 3H), 1.18 (m, 1H), 2.18 (m, 3H), 2.31 (s, 3H), 4 69 (sextet, 1H), 5 49 (bs, 1H), 6 42 (d, 1H), 6 79 (t, 2H), 6.86 (t, 1H), 6.96 (dd, 1H), 7.05-7 22 (m, 6H).

MS m/z: 465 (M+1)

[00542] (±)-*Cis*-N-[1-(4-Fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-trifluoromethyl-phenyl)-propionamide (B-13)

[00543] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-trifluoro-methyl-phenyl)-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, propionyl chloride for acetyl chloride and 4-trifluoromethylphenylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ 1.15 (t, 3H), 1.17 (d, 3H), 1.20 (m, 1H), 2.29 (m, 3H), 4.79 (sextet, 1H), 5 62 (bs, 1H), 6.49 (d, 1H), 6 87 (m, 3H), 7.19-7 28 (m, 6H), 7.41 (d, 1H), 7.69 (d, 1H).

MS m/z 485 (M+1).

[00544] **(±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-14)**

[00545] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride

[00546] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (**B-18** & **B-17**, respectively).

^{1}H-NMR ($CDCl_3$) δ: 1.14 (t, 3H), 1.15 (d, 3H), 1 25 (t, 1H), 2.29 (m, 3H), 3.74 (s, 3H), 4 74 (sextet, 1H), 5.61 (bs, 1H), 6.53 (d, 1H), 6.68 (d, 2H), 6.93 (t, 1H), 7.14-7 28 (m, 6H), 7.38 (d, 2H).

MS m/z 463 (M+1).

[00547] **(±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-15)**

[00548] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride

[00549] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (**B-34** & **B-35**, respectively)

^{1}H-NMR ($CDCl_3$) δ: 1 14 (d, 3H), 1.25 (t, 1H), 2.04 (s, 3H), 2.29 (m, 1H), 3.74 (s, 3H), 4.74 (sextet, 1H), 5 61 (bs, 1H), 6 53 (d, 1H), 6.68 (d, 2H), 6 93 (t, 1H), 7.14-7 28 (m, 6H), 7.38 (d, 2H).

MS m/z· 449 (M+1)

[00550] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-16)

[00551] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (±)-*Cis*-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide (0.548 g, 0 001 mol) was dissolved in dichloromethane and a solution of BBr_3 (1 0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for 4h or until no starting material remained. The reaction was washed with sat $NaHCO_3$ carefully and brine. The organics were dried over $MgSO_4$, filtered and concentrated down The phenol was concentrated down and the residue was purified by Biotage flash chromatography using 100 % EtOAc to give a white solid , 74 % yield.

^{1}H-NMR ($CDCl_3$) δ 1 09 (d, 3H), 1 11 (t, 3H), 1 19 (m, 1H), 2 26 (m, 3H), 4.74 (sextet, 1H), 5.54 (bs, 1H), 6 46 (d, 1H), 6.53 (d, 1H), 6.96 (t, 1H), 7.14-7.40 (m, 9H).

MS m/z 415 (M+1).

[00552] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-p-tolyl-propionamide (B-21)

[00553] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-p-tolyl propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, propionyl chloride for acetyl chloride and 4-tolylboronic acid for 4-chlorophenylboronic acid

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.05-1 21 (m, 7 H), 2 11 – 2.54 (m, 6 H), 4.73 (ddd, 1 H), 5.56 (br s, 1 H), 6 37 d, 1 H), 6.8 – 7.0 (m, 3 H), 7.1 – 7.4 (m, 8 H)

MS m/z: 431 (M + 1).

[00554] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-22)

[00555] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride.

[00556] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 95% hexane/5% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-phenyl)-

N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (**B-26** & **B-27**, respectively).

^{1}H-NMR ($CDCl_3$) δ. 1 1 (d ,3H), 1.1 (m, 1 H), 2 0 (d ,3 H), 2 3 (m, 1 H), 4.7 (m,1 H), 5.6 (m, 1 H), 6.5 (d, 1H),6 7-7 0 (m, 3H), 7.1-7.4 (m, 8 H)

MS m/z 436 (M+1)

[00557] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-24)

[00558] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 5-methyl-2-thiophenecarbonyl chloride for 4-dimethylaminobenzoyl chloride

[00559] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-Chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (**B-28** & **B-25**, respectively).

^{1}H-NMR ($CDCl_3$) δ 1 1 (3H, d), 1.1 (1H, m), 2.0 (3H, d), 2.3 (1H, m), 2 4 (3H, s), 4 7 (1H, m), 5.6 (1H, m), 6 4 (1H, m), 6.6 (1H, m), 7.0 (1H, m), 7.1 (1H, m), 7 2-7.4 (6H, m).

MS m/z 439 (M+1).

[00560] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-29)

[00561] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 5-methyl-2-thiophenecarbonyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.2 (7H, m), 2.1-2 3 (3H, m), 2.3 (3H, s), 4.8 (1H, m), 5.6 (1H, m), 6 .2-6.4 (2H, m), 6.8-7.4 (8H, m).

MS m/z: 452 (M+2).

[00562] (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (B-30)

[00563] (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. (±)-

Cis-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-propionamide (140 mg, 0 31 mmol) was dissolved in DMF (5 mL) at room temperature Sodium hydride (60 % in oil, 32 mg, 0.81 mmol) was added and the mixture allowed to stir 30 min Ethyl 4-bromobutyrate (207 mg, 1 06 mmol) was added and the reaction was allowed to stir over night. Ethanol was added and the reaction was concentrated *in vacuo* The crude residue was purified by silica gel chromatography (80/20 hexanes/ethyl acetate – 50/50 hexanes ethyl acetate gradient) to afford the product (171 mg, 0.304 mmol, 98 %)

^{1}H-NMR ($CDCl_3$) δ 1 1-1 2 (7H, m), 1 3 (3H, t), 2.1 (2H, m), 2.3 (3H, m), 2 5 (2H, t), 3.9 (2H, t), 4.2 (2H, q), 4.8 (1H, m), 5.6 (1H, m), 6 5 (1H, d), 6.7 (2H, d), 6.9 (1H, t), 7 1-7.3 (6H, m), 7.4 (2H, m)

MS m/z 563 (M+1).

[00564] (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (B-31)

[00565] (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid was prepared from (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester Potassium carbonate (300 mg) was dissolved in water (5 mL) and (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (171 mg, 0 303 mmol) was dissolved in methanol (5 mL) was added. The reaction was allowed to stir over night at room temperature The methanol was removed *in vacuo* and hydrochloric acid (1 N) was added until acidic. Dichloromethane was added, extracted 2x, the combined organics were dried over magnesium sulfate, filtered and concentrated to afford the carboxylic acid (50 mg, 31 %).

^{1}H-NMR ($CDCl_3$) δ 1 1-1.2 (7H, m), 2 0 (2H, m), 2.3 (2H, m), 2.4 (3H, m), 3.3 (1H, s), 4 0 (2H, t), 4.8 (1H, m), 5.6 (1H, m), 6 5 (1H, d), 6 7 (2H, d), 6.9 (1H, t), 7 1-7 3 (3H, m), 7 4-7.6 (5H, m)

MS m/z· 535 (M+1).

[00566] (±)-*Cis*-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-propionamide (B-32)

[00567] (±)-*Cis*-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-propionamide was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (700 mg, 1 42 mmol) was dissolved in DMF (10 mL) at room temperature. Sodium hydride (60 % in oil, 227 mg, 5.68 mmol) was added and the mixture allowed to stir 30 min. Bromoacetonitrile (850 mg, 7 11 mmol) was added and the reaction was allowed to stir over night Ethanol was added and the

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reaction was concentrated *in vacuo* The crude residue was purified by silica gel chromatography (30/70 ethyl acetate/dichloromethane) to afford the product (320 mg, 42 %)

[00568] The nitrile (140 mg, 0 25 mmol) was dissolved in toluene, sodium azide (160 mg, 2 5 mmol) and triethylammonium hydrochloride (345 mg, 2.5 mmol) were added and the mixture was heated to 80 °C over night Reaction was cooled to room temperature and water was added, followed by hydrochloric acid (1 N) until acidic. The aqueous solution was extracted three times with dichloromethane The combined extracts were dried over magnesium sulfate, filtered, dried and concentrated The crude product was triturated with ethyl ether/hexanes to yield a white solid (82 mg, 63 %).

^{1}H-NMR ($CDCl_3$) δ 1.0-1.2 (7H, m), 2 2-2.4 (3H, m), 4.8 (1H, m), 5 2 (2H, dd), 5 6 (1H, m), 6.7 (2H, m), 6 9 (1H, t), 7 1 (2H, d), 7 2-7.6 (7H, m)

MS m/z 531 (M+1)

[00569] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-isobutoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-33)

[00570] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-isobutoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-isobutyloxybenzoyl chloride for 4-dimethylaminobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ. 0 9-1 0 (8H, m), 1.2 (3H, d), 2 0 (3H, s), 2.3 (1H, m), 3 6 (2H, d), 4 7 (1H, m), 5 6 (1H, m), 6.5 (1H, d), 6.6 (2H, d), 6.9 (1H, m), 7.1-7 4 (8H, m).

MS m/z 491 (M+1).

[00571] (±)-*Cis*-N-(4-chloro-phenyl)-N-{1-[4-(3-hydroxy-2,2-dimethyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (B-37)

[00572] (±)-*Cis*-N-(4-chloro-phenyl)-N-{1-[4-(3-hydroxy-2,2-dimethyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (210 mg, 0.484 mmol) was dissolved in DMF (10 mL) at room temperature. Potassium carbonate (1g, 7.1 mmol) was added, followed by 3-bromo-2,2-dimethyl-propan-1-ol (813 mg, 4 84 mmol), the reaction was heated to 95 °C and stirred over night The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (95/5 dichloromethane/ethyl acetate – 70/30 dichloromethane/ethyl acetate) to afford the pure ester (110 mg, 44 %).

^{1}H-NMR ($CDCl_3$) δ 1 0 (6H, s), 1.1 (3H, d), 1.1 (1H, m), 1.7 (1H, br), 2 0 (3H, s), 2.3 (1H, m), 3 5 (2H, s), 3 7 (2H, s), 4 8 (1H, m), 5.6 (1H, m), 6.5 (1H, d), 6 7 (2H, d), 6 9 (1H, t), 7.1-7.3 (7H, m), 7 4 (1H, d).
MS m/z: 521 (M+1).

[00573] (±)-*Cis*-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid methyl ester (B-38)

[00574] (±)-*Cis*-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid methyl ester was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (400 mg, 0.92 mmol) was dissolved in DMF (25 mL) at room temperature Potassium carbonate (1g, 7.1 mmol) was added, followed by 3-bromo-2,2-dimethyl-propionic acid methyl ester (400 mg, 0.92 mmol), the reaction was heated to 95 °C and stirred over night. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo* The crude product was purified by silica gel chromatography (95/5 dichloromethane/ethyl acetate – 70/30 dichloromethane/ethyl acetate) to afford the pure ester (40 mg, 8 %)
^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1 1 (1H, m), 1.3 (6H, s), 2 0 (3H, s), 2.3 (1H, m), 3 7 (3H, s), 3.9 (2H, dd), 4.8 (1H, m), 5.6 (1H, m), 6 5 (1H, d), 6.7 (2H, d), 6 9 (1H, t), 7.1-7.3 (7H, m), 7.4 (1H, d)
MS m/z: 549 (M+1)

[00575] (±)-*Cis*-(4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-acetic acid (B-39)

[00576] (±)-*Cis*-(4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-acetic acid was made from (±)-*cis*-N-(4-cyanomethyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (±)-*Cis*-N-(4-cyanomethyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-methoxybenzoylchloride for 4-dimethylaminobenzoyl chloride and 4-(phenylboronic acid)-acetonitrile for 4-chlorophenylboronic acid. (±)-*Cis*-N-(4-cyanomethyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in ethanol (4 mL), potassium hydroxide (120 mg in 0 3 mL water) was added and the reaction was heated at 80 °C over night. The ethanol was removed *in vacuo* and hydrochloric acid (1 N) was added until acidic Dichloromethane was added, extracted 2x; the combined organics were dried over magnesium sulfate, filtered and concentrated to afford the carboxylic acid (30 mg) after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.1 (1H, m), 2.0 (3H, s), 2 3 (1H, m), 3.6 (2H, s), 3 8 (3H, s), 4.8 (1H, m), 5 7 (1H, m), 6.5 (1H, m), 6 6 (2H, m), 6.9 (1H, m), 7 1-7 3 (8H, m).
MS m/z· 495 (M+23)

[00577] (±)-*Cis*-3-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid (B-40)

[00578] (±)-*Cis*-3-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid was made following the procedure for (±)-*cis*-(4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-acetic acid, substituting 3-cyanophenylboronic acid for 4-(phenylboronic acid)-acetonitrile.

[00579] Basic nitrile hydrolysis using 1N NaOH in methanol and water afforded both the carboxylic acid and the primary amide, (±)-*cis*-3-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzamide.

^{1}H-NMR ($CDCl_3$) δ· 1.1 (3H, d), 1 1 (1H, m), 2 0 (3H, s), 2.3 (1H, m), 3 8 (3H, s), 4.8 (1H, m), 5 6 (1H, m), 6.5 (1H, d), 6 6 (2H, d), 6.9 (2H, m), 7 1-7.5 (5H, m), 7 9-8 2 (2H, m).
MS m/z 481 (M+23)

[00580] (±)-*Cis*-3-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzamide (B-41)

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1 1 (1H, m), 2.0 (3H, s), 2.3 (1H, m), 3.8 (3H, s), 4.8 (1H, m), 5 7 (1H, m), 6 5 (1H, m), 6.6 (2H, m), 6.9 (1H, m), 7 1-7 3 (4H, m), 7.4-7 6 (2H, m), 7.7-7.8 (2H, m).
MS m/z 480 (M+23).

[00581] (±)-*Cis*-N-(4-Chloro-phenyl)-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-44)

[00582] (±)-*Cis*-N-(4-Chloro-phenyl)-N-[1-(isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 5-isoxazolecarbonyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 14 (3H, d; overlapping 3H, t, and 1H, t), 2 30 (overlapping 2H, q, and 1H, m),4 75 (1H, m), 5.45 (1H, m), 6.00 (1H, d), 6 80 (1H,d), 7.10-7.40 (7H, m), 8 05 (1H, s)
MS m/z: 424 (M + 1).

[00583] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-cyclopentyloxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-45)

[00584] (±)-*Cis*-N-(4--chloro-phenyl)-N-[1-(4-cyclopentyloxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. To a solution of (±)-*cis*-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide in dimethylformamide was added cyclopentyl bromide, potassium carbonate (3.0 equiv), potassium iodide (catalytic) and heated to 65°C overnight. Reaction mixture was filtered for removal of inorganic salts and concentrated Crude mixture was purified by flash chromatography on silica gel using gradient elution ethyl acetate- methanol (2-20% methanol)

^{1}H-NMR ($CDCl_3$) δ 1 15 (3H, d; overlapping 1H, t), 1 57 (2H, m), 1 79 (3x2H, m), 2.04(3H,s), 2.30(1H,m), 4 60- 4 80 (1H, q, 1H, m), 5 60 (1H, m), 6.50 (1H, d), 6 62 (1H, d), 6.90 (1H, t), 7 10-7.30 (9H, m), 7 40 (1H,d).

MS m/z 504 (M + 1).

[00585] (±)-*Cis*-N-{1-[4-(4-Acetyl-piperazin-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (B-46)

[00586] (±)-*Cis*-N-{1-[4-(4-Acetyl-piperazin-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide. (±)-*Cis*-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (1.07 g, 2.39 mmol) was dissolved in pyridine (5 mL) and trifluoro-methanesulfonic anhydride (703 uL, 2 5 mmol) was added The reaction was stirred at room temperature 3 h The reaction was partitioned between ether and water, and the aqueous was extracted three times with ether. The combined extracts were dried over sodium sulfate, filtered and concentrated. The crude triflate was purified by silica gel chromatography (70/30 hexanes/ethyl acetate – 40/60 hexanes/ethyl acetate gradient) to afford (1.0g 74%) of pure material.

[00587] To the triflate, $Pd_2(dba)_3$, BINAP, cesium carbonate, 18-crown-6 ether in toluene was added N-acetyl piperazine and reaction mixture was heated to reflux for 18 hours. Reaction mixture was cooled to room temperature and filtered through Celite ® and concentrated. Crude mixture was purified by flash chromatography on silica gel using gradient elution ethyl acetate-methanol (2-20%).

^{1}H-NMR ($CDCl_3$) δ. 1.13 (3H, d; overlapping 1H, t), 2 02 (3H, s), 2.10 (3H, s), 2.35 (1H, m), 3 20(2x2H,m), 3 60 (2H, t), 3.70 (2H, t), 4.80 (1H, m), 5.65 (1H, m), 6 55 (1H, d), 6.70 (1H, d), 6 95 (1H, t), 7.10-7.40 (9H, m).

MS m/z. 546 (M + 1)

[00588] (±)-*Cis*-N-(3-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-50)

[00589] (±)-*Cis*-N-(3-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-fluorobenzoylchloride for 4-dimethylaminobenzoyl chloride and 3-chlorophenylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.16-1.26 (4H, m), 2.05 (3H, s), 2 25 - 2.39 (1H, m), 4.69 - 4.88 (1H, m), 5 47 - 5 68 (1 H, broad), 6.49 (1 H, d), 6.84-6.97 (4 H, m), 7 18 - 7.42 (7 H, m)

MS m/z 437(M^+), 439(M+2).

[00590] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-phenoxy-phenyl)-acetamide (B-51)

[00591] (±)-*Cis*-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-phenoxy-phenyl)-acetamide was made following general procedure B, substituting 4-fluorobenzoylchloride for 4-dimethylaminobenzoyl chloride and 4-phenoxyphenylboronic acid for 4-chlorophenylboronic acid

^{1}H-NMR ($CDCl_3$) δ 1.16-1.18 (4H, m), 2.06 (3H, s), 2.34-2 38 (1H, m), 4.74-4 82 (1H, m), 5 29 (1H, br), 6.47 (1H, d), 6.83-7 40 (16H, m).

MS m/z. 496 (M+1)

[00592] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-pyridin-2-yl-acetamide (B-52)

[00593] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-pyridin-2-yl-acetamide was made following general procedure B, substituting 3-methoxy benzoyl chloride for 4-dimethylaminobenzoyl chloride and synthesis of the N-pyridinyl instead of the 4-chlorophenyl was accomplished using the following procedure.

[00594] $Pd_2(dba)_3$ (0.05 equ), and rac-BINAP (0.1 equ.) were added to a flask with degassed toluene and stirred for 1h To the above solution was added 2-bromopyridine (1.1 equ) and NaO^tBu (1.1 equ.) and stirred for 30 min (±)-*Cis*-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone was dissolved in degassed toluene and added to the solution and heated to 100 °C for 17h. The reaction was diluted with ether and filtered through celite and concentrated down The compound was purified by Biotage with 20% EtOAc/80% Hexane to 30% EtOAc/70 %Hexane to 50 % EtOAc/50% Hexane to give 43% of the product (±)-*Cis*-(3-methoxy-phenyl)-[2-methyl-4-(pyridin-2-ylamino)-3,4-dihydro-2H-quinolin-1-yl]-methanone was acetylated with acetyl chloride as previously described to give (±)-*cis*-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-pyridin-2-yl-acetamide.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, 3H), 1.24 (t, 1H), 2 02 (s, 3H), 2 43 (m, 1H), 3.61 (s, 3H), 4.81 (sextet, 1H), 5.65 (bs, 1H), 6 52 (d, 1H), 6.75 (s, 1H), 6 79 (d, 2H), 6.90 (t, 1H), 7.07 (t, 1H), 7.14 (t, 1H), 7.25-7.33 (m, 2H), 7.49 (d, 1H), 7.77 (t, 1H), 8 56 (s, 1H).
MS m/z 416.0 (M+1).

[00595] (±)-*Cis*-N-cyclohexyl-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-53)

[00596] (±)-*Cis*-N-cyclohexyl-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-methoxy benzoyl chloride for 4-dimethylaminobenzoyl chloride and synthesis of the N-cyclohexyl instead of the 4-chlorophenyl was accomplished using the following procedure

[00597] (±)-*Cis*-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone (1.0 equ.) , and cyclohexanone (1 0 equ) were dissolved in ethanol and a catalytic amount of acetic acid was added The reaction was stirred for ~30 minutes and $NaBH_4$ (1 0 equ.) was added and stirred for an additional 2 h at room temperature. Additional $NaBH_4$ was added (1 0 equ.) and stirred for an additional 12h The reaction was concentrated down and partitioned between CH_2Cl_2 and 1N NaOH. The organics were separated and dried over Na_2SO_4, filtered and concentrated down The compound was purified by Biotage with 30% EtOAc/70% hexane to 50 % EtOAc/50% hexane give 96 % of the product. Cis-(±)-N-(4-cyclohexylamino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone was acetylated with acetyl chloride as previously described to give cis-(±)-N-cyclohexyl-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide
^{1}H-NMR ($CDCl_3$) δ: 1.1-1 45 (m, 6H), 1.5-1 75 (m, 3H), 1.85-2.1 (m, 3H), 2.3 (s, 3H), 2.4 (m, 1H), 2 7 (m, 1H), 3 5 (q, 1H), 3.63 (s, 3H), 3 7 (m, 1H), 4.3 (dd, 1H), 4 90 (sextet, 1H), 6.6 (t, 1H), 6.7 (d, 1H)< 6 8 (s, 1H), 6.85 (m, 2H), 7 0 (m, 3H).
MS m/z. 421 (M+1).

[00598] (±)-*Cis*-N-(5-chloro-pyridin-2-yl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-54)

[00599] (±)-*Cis*-N-(5-chloro-pyridin-2-yl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-methoxy benzoyl chloride for 4-dimethylaminobenzoyl chloride and addition of the N-4-chloropyridinyl instead of the 4-chlorophenyl was accomplished using the following procedure

[00600] To a flask was added $Pd_2(dba)_3$ (molar 0.05 equ), and rac-BINAP (0.1 equ) in degassed toluene and stirred for 1h. To the above solution was added 2,5-dichloropyridinepyridine (1.1 equ.) and NaO^{t}Bu (1.1 equ) and stirred for 30 min The corresponding amine, (±)-*cis*-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone was dissolved in degassed toluene and

added to the solution and heated to 60 °C for 40 h. The reaction was diluted with ether and filtered through celite and concentrated down The compound was purified by Biotage with 20% EtOAc/80% Hexane to give 45 % of the product (±)-*Cis*-[4-(5-chloro-pyridin-2-ylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(3-methoxy-phenyl)-methanonewas acetylated with propionyl chloride as previously described to give (±)-*cis*-N-(5-chloro-pyridin-2-yl)-N-[1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide

^{1}H-NMR ($CDCl_3$) δ 1.14 (t, 3H), 1 15 (d, 3H), 1 22 (m, 1H), 2.31 (m, 3H), 4 79 (sextet, 1H), 5 64 (bs, 1H), 6.44 (d, 1H), 6 81-6 92 (m, 3H), 7.10-7.22 (m, 4H), 7 43 (d, 1H), 7.72 (dd, 1H), 8 50 (d, 1H).

MS m/z: 452 (M+1).

[00601] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,5-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-55)

[00602] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,5-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-toluidine for aniline and 4-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride The reaction was non-selective and also (±)-*cis*- N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was obtained in a 1:1 mixture with the product.

^{1}H-NMR ($CDCl_3$) δ: 1.07 (d, 3H), 1.25 (t, 1H), 1.91 (s, 3H), 2.15 (m, 1H), 2 43 (s, 3H), 3 76 (s, 3H), 4.26 (sextet, 1H), 6 28 (d, 1H), 6.33 (t, 1H), 6.58 (t, 1H), 6 62 (d, 2H), 6.77 (t, 1H), 6.88 (d, 3H), 7.28 (m, 2H), 7.44 (d, 1H)

MS m/z 463.0 (M+1)

[00603] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-56)

[00604] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-toluidine for aniline and 4-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride. The reaction was non-selective and also (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,5-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was obtained in a 1 1 mixture with the titled compound

[00605] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (**B-58 & B-57**, respectively).

^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 3H), 1 26 (t, 1H), 2.03 (s, 3H), 2 05 (s, 3H), 2 27 (m, 1H), 3.76 (s, 3H), 4 75 (sextet, 1H), 5 59 (bs, 1H), 6.35 (s, 1H), 6 68 (d, 2H), 6 95 (d, 1H), 7.18 (m, 1H), 7 20 (d, 2H), 7 37 (d, 2H)
MS m/z 463 5 (M+1)

[00606] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-59)

[00607] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-anisidine for aniline, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1 08 – 1.22 (m, 7 H), 2 09 – 2.38 (m, 3 H), 3.79 (s, 3 H), 4 77 (ddd, 1 H), 5.58 (br s, 1 H), 6.41 – 6.50 (m, 2 H), 6.82 – 6 94 (m, 3 H), 7.16 – 7.32 (m, 4 H), 7.35 – 7 44 (m, 2 H).
MS m/z = 481 (M + 1)

[00608] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-60)

[00609] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide using the procedure described previously for the preparation of (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1 04 – 1.18 (m, 7 H), 2 07 – 2.41 (m, 5 H), 4 76 (ddd, 1 H), 5 50 (br s, 1 H), 6.27 (d, 1 H), 6.36 (d, 1 H), 6 65 (s, 1 H), 6 70 – 6 91 (m, 3 H), 7.03 – 7.44 (m, 4 H).
MS m/z 467 (M + 1)

[00610] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-61)

[00611] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 3-toluidine for aniline, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, and propionyl chloride for acetyl chloride.
^{1}H-NMR (300 MHz, $CDCl_3$) δ· 1 10 (m, 7 H), 2 04 (s, 3H), 2.14 – 2.32 (m, 3 H), 4.74 (ddd, 1H), 5.57 (br s, 1 H), 6 26 (s, 1 H), 6.81 – 6 98 (m, 4 H), 7.11 – 7 33 (m, 4 H), 7.31 – 7 43 (m, 2 H).

MS m/z 465 (M + 1).

[00612] (±)-*Cis*-[4-[(4-Chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester (B-62)

[00613] (±)-*Cis*-[4-[(4-Chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide following the phenol alkylation procedure used to make (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester. Methyl bromoacetate was substituted for ethyl-4-bromobutyrate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.07 – 1 22 (m, 7 H), 2.10 – 2 38 (m, 3 H), 3 80 (s, 2 H), 4.58 (s, 3 H), 4.75 (m, 1 H), 5.54 (br s, 1 H), 6.39 (m, 2 H), 6.81 – 6.94 (m, 3 H), 7.18 – 7.35 (m, 5 H, 7.36 – 7.44 (m, 2 H)

MS m/z. 539 (M + 1)

[00614] (±)-*Cis*-N-(4-Chloro-phenyl)-N-[6-(2-diethylamino-ethoxy)-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-63)

[00615] (±)-*Cis*-N-(4-Chloro-phenyl)-N-[6-(2-diethylamino-ethoxy)-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide following the phenol alkylation procedure used to make (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester. (2-Bromo-ethyl)-diethyl-amine was substituted for ethyl-4-bromobutyrate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 – 1.11 (m, 13 H), 2.09 – 2.38 (m, 3 H), 2.51 – 2 77 (m, 4 H), 2.79 – 2 92 (m, 2 H), 3.86 – 4.08 (m, 2 H), 4 76 (ddd, 1 H), 5.58 (br s, 1 H), 6.34 – 6.51 (m, 2 H), 6.78 – 6 94 (m, 3 H), 7.14 – 7 31 (m, 4 H), 7.37 – 7.42 (m, 2 H)

MS m/z: 566 (M + 1)

[00616] (±)-*Cis*-2-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-2-methyl-propionic acid ethyl ester (B-64)

[00617] (±)-*Cis*-2-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-2-methyl-propionic acid ethyl ester was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide following the phenol alkylation procedure used to make (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester. 2-Bromo-2-methyl-propionic acid ethyl ester was substituted for ethyl-4-bromobutyrate.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.13 – 1 28 (m, 10 H), 1 56 (s, 3 H), 1.58 (s, 3 H), 2.16 – 2 29 (m, 3 H), 4 73 (ddd, H), 5 56 (br s, 1 H), 6.31 – 6.39 (m, 2 H), 6.76 – 6.88 (m, 3 H), 7 16 – 7 22 (m, 4 H), 7.38 – 7 41 (m, 2 H)

MS m/z· 581 (M + 1).

[00618] (±)-*Cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid (B-65)

[00619] ±)-*Cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid was prepared from (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester To a solution of (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester (83 mg, 0 155 mmol) in methanol (3 mL) was added sodium hydroxide (1 M in water, 310 uL, 0.310 mmol). The reaction was stirred at room temperature 3 h and concentrated under reduced pressure to remove methanol. The pH of the remaining aqueous solution was adjusted to 6 with 1 M hydrochloric acid. The suspension was extracted twice with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, filtered and concentrated to afford the carboxylic acid (76 mg, 94 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.09 – 1 26 (m, 7 H), 2.08 – 2 18 (m, 3 H), 4.58 (AB q, 2 H), 4.79 (ddd, 1 H), 5.57 (br s, 1 H), 6.40 (m, 2 H), 6.86 (m, 3 H), 7.09 – 7.30 (m, 4 H), 7.35 – 7.46 (m, 2 H), 8.18 (br s, 1 H).

MS m/z: 523 (M - 1).

[00620] (±)-*Cis*-2-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-2-methyl-propionic acid (B-66)

[00621] (±)-*Cis*-2-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-2-methyl-propionic acid was prepared from (±)-*cis*-2-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-2-methyl-propionic acid ethyl ester. The saponification conditions detailed in the procedure for the synthesis of (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid were used.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.04 – 1 21 (m, 7 H), 1.54 – 1 66 (m, 6 H), 2.12 – 2.37 (m, 3 H), 4 77 (ddd, 1 H), 5 53 (br s, 1 H), 6.37 (d, 1 H), 6.48 (d, 1 H), 6.66 – 6 92 (m, 1 H), 7.12 – 7 26 (m, 4 H), 7 43 (m, 2 H), 9.00 (br s, 1 H)

MS m/z 553 (M + 1).

[00622] (±)-*Cis*-N-[6-carbamoylmethoxy-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide (B-67)

[00623] (±)-*Cis*-N-[6-carbamoylmethoxy-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide was prepared from (±)-*cis*-4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester. To solid (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid methyl ester (76 mg, 0.14 mmol) was added a solution of ammonia in methanol (2 M, 10 mL). The resulting solution was stirred over night at room temperature and concentrated The resulting crude amide was purified by silica gel chromatography (100 % hexanes – 100 % ethyl acetate gradient) to afford pure product (59 mg, 76 %)

^{1}H-NMR (300 MHz, $CDCl_3$) δ. 1 10 – 1 23 (m, 7 H), 2 16 – 2.39 (m, 3 H), 4 44 (s, 2 H), 4/77 (ddd, 1 H), 5.56 (br s, 1 H), 6 25 (br s, 1 H), 6 40 – 6.62 (m, 3 H), 7.16 – 7.26 (m, 4 H), 7.35 – 7.48 (m, 2 H)
MS m/z 524 (M + 1)

[00624] (±)-*Cis*-N-[6-Bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide (B-69)

[00625] (±)-*Cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide was made following general procedure B, substituting 4-bromoaniline for aniline and 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 1-1.2 (7 H, m), 2 1-2 3 (3 H, m), 4 8 (1 H, m), 5 6 (1 H, m), 6 4 (1 H, d), 6 9 (3 H, t), 7.1 (1 H, m), 7.2 (4 H, m), 7.4 (3 H, m).
MS m/z. 531 (M+2)

[00626] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-6-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-70)

[00627] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-6-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made from (±)-*cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide (±)-*Cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide was dissolved in toluene, followed by $Pd_2(dba)_3$, BINAP, sodium tert-butoxide, and morpholine. The reaction mixture was heated to 90 °C for 24 hours The reaction mixture was cooled to room temperature and filtered through Celite ® and concentrated. Crude mixture was purified by flash chromatography on silica gel using a gradient elution of hexane-ethylacetate (10-50%).

^{1}H-NMR ($CDCl_3$) δ 1 1-1.2 (7 H, m), 2 1-2 3 (3 H, m), 3 1 (4 H, t), 3.8 (4 H, t), 4.8 (1 H, m), 5 6 (1 H, m), 6 3 (1 H, d), 6.4 (1 H, m), 6.7 (1 H, s), 6 9 (3 H, m), 7 1-7.4 (5 H, m)
MS m/z 536 (M+1)

[00628] (±)-*Cis*- -(4-chloro-phenyl)-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-71)

[00629] (±)-*Cis*-N-(4-chloro-phenyl)-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made in the same way as (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-6-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide except diethylamine was substituted for morpholine. The reaction was non-selective and yielded (±)-*cis*-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-diethylamino-phenyl)-propionamide in addition to the titled compound
^{1}H-NMR ($CDCl_3$) δ: 1.1-1 3 (13 H, m), 1 6 (1 H, m), 2.1-2.3 (3 H, m), 3.3 (4 H, m), 4.7 (1 H, m), 5.6 (1 H, m), 6.2 (1 H, m), 6.3 (1 H, m), 6 5 (1 H, s), 6.9 (2 H, m), 7.3 (4 H, m), 7.4 (2 H, m)
MS m/z: 523 (M+2).

[00630] (±)-*Cis*-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N(4-diethylamino-phenyl)-propionamide (B-72)

[00631] (±)-*Cis*-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N(4-diethylamino-phenyl)-propionamide was made in the same way as (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-6-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide except diethylamine was substituted for morpholine The reaction was non-selective and yielded (±)-*cis*-N-(4-chloro-phenyl)-N-[6-diethylamino-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide in addition to the titled compound
^{1}H-NMR ($CDCl_3$) δ· 1.1-1 3 (19 H, m), 2.3 (3 H, m), 3 3 (8 H, m), 4 7 (1 H, m), 5 6 (1 H, m), 6.1 (1 H, m), 6 2 (1 H, m), 6 6 (3 H, m), 6.9 (1 H, m), 7.1 (3 H, m), 7.3 (2 H, m).
MS m/z 560 (M+2)

[00632] (±)-*Cis*-3-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yl]-acrylic acid (B-73)

[00633] (±)-*Cis*-3-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yl]-acrylic acid was made from (±)-*cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide To a solution of (±)-*cis*-N-[6-bromo-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide (250 mg, 0.47mmol), TEA (0.2 ml, 1.4mmol), palladium acetate (11 mg, 0.047mmol),

1,3-Bis(diphenylphosphino)propane (39mg, 0 094mmol), in 10 ml DMF was added 0.13 ml methyl acrylate (1 41mmol). The resulting reaction mixture was heated to 80 °C overnight. The mixture was filtered through celite and the filtrate was concentrated under vacuum. The residue was purified by silica gel chromatography, eluting with ethyl acetate-hexane (2:3) to give (±)-*cis*-3-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yl]-acrylic acid methyl ester (110 mg, 44%).

[00634] To a solution of (±)-*cis*-3-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yl]-acrylic acid methyl ester (110 mg, 0.21mmol) in 4 ml methanol was added 50 mg K_2CO_3,(0 36mmol, in 2 ml water) The resulting reaction mixture was stirred at room temperature overnight. The methanol was removed under vacuum 1M HCl was added until the mixture was acidic. Dichloromethane (25 ml) was added Organic layer was dried with magnesium sulfate. Dichloromethane was removed under vacuum The residue was purified by HPLC to give 10 mg title compound.

^{1}H-NMR ($CDCl_3$) δ· 1.0-1.2 (7 H, m), 2 4 (2 H, m), 2 5 (1 H, m), 3.3 (1 H, br), 4.8 (1 H, m), 5 6 (1 H, m), 6 4 (1 H, d), 6.6 (1 H, d), 7 0 (2 H, t), 7 2-7 6 (9 H, m).

MS m/z· 522 (M+2)

[00635] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2,8-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-74)

[00636] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2,8-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 2-toluidine for aniline and 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1 11 (3H, d; overlapping 1H, t), 1.76 (3H,s), 2.00 (3H, s), 2 35 (1H, m), 3 55(3H,s), 5 00 (1H, m), 5 60 (1H, m), 6.65 (1H, s), 6 80 (1H, t), 6.85 (1H,t), 6.95 (1H, t), 7 15 (1H, t), 7.25 (1H, t), 7.25-7.55 (6H, m)

MS m/z 429(M + 1).

[00637] (±)-*Cis*-N-(4-Chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2,6-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-75)

[00638] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2,6-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-toluidine for aniline and 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d; overlapping 1H, t), 2.02 (3H, s), 2.33-2 35 (3H,s; overlapping 1H, m), 3 63 (3H,s), 4.80 (1H, m), 5.60 (1H, m), 6.44 (1H, d), 6.70-6.85 (3H, complex), 7.05 (1H, t), 7.15 (1H, s), 7 25-7.55 (6H, complex).

MS m/z: 429(M + 1).

[00639] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-76)

[00640] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(3-methoxy-benzoyl)-2-methyl-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-trifluoromethylaniline for aniline and 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d; overlapping 1H, t), 2 03 (3H, s), 2.38 (1H, m), 3 63(3H,s), 4.80 (1H, m), 5.60 (1H, m), 6.60 (1H, d), 6 70 (1H, d), 6.80 (1H,dd), 7.15 (1H, t), 7.25-7.40 (6H, m), 7.60 (1H, s).

MS m/z 483 (M + 1).

[00641] (±)-*Cis*-N-(4-chloro-phenyl)-N-[6-methoxy-1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-77)

[00642] ±)-*Cis*-N-(4-chloro-phenyl)-N-[6-methoxy-1-(3-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-methoxyaniline for aniline and 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ 1 12 (3H, d; overlapping 1H, t), 2 02 (3H, s), 2.35 (1H, m), 3.63 (3H, s), 3 76 (3H,s), 4.80 (1H, m), 5 60 (1H, m), 6.44 (1H, s), 6.70-6 95 (4H, complex), 7 15 (1H, t), 7 25-7 55 (6H,m).

MS m/z: 445 (M + 1).

[00643] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-78)

[00644] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(thiophene-2-carbonyl)-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-trifluoromethylaniline for aniline and 2-thiophene carbonyl chloride for 4-dimethylaminobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 14 (3H, d; overlapping 1H, t), 2.02 (3H, s), 2 35 (1H, m), 4 80 (1H, m), 5 65 (1H, m), 6 65 (1H, d), 6.80 (1H,d), 7 00 (1H, d), 7.20 (overlapping 2x1H,d), 7.24-7.42 (3H, m), 7.60 (1H, s).

MS m/z· 539 (M + 1).

[00645] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-79)

[00646] ±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(5-methyl-thiophene-2-carbonyl)-6-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 4-trifluoromethylaniline for aniline and 5-methyl-2-thiophene carbonyl chloride for 4-dimethylaminobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 14 (3H, d; overlapping 1H, t), 2.02 (3H, s), 2.35 (1H, m), 2 40(3H,s), 4 80 (1H, m), 5.65 (1H, m), 6 45 (1H, d), 6.55 (1H,d), 7.00 (1H, d), 7 20 (overlapping 2x1H,d), 7.24-7.42 (3H, m), 7.55 (1H, s)

MS m/z 554 (M + 1).

[00647] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-80)

[00648] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-7-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 3-trifluoromethylaniline for aniline, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride. A mixture of the 5 and 7 position isomer was obtained.

^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d; overlapping 1H, t), 2.20-2.40 (2H, q, 1H, m), 4.80 (1H, m), 5.65 (1H, m), 6 70 (1H, s), 6 95 (2x1H, t), 7.10-7.60 (8H, m)

MS m/z 519 (M + 1).

[00649] (±)-*Cis*-N-[7-bromo-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (B-81)

[00650] (±)-*Cis*-N-[7-bromo-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide was made following general procedure B, substituting 3-bromoaniline for aniline A mixture of the 5 and 7 position isomer was obtained

[00651] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-isopropyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-82)

[00652] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-isopropyl-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-isopropylaniline for aniline. A mixture of the 5 and 7 position isomer was obtained.

^{1}H-NMR (CDCl3) δ: 0.89 (2x3H, t), 1.15 (3H, d; overlapping 1H, t), 2 01 (3H, s), 2 33 (1H, m), 2.60(1H, m), 2.87(2x3H, s), 4.80 (1H, m), 5.65 (1H, m), 6.40 (overlapping 1H, s, 2H, d), 6.90 (1H, d), 7 10 (1H, d), 7.15-7.35 (5H, m) 7 40(1H,d).

MS m/z 505 (M + 1).

[00653] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-7-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-83)

[00654] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-7-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made from (±)-*cis*-N-[7-bromo-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (±)-*Cis*-N-[7-bromo-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide was dissolved in toluene, followed by $Pd_2(dba)_3$, BINAP, sodium tert-butoxide, and morpholine. The reaction mixture was heated to 90°C for 24 hours. The reaction mixture was cooled to room temperature and filtered through Celite ® and concentrated. Crude mixture was purified by flash chromatography on silica gel using gradient elution hexane-ethylacetate (10-50%)

^{1}H-NMR (CDCl3) δ: 1.11 (3H, d; overlapping 1H, t), 1.99 (3H, s), 2.33 (1H, m), 2.60-2 80 (2x2H, m), 2 89(2x3H, s), 3.70(2x2H, m), 4.70 (1H, m), 5 60 (1H, m), 6.10 (1H, s), 6 44 (2x1H, d), 7 00-7 40 (8H, m)

MS m/z: 548 (M + 1).

[00655] (±)-*Cis*-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-diethylamino-phenyl)-acetamide (B-84)

[00656] (±)-*Cis*-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-diethylamino-phenyl)-acetamide was made in the same way as (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-7-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide except diethylamine was substituted for morpholine. The reaction was non-selective and yielded (±)-*cis*-N-(4-chloro-phenyl)-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide in addition to the titled compound.

^{1}H-NMR (CDCl3) δ: 0 78 (2x3H, t), 1 15 (overlapping 3H, d; 1H, t), 1.98 (3H, s), 2.33 (1H, m), 2.87(2x3H, s), 2.90-3.10(2x2H, q), 4.70 (1H, m), 5 60 (1H, m), 5 90(1H, s), 6.46 (3x1H, d),7 00-7.40 (7H, m)

MS m/z 557(M + 1).

[00657] (±)-*Cis*-N-(4-chloro-phenyl)-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-85)

[00658] (±)-*Cis*-N-(4-chloro-phenyl)-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made in the same way as (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-7-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-

yl]-acetamide except diethylamine was substituted for morpholine. The reaction was non-selective and yielded (±)-*cis*-N-[7-diethylamino-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-diethylamino-phenyl)-acetamide in addition to the titled compound.
^{1}H-NMR (CDCl3) δ: 0.78 (2x3H, t), 1.15 (overlapping 2x3H, t; 3H, d, 1H, t), 2.00 (3H, s), 2.33 (1H, m), 2.76(2x3H, s), 2 80-3.00(2x2H, q), 3.24(2x2H, q), 4.60 (1H, m), 5 60 (1H, m), 5 90(1H, s), 6.46 (2x1H, d), 6.60 (1H, m), 6.90 (2x1H, d), 7 00-7 20 (6H, m)
MS m/z: 609(M + 1).

[00659] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-5-methoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-86)

[00660] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-5-methoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was prepared following general procedure B, substituting 3-anisidine for aniline, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR ($CDCl_3$) δ. 1.09-1.14 (6H, m), 1.50-1.66 (1H, m), 1.97-2.34 (3H, m), 3.83 (3H, s), 4.65 (1H, q), 5.70-5.80 (1H, br), 6 08 (1H, d), 6.68 (1H, d). 6.81-6.89 (3H, m), 7.14-7.18 (4H, m), 7 33-7 36 (2H, m).
MS m/z 481 (M+1).

[00661] (±)-*Cis*-2,2-dimethyl-propionic acid 4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yl ester (B-87)

[00662] (±)-*Cis*-2,2-dimethyl-propionic acid 4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yl ester was prepared following general procedure B, substituting 2,2-dimethyl-propionic acid 3-amino-phenyl ester for aniline.
^{1}H-NMR ($CDCl_3$) δ 1 11-1.25 (13H, m), 2.02 (3H, s), 2.20-2.40 (1H, m), 2 92 (6H, s), 4.60-4 72 (1H, m), 5.45-5.55 (1H, br), 6.26 (1H, s), 6.46 (2H, d), 6 85 (1H, d), 7.09-7.39 (7H, m).
MS m/z 562 (M+1).

[00663] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-88)

[00664] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made from (±)-*cis*-2,2-dimethyl-propionic acid 4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yl ester. (±)-*Cis*-2,2-dimethyl-propionic acid 4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yl ester (100 mg, 0.178 mmol) was

dissolved in tetrahydrofuran and sodium hydroxide (1 M, 356 uL, 0.356 mmol) was added. The mixture was stirred at room temperature 4 hours, then heated at reflux 2 h. The mixture was cooled to rt, acidified, concentrated and purified by silica gel chromatography (20 mg, 23 %).
^{1}H-NMR (MeOD) δ. 1.06-1 08 (4H, m), 2 00 (3H, s), 2 35-2.45 (1H, m), 2.93 (6H, s), 4.65-4 68 (1H, m), 5.42-5.50 (1H, br), 6 07 (1H, s), 6.53 (2H, d), 6.63 (1H, d), 7 10-7.20 (3H, m), 7 35-7.48 (4H, m)
MS m/z 478 (M+1).

[00665] (±)-*Cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid ethyl ester (B-89)

[00666] (±)-*Cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid ethyl ester was prepared from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide, following the alkylation conditions described for the synthesis of (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester, substituting ethyl bromoacetate for ethyl 4-bromobutyrate
^{1}H-NMR (MeOD) δ· 1.10-1 38 (7H, m), 2.00 (3H, s), 2.39-2.45 (1H, m), 2.94 (6H, s), 4.04-4.20 (2H, m), 4.29 (2H, s), 4.60-4.75 (1H, m), 5.40-5 50 (1H, br), 6.16 (1H, s), 6.54 (2H, d), 6 79 (1H, d), 7 08 (2H, d), 7 20-7 48 (5H, m)
MS m/z 564 (M+1).

[00667] (±)-*Cis*-2-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetamide (B-90)

[00668] (±)-*Cis*-2-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetamide was prepared from (±)-*cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid ethyl ester, via the same amidation procedure used in the synthesis of (±)-*cis*-N-[6-carbamoylmethoxy-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide.
^{1}H-NMR (MeOD) δ: 1 09-1 15 (4H, m), 2.00 (3H, s), 2 39-2 45 (1H, m), 2 94 (6H, s), 4.04-4.20 (2H, m),4 60-4 75 (1H, m), 5 40-5.50 (1H, br), 6 14 (1H, s), 6.53 (2H, d), 6 81 (1H, d), 7.09 (2H, d), 7.20-7.48 (5H, m).
MS m/z:535 (M+1)

[00669] (±)-*Cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid (B-91)

[00670] (±)-*Cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid was prepared from (±)-*cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid ethyl ester following the saponification procedure described above for the synthesis of (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid

^{1}H-NMR (MeOD) δ 1.08-1.10 (4H, m), 1 98 (3H, s), 2.39-2.45 (1H, m), 2 93 (6H, s), 4 20 (2H, s), 4 61-4.70 (1H, m), 5.40-5 50 (1H, br), 6 17 (1H, s), 6.53 (2H, d), 6 79 (1H, d), 7.08 (2H, d), 7.28-7.48 (5H, m)

MS m/z 536 (M+1).

[00671] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-(2-hydroxy-2-methyl-propoxy)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-92)

[00672] ±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-(2-hydroxy-2-methyl-propoxy)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared from (±)-*cis*-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-acetic acid ethyl ester was using the same alkylation procedure described for the synthesis of (±)-*cis*-N-{1-[4-(2-hydroxy-2-methyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide

^{1}H-NMR ($CDCl_3$) δ: 1.01-1.20 (4H, m), 1.30 (6H, s), 2.01 (3H, s), 2.20-2 40 (1H, m), 2 92 (6H, s), 3.70 (2H, s), 4.65-4.72 (1H, m), 5.45-5 55 (1H, br), 6.13 (1H, s), 6 45 (2H, d), 6 65 (1H, d), 7 12-7.46 (7H, m).

MS m/z:551 (M+1)

[00673] (±)-*Cis*--N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-ethoxy-2-methyl-1,2,3.4-tetrahydro-quinolin-4-yl]-acetamide (B-93)

[00674] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-ethoxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide using the same alkylation procedure described for the synthesis of (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester, substituting ethyl iodide for ethyl-4-bromobutyrate.

^{1}H-NMR ($CDCl_3$) δ 1 01-1.20 (7H, m), 2 01 (3H, s), 2 20-2.40 (1H, m), 2 92 (6H, s), 3.60 (2H, q), 4.65-4 72 (1H, m), 5 45-5.55 (1H, br), 6 15 (1H, s), 6 44 (2H, d), 6.69 (1H, d), 7 11-7.46 (7H, m)

MS m/z 506 (M+1).

[00675] (±)-*Cis*-4-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-butyric acid ethyl ester (B-94)

[00676] (±)-*Cis*-4-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-butyric acid ethyl ester was made from (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-7-hydroxy-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide using the same alkylation procedure described for the synthesis of (±)-*cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.11 (4 H, m), 1 23 (3 H, t), 1.81-1.85 (2 H, m), 2.01 (3 H, s), 2.30-2 33 (3 H, m), 2.92 (6 H, s), 3.50-3.54 (1 H, m), 3 72-3.76 (1 H, m), 4 09 (2 H, q), 4 66-4.73 (1 H, m), 5 57-5.63 (1 H, m), 6.14 (1 H, s), 6.46 (2 H, d), 6 68 (1 H, d), 7.11-7.39 (7 H, m)

MS m/z 593 (M+1).

[00677] (±)-*Cis*-4-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-butyric acid (B-95)

[00678] (±)-*Cis*-4-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-butyric acid was made from (±)-*cis*-4-[4-[acetyl-(4-chloro-phenyl)-amino]-1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-7-yloxy]-butyric acid ethyl ester following the saponification conditions described for the synthesis of (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.08-1.11 (4H, m), 1.80-1 86 (2H, m), 1.99 (3H, s), 2.28-2 35 (3H, m), 2.89 (6H, s) 3.37-3.46 (1H, m), 3.66-3.73 (1H, m), 4.64-4 72 (1H, m), 5.54-5 63 (1H, m), 6.07 (1H, s), 6.52 (2H, d), 6.67 (1H, d), 7 08-7 36 (7H, m).

MS m/z: 564 (M+1).

[00679] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-96)

[00680] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2,7-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-toluidine for aniline Both the 5 and 7-position isomers were obtained in this procedure

^{1}H-NMR ($CDCl_3$) δ 1 11 (3H, d), 1 45-1.59 (4H, m), 2.02-2.07 (3H, m), 2.24-2.28 (1H, m), 2.92 (6H, s) 4.67-4.74(1H, m), 5 52-5.59 (1H,m), 6 43-6.45 (3H, m), 6 95 (1H, d), 7.13-7.22 (6H, m), 7.35-7 43 (1H, m)

MS m/z 307 (M).

[00681] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-phenethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-97)

[00682] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-phenethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, 3-phenyl-propionaldehyde for acetaldehyde and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (dt, 3H), 1 25 (m, 1H), 1.54 (m, 1H), 1.97 (m, 1H), 2.30 (m, 3H), 2 56 (t, 2H), 4.85 (sextet, 1H), 5.66 (bs, 1H), 6.44 (d, 1H), 6.86 (t, 2H), 6.93 (m, 2H), 7.03 (d, 2H), 7 12-7 29 (m, 8H), 7 37 (d, 2H)

MS m/z 542 (M+1)

[00683] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-(2-cyano-ethyl)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-98)

[00684] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-(2-cyano-ethyl)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, 4-oxobutyrylnitrile for acetaldehyde and propionyl chloride for acetyl chloride

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.19 – 1.23 (m, 4 H), 1.65 – 1 79 (m, 2 H), 2.07 – 2.57 (m, 5 H), 4 90 (ddd, 1 H), 5 61 (br s, 1 H), 6 61 (d, 1 H), 6.86 (m, 2 H), 6.95 (dd, 1 H), 7.14 – 7.43 (m, 8 H).

MS m/z = 490 (M + 1).

[00685] (±)-*Cis*-N-[2-ethyl-1-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (B-99)

[00686] (±)-*Cis*-N-[2-ethyl-1-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure B, substituting 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride, propionyl aldehyde for acetaldehyde and phenylboronic acid for 4-chlorophenylboronic acid

^{1}H-NMR ($CDCl_3$) δ: 0 8 (3H, t),1.3 (2H, m), 1 6 (1H, m), 2 0 (3H, s), 2 3 (1H, m), 3.7 (3H, s), 4.7 (1H, m), 5.7 (1H, m), 6 5 (1H, d), 6 7 (1H, s), 6.8 (2H, m), 6 9-7 4 (9H, m)

MS m/z 429 (M+1)

[00687] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (B-100)

[00688] (±)-*Cis*-N-[1-(3-methoxy-benzoyl)-2-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made following general procedure B, substituting 3-methoxybenzoyl chloride for 4-dimethylaminobenzoyl chloride, benzaldehyde for acetaldehyde and phenylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.5 (1H, m), 2.0 (3H, s), 2 5 (1H, m), 3.6 (3H, s), 5.7 (1H, t) 5 8 (1H, m), 6.6 (1H, d), 6.9 (2H, m), 6.9-7 4 (15H, m).

MS m/z 494 (M-18).

[00689] (±)-*Cis*-4-(acetyl-phenyl-amino)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid ethyl ester (B-101)

[00690] (±)-*Cis*-4-(acetyl-phenyl-amino)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid ethyl ester was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, ethyl glyoxylate for acetaldehyde and phenylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, t), 1.2 (1H, m), 2 0 (3H, s), 2 5 (1H, m), 4 1 (2H, q), 5.0 (1H, t), 5.7 (1H, m), 6.6 (1H, d), 6.8-7.0 (4H, d), 7 1-7.4 (8H, m)

MS m/z 461 (M+1).

[00691] (±)-*Cis*-4-(acetyl-phenyl-amino)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid (B-102)

[00692] (±)-*Cis*-4-(acetyl-phenyl-amino)-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid was made from (±)-*cis*-4-(acetyl-phenyl-amino)-1-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid ethyl ester by basic hydrolysis with 1N sodium hydroxide, ethanol and water.

^{1}H-NMR ($CDCl_3$) δ 1 2 (1H, m), 2.0 (3H, s), 2 6 (1H, m), 5 0 (1H, t), 5.6 (1H, m), 6.6 (1H, d), 6.9-7.0 (3H, m), 7.2 (2H, m), 7.3-7.5 (7H, m).

MS m/z: 433 (M+1).

[00693] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-propyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-103)

[00694] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-propyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, butyryl aldehyde for acetaldehyde and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 0.8 (3H, t), 1.1-1.2 (7H, m), 1.4 (1H, m), 2.1-2 3 (3H, m), 4 8 (1H, m), 5.6 (1H, m), 6.7 (1H, d), 6.9-7.1 (4H, m), 7.2-7 5 (7H, m).
MS m/z 479 (M+1)

[00695] (±)-*Cis*-propionic acid 4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-2-ylmethyl ester (B-104)

[00696] (±)-*Cis*-propionic acid 4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-2-ylmethyl ester was prepared following general procedure B, substituting propionic acid 2-oxo-ethyl ester for acetaldehyde, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride
^{1}H-NMR ($CDCl_3$) δ 0.8 (3H, t), 1 1 (3H, t), 1.1 (1H, m), 2 1 (2H, m), 2 2 (3H, s), 3 8 (1H, m), 4.2 (1H, m), 5 0 (1H, m), 5.4 (1H, m), 6.4 (1H, d), 6 8 (3H, m), 7 1-7 4 (8H, m).
MS m/z 523 (M+1).

[00697] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-105)

[00698] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-hydroxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was prepared from (±)-*cis*-propionic acid 4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-2-ylmethyl ester using the saponification conditions utilized in the synthesis of (±)-*cis*-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yloxy]-acetic acid
^{1}H-NMR ($CDCl_3$) δ 1.1 (3H, t), 1.3 (1H, m), 1 8 (1H, m), 2.1 (2H, m), 3.4 (1H, t), 3.6 (2H, m), 4 2 (1H, m), 6 2 (1H, m), 6.4 (1H, d), 6 7 (2H, t), 6.8-7.0 (5H, m), 7.1-7.3 (4H, m).
MS m/z 367 (M-99)

[00699] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-diethylaminomethyl-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-106)

[00700] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-diethylaminomethyl-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting diethylamino-acetaldehyde for acetaldehyde, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ· 0.8 (6H, m), 1.1 (3H, t), 1 1 (1H, m), 1.8 (2H, m), 2.2-2.5 (6H, m), 2.6 (1H, m), 4.8 (1H, m), 5 7 (1H, m), 6.4 (1H, d), 6.9 (3H, m), 7.1-7.4 (8H, m).
MS m/z 523 (M+2).

[00701] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methoxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-107)

[00702] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methoxymethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was prepared following general procedure B, substituting methoxyacetaldehyde for acetaldehyde, 4-fluorobenzoyl chloride for 4-dimethylamino-benzoyl chloride, and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ· 1.1 (3H, t), 1.3 (1H, m), 1.8 (1H, m), 2 1 (1H, m), 3.4 (4H, m), 3 6 (2H, m), 4 2 (1H, m), 6 3 (1H, m), 6.5 (1H, d), 6.7 (1H, m), 6.8-7.0 (4H, m), 7.1-7.4 (6H, m).

MS m/z: 381 (M-99).

[00703] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-108)

[00704] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-phenyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following general procedure B, substituting benzaldehyde for acetaldehyde, 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride, and propionyl chloride for acetyl chloride

^{1}H-NMR ($CDCl_3$) δ 1.1-1 2 (3 H, m), 1 2 - 1.4 (1 H, m), 2 2 - 2.4 (2 H, m), 2.4 - 2 6 (1 H, m), 5 6 (1 H, t), 5 8 (1 H, m), 6.6 (1 H, d), 6.8 (2 H, m), 7.0 (1 H, m), 7.2-7.4 (13 H, m)

MS m/z. 513 (M + 1).

[00705] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-109)

[00706] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was prepared following general procedure B, substituting N-(4-chloro-phenyl)-N-vinyl-propionamide for N-vinyl carbamic acid benzyl ester and trifluoroacetaldehyde for acetaldehyde in the synthesis of 11 and 4-fluorobenzoyl chloride for 4-dimethylaminobenzoyl chloride and propionyl chloride for acetyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1 1-1.2 (3 H, m), 1.6 (1 H, br), 2.2 - 2 4 (3 H, m), 3.8 (3 H, s), 5.5 (1 H, m), 5.6 (1 H, m), 6.5 (1 H, s), 6.8 (1 H, s), 6.9 (2 H, t), 7.1 - 7.3 (4 H, m), 7.4 (2 H, d).

MS m/z 535 (M+1)

[00707] (±)-*Cis*-N-(4-chloro-phenyl)-N-[6-methoxy-1-(3-methoxy-benzoyl)-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-110)

[00708] (±)-*Cis*-N-(4-chloro-phenyl)-N-[6-methoxy-1-(3-methoxy-benzoyl)-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide was made following the procedure for the synthesis of

(±)-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide, substituting 3-methoxybenzoyl chloride for 4-fluorobenzoyl chloride
^{1}H-NMR ($CDCl_3$) δ· 1.1 - 1.2 (3 H, m), 1 6 (1 H, br), 2.2 - 2.4 (3 H, m), 3.7 (3 H, s), 3.8 (3 H, s), 5.5 (1 H, m), 5.6 (1 H, m), 6.5 (2 H, m), 6 6 (1 H, m), 6.8 (3 H, m), 7 1 (1H, t), 7.2 (2H, d), 7 4 (2H, d).
MS m/z. 547 (M+1)

[00709] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(furan-2-carbonyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide (B-111)

[00710] (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(furan-2-carbonyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide propionamide was made following the procedure for the synthesis of (±)-*cis*-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-6-methoxy-2-trifluoromethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide, substituting 2-furoyl chloride chloride for 4-fluorobenzoyl chloride
^{1}H-NMR ($CDCl_3$) δ: 1.1 - 1 2 (3 H,m), 1.6 (1 H, br), 2.2 - 2.4 (3 H, m), 3.8 (3 H, s), 5.4 (2 H, m), 6.0 (1 H, m), 6 3 (1 H, m), 6.8 (1 H, m), 6.9 (1 H, s), 7.0 (1 H, m), 7.2 (2 H, m), 7.4 (3 H, m)
MS m/z: 507 (M+1).

[00711] (±)-*Cis*-N-[2-benzyl-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide (B-112)

[00712] (±)-*Cis*-N-[2-benzyl-1-(4-fluoro-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-propionamide was made following general procedure B, substituting phenylacetaldehyde for acetaldehyde, 4-fluorobenzoyl chloride for 4-dimethylamionbenzoyl chloride, and propionyl chloride for acetyl chloride.
^{1}H-NMR ($CDCl_3$) δ: 1 14 (3 H, t), 2.05 - 2.52 (5 H, m), 3 18 - 3.24 (1 H, m), 4.89 - 4.93 (1 H, m) 5.45 - 5.55 (1 H, br), 6.46 (1 H, d), 6.83 - 7.37 (16 H, m).
MS m/z 528 (M+1).

[00713] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (B-113)

[00714] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure B, substituting 3-methylisoxazole-5-carbonyl chloride for 4-dimethylamionbenzoyl chloride.

[00715] (±)-*Cis*-N-(4-chloro-phenyl)-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was separated by chiral HPLC using a chiral cel OD column and eluting with 90% hexane/10% ethanol isocratic system to give (2*R*,4*S*)- and (2*S*,4*R*)-*cis*-N-(4-chloro-

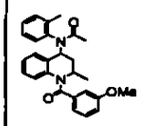
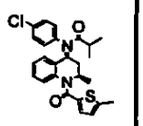
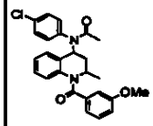
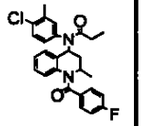
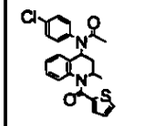
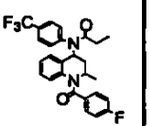
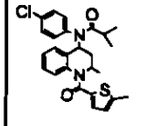
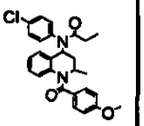
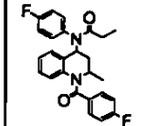
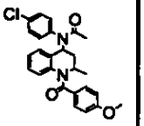
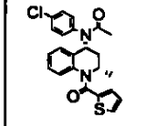
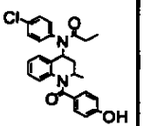
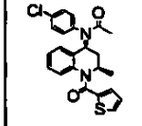
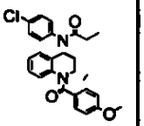
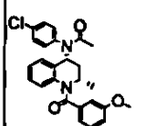
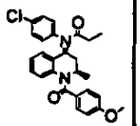
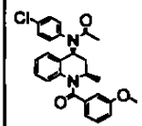
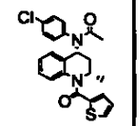
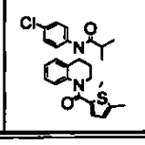
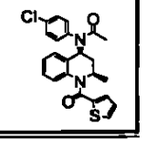
phenyl)-N-[2-methyl-1-(3-methyl-isoxazole-5-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (**B-42** & **B-36**, respectively)

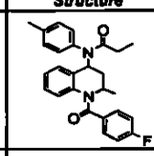
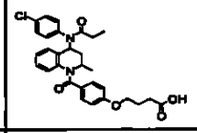
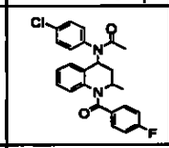
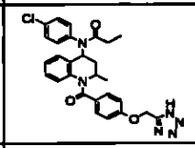
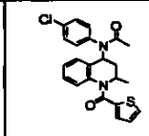
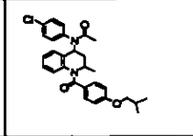
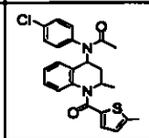
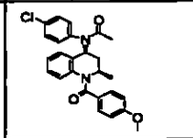
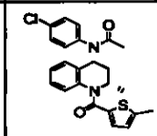
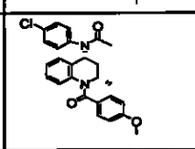
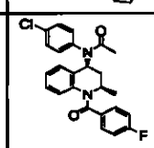
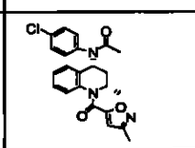
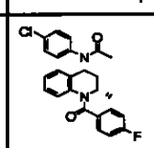
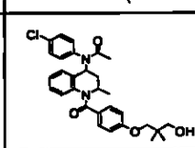
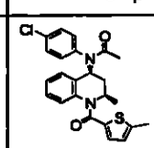
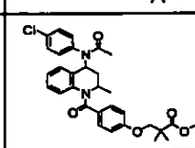
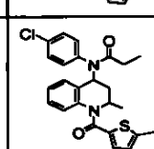
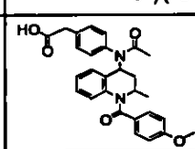
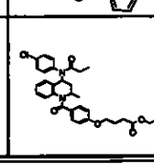
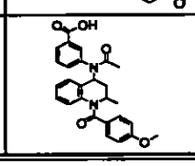
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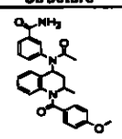
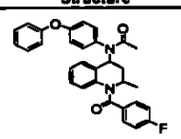
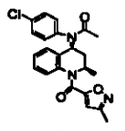
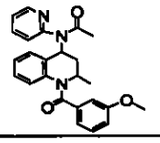
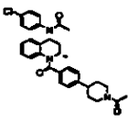
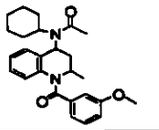
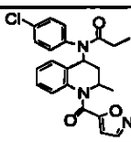
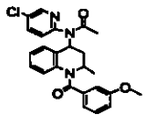
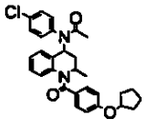
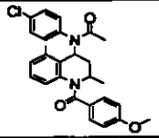
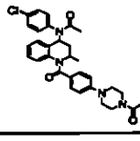
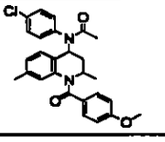
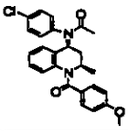
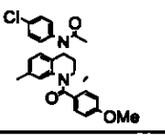
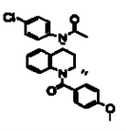
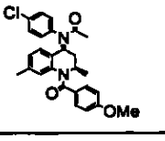
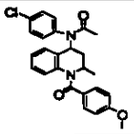
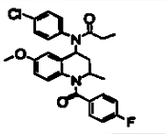
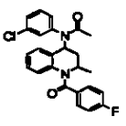
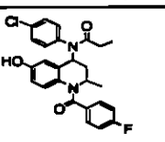
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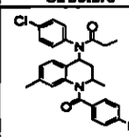
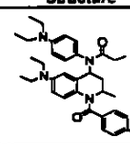
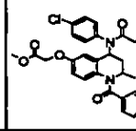
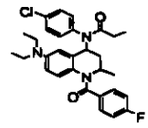
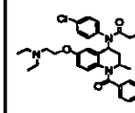
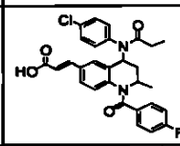
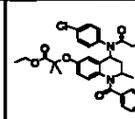
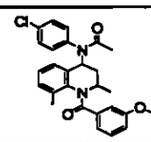
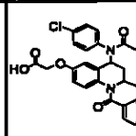
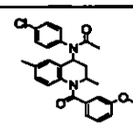
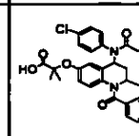
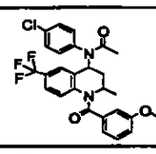
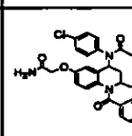
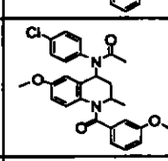
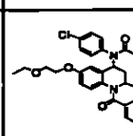
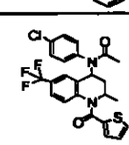
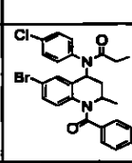
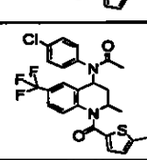
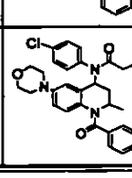
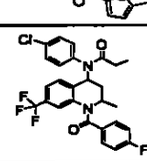
[00716] Compounds **B-114- B-147** can be prepared by the schemes set forth in Scheme 13 and 14 and by the general procedures B and others described herein. Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

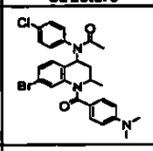
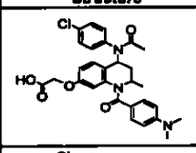
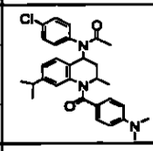
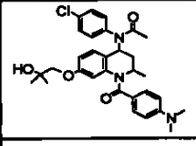
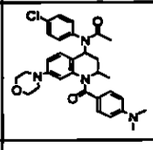
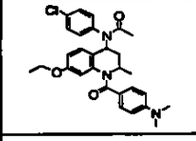
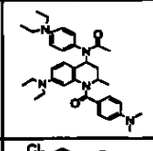
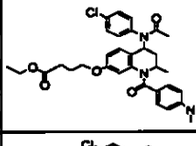
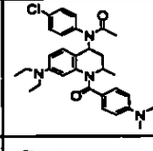
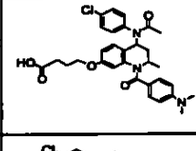
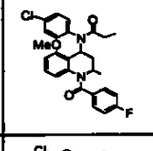
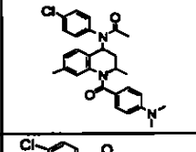
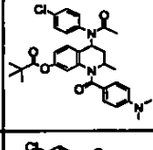
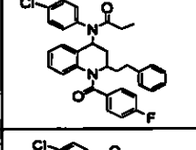
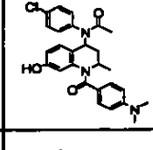
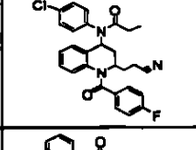
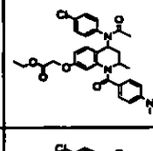
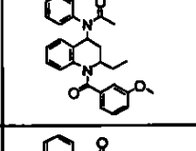
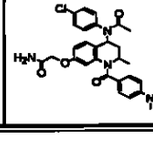
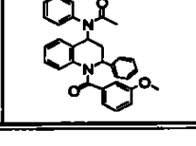
Table 2: Compounds Derived from General Procedure B

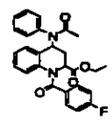
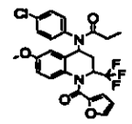
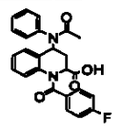
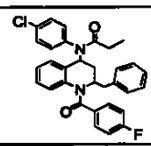
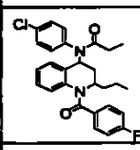
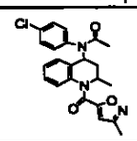
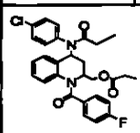
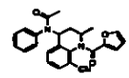
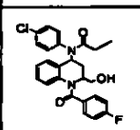
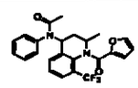
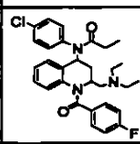
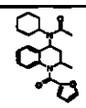
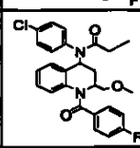
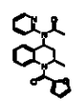
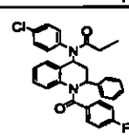
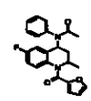
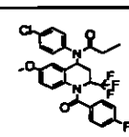
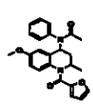
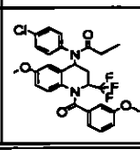
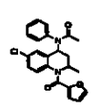
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B-4		B-14	
B-5		B-15	
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B-8		B-18	
B-9		B-19	
B-10		B-20	

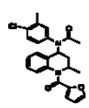
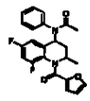
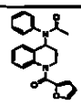
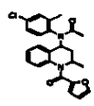
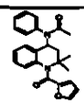
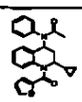
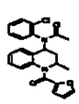
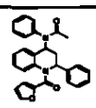
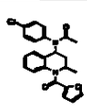
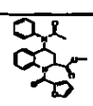
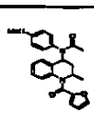
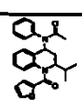
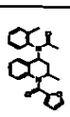
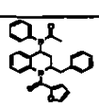
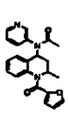
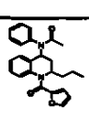
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B-29		B-39	
B-30		B-40	

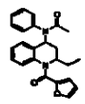
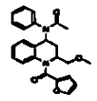
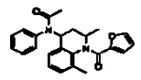
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B-50		B-60	

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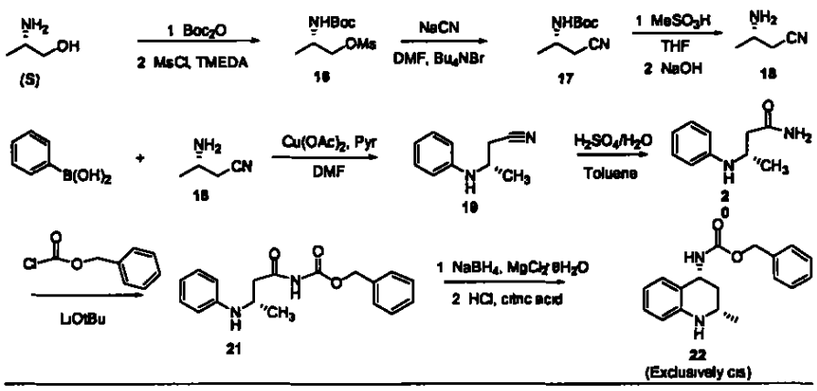
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B-87		B-97	
B-88		B-98	
B-89		B-99	
B-90		B-100	

No	Structure	No	Structure
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B-104		B-114	
B-105		B-115	
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B-108		B-118	
B-109		B-119	
B-110		B-120	

No	Structure	No	Structure
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B-124		B-134	
B-125		B-135	
B-126		B-136	
B-127		B-137	
B-128		B-138	
B-129		B-139	
B-130		B-140	

No.	Structure	No	Structure
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B-142			
B-143			
B-144			
B-145			
B-146			
B-147			

Scheme 13



[00717] Methanesulfonic acid 2-(*S*)-tert-butoxycarbonylamino-propyl ester (16)

[00718] To a room temperature solution of *S*-2-amino-propan-1-ol (28 23 g, 0 375 mol) in ethyl acetate (300 mL) was added BOC anhydride (86 13 g, 0.395 mol) dissolved in 30 mL of ethyl acetate via an addition funnel (exothermic). The solution turns cloudy then clear The reaction mixture was stirred for approximately 30 minutes Tetramethylethylenediamine (TMEDA) (59 6 mL, 0 395 mol) was added and the reaction mixture was cooled to approximately 0°C. Methanesulfonyl chloride (30.6 mL, 0 395 mol) was added to the reaction mixture over a 30-minute period After stirring for 2 5 hour at 0°C, during which time a white precipitate formed. The reaction mixture was filtered and the filtrate was concentrated to ½ volume and poured into hexanes (800mL) and rapidly stirred The mixture was cooled in an ice-bath for 2 h and then filtered to give 82 g (86%) of methanesulfonic acid 2-(*S*)-tert-butoxycarbonylamino-propyl ester.

^{1}H NMR (300 MHz, $CDCl_3$) δ1 23 (d, 3H), 1 44 (s, 9 H), 3.03 (s, 2 H), 3.96 (m, 1 H), 4.15 (dd, 1 H), 4 23 (dd, 1 H), 4 58 (bs, 1 H).

[00719] (*S*)-(2-Cyano-1-methyl-ethyl)-carbamic acid tert-butyl ester (17)

[00720] Sodium cyanide (48.92g, 0.421 mol) was added to dimethylformamide (DMF) (420 mL) and the mixture was stirred at 35°C for 30 minutes. Tetrabutylammonium bromide (5.22g, 0.016 mol) was added and the reaction mixture was stirred for an additional 2 h at 35°C Methanesulfonic acid 2-(S)-tert-butoxycarbonylamino-propyl ester (82.03 g, 0.324 mol) was added and the reaction mixture was stirred at 35°C overnight. Add an additional 5.22g of tetrabutylammonium bromide (0 016 mol) was added and stirred overnight at 35°C. The mixture was then partitioned between 1200 mL water and 1600 mL of ethyl acetate. The resulting organic and aqueous phases were separated and extracted

sequentially 2 times with 800 mL of ethyl acetate The combined extracts were washed 3 times with 500mL of water and a saturated solution of sodium chloride in water. The organic layer was dried over magnesium sulfate, filtered and concentrated to afford a solid in 84% of (*S*)-(2-cyano-1-methyl-ethyl)-carbamic acid tert-butyl ester.

[00721] (*S*)-3-Amino-butyronitrile (18)

[00722] To a solution of (*S*)-(2-cyano-1-methyl-ethyl)-carbamic acid tert-butyl ester (50 29 g, 0 273 mol) dissolved in THF (550 mL) was added methanesulfonic acid (44 mL, 0.682 mol) and stirred for 20 minutes The reaction mixture was heated to 65°C for approximately 3 h (make sure the reaction is vented during this time) The mixture was allowed to cool to ambient temperature The resulting solids were isolated by filtration to afford the title compound. The solids were suspended in dichloromethane, and 300 mL of sat Na_2CO_3 and the pH was adjusted to 13 with 6M NaOH (~20 mL). Extract 2X 500mL dichloromethane. Combine the organics and wash with a saturated solution of sodium chloride in water. The organic layer was dried over sodium sulfate, filtered and concentrated to give (S)-3-amino-butyronitrile in 64% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ1 23 (d, 3 H),1.46 (bs, 2 H), 2.34 (dd, 1 H), 2.43 (dd, 1 H), 3.34 (sextet, 1 H).

[00723] (*S*)-3-Phenylamino-butyronitrile (19)

[00724] (*S*)-3-Amino-butyronitrile (2 51g, 0.030 mol) was dissolved in 40 mL of DMF, phenyl boronic acid (4.73g, 0 0389 mol), $Cu(OAc)_2$ (7.06g, 0 0389 mol) and pyridine (6 29 mL, 0.077 mol) were added and the reaction was heated to 65 °C open to the air until no starting material was apparent by LCMS (It is very important that this reaction not be run under argon or nitrogen, it needs the air to catalyze the reaction. Also, the reaction should be stirred very vigourously to allow the air to mix with the reaction) Once the starting material was gone (~ 18 h), the reaction was allowed to cool to room temperature and poured into ethyl acetate and filter. Wash the precipitate well with ethyl acetate The filtrate is washed 2 times with H_2O and dried over Na_2SO_4, filtered and concentrated. Isco chromatography (100% hexane to 30% ethyl acetate/ 70% hexane gradient) afforded the N-phenyl nitrile in 2.13g (41%) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.44 (d, 3 H),2.61 (d, 2 H), 3.64(bs, 1 H), 3.90 (bs, 1 H), 6.60 (d, 2 H), 6 77 (t, 1 H), 7 18-7.26 (m, 2 H)

[00725] (*S*)-3-Phenylamino-butyramide (20)

[00726] To a solution of (*S*)-3-phenylamino-butyronitrile (6 06g, 0.0378mol) in toluene (150 mL) was added a cooled solution of conc sulfuric acid in H_2O (20.12 mL H_2SO_4/ 3 mL)- (The ratio of toluene to acid/H_2O is very important and should be followed strictly) Stir the biphasic mixture at

room temperature for 0.5 h and warm to 35 °C and stir for 22h The reaction was cooled to room temperature and quenched with 13g of Na_2CO_3 in water (add slowly some foaming). Separate the organic and extract 2 x EtOAc. Combine all the organics and wash the organics with brine, dry over $MgSO_4$, filter and concentrate to give the desired product in 2.11g (90%)

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, 3 H), 2 40 (dd, 1 H), 2.48 (dd, 1 H), 3.73 (bs, 1 H), 3 92 (sextet, 1 H), 5 52 (bs, 1 H), 6.00 (bs, 1 H), 6.66 (d, 2 H), 6.74 (t, 1 H), 7 19 (m, 2 H)

[00727] (*S*)-(3-Phenylamino-butyryl)-carbamic acid benzyl ester (21)

[00728] A clean, dry and nitrogen gas purged flask was charged with (*S*)-3-phenylamino-butyramide (3 25g, 0 018 mmol) in THF (65 mL) and the mixture was cooled to -10°C. Benzyl chloroformate (3 12 mL, 0.022 mmol) was then added followed by the slow addition of 1.0 M lithium tert-butoxide in THF solution (18 mL). The lithium tert-butoxide solution was added at such a rate that the internal temperature remained below 0°C. Fifteen minutes after the completion of base addition, the reaction (starting material gone by TLC) was quenched by adding EtOAc (65 mL) and 1 0 M hydrochloric acid (10 mL) The aqueous phase was then basified with 1N NaOH. The aqueous phase was extracted 3 x EtOAc The organics were collected together and with saturated aqueous sodium chloride solution (130 mL). The phases were separated, the organic layer was dried ($MgSO_4$), filtered, and concentrated Flash chromatography using a Biotage system (10% EtOAc/ 90% hexane to 20% EtOAc/ 80% Hexane) afforded the title compound in 82% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1 30 (d, 3 H), 2 87 (dd, 1 H), 3.04 (dd, 1 H), 3.80 (bs, 1 H), 4.02 (m, 1 H), 5 17 (s, 2 H), 6.62 (d, 2 H), 6 73 (t, 1 H), 7.17 (t, 2 H), 7.37 (s, 5 H), 8.13 (bs, 1 H).

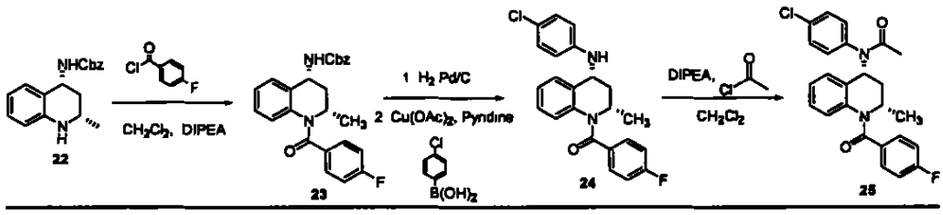
[00729] (2*S*, 4*R*)-(2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (22)

[00730] A clean, dry flask was charged with (S)-(3-phenylamino-butyryl)-carbamic acid benzyl ester (0.821 g, 2.63 mmol) followed by reagent grade ethanol (20 mL) and cooled to -10 °C. Sodium borohydride (0 070 g, 1.84 mmol) was added to the solution in one portion Nitrogen gas purging is maintained for 5 minutes A solution of 3 3 M aqueous magnesium chloride solution (0 561 g $MgCl_2$ $6H_2O$ in 1.5 mL water) was added at such a rate that the internal temperature did not exceed -5 °C Once addition was completed, the reaction solution was warmed to 0 °C for 30 min. The reaction was quenched with methylene chloride (10 mL), and 1 M hydrochloric acid/citric acid solution (10 52 mL 1 N HCl, and 1.38 g citric acid). This bilayer was stirred at room temperature for six hours. The reaction mixture was diluted with ethyl acetate (200 mL) and neutralized with sat aqueous $NaHCO_3$ solution (pH = 10). The organics were collected together and washed with sat. NaCl solution and dried over Na_2SO_4, filtered and concentrated. Flash chromatography using an Isco system (100% hexane to 50% EtOAc/ 50% hexane gradient) afforded the title compound (0 733 g) (91 %).

^{1}H-NMR (300 MHz, $CDCl_3$) δ· 7.38 (m, 5 H), 7 17 (d, 1 H), 7.02 (t, 1 H), 6 68 (t, 1H, C6-H), 6.47 (d, 1H), 5.17 (bs, 2H), 5.07 (m, 1H), 4.92 (d, 1H), 3.78 (bs, 1H), 3 57 (m, 1H), 2 30 (m, 1H), 1.47 (q, 1H), 1.21 (d, 3H)

General Procedure C

Scheme 15



[00731] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (25)

[00732] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (1.0 g, 3.38 mmol) in methylene chloride (50 mL) at room temperature was added diisopropylethylamine (650 uL, 3.72 mmol) followed by 4-fluorobenzoyl chloride The reaction was stirred over night at room temperature The mixture was poured into water and extracted with ethyl acetate. The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford the pure amide (720 mg, 51 %).

[00733] (2*S*,4*R*)-[1-(4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (720 mg, 1.73 mmol) was dissolved in ethanol (30 mL). The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen. Reaction was complete after 4 h. The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution was filtered through an Celite ® and concentrated to afford the crude amine

[00734] To a solution of (2*S*, 4*R*)- (4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-fluoro-phenyl)-methanone (1 0 g, 3 5 mmol) in DMF (20 mL, dry) was added 4-chlorophenylboronic acid (1 1 g, 7.0 mmol), pyridine (850 uL, 10.5 mmol) and copper(II)acetate (1.27 g, 7.0 mmol). The heterogeneous green mixture was stirred open to air for 1 h and then warmed to 60 °C and stirred over night (14 h). The mixture was then cooled to rt, poured into rapidly stirred ethyl acetate (150 mL); solids were removed by filtration through Celite ® The extracts were washed several times with water and then once with brine. The extracts were then dried over anhydrous magnesium sulfate,

filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford the aniline product (250 mg, 18 %) as a yellow oil

[00735] To a solution of (2*S*, 4*R*)- [4-(4-chloro-phenylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(4-fluoro-phenyl)-methanone (250 mg, 0 636 mmol) in methylene chloride (5 mL) was added diisopropylethylamine (120 uL, 0 70 mmol) followed by acetyl chloride (90 uL, 1.27 mmol) The mixture was stirred at rt 4 h The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (200 mg, 71 %)

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.1 (1H, m), 2 0 (3H, d), 2 3 (1H, m), 4.7 (1H, m), 5.6 (1H, m), 6.5 (1H, d),6 7-7.0 (3H, m), 7 1-7 4 (8H, m).

MS m/z 436 (M+1).

[00736] (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-1)

[00737] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure C, substituting 4-bromobenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the morpoline was done following the same procedure as described for(±)-N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-6-morpholin-4-yl-1,2,3,4-tetrahydro-quinolin-4-yl]-propionamide.

^{1}H-NMR ($CDCl_3$) δ· 1.13 (d, 3H), 1.22 (t, 1H), 2.03 (s, 3H), 2.29 (s, 1H), 3.31 (t, 4H), 3 80 (t, 4H), 4.75 (sextet, 1H), 5.61 (bs, 1H), 6.58 (d, 1H), 6.64 (d, 2H), 6.94 (t, 1H), 7.15 (d, 2H), 7.18 (t, 1H), 7.21 (d, 2H), 7.28 -7 39 (m, 3H).

MS m/z: 505.4 (M+1).

[00738] (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (C-2)

[00739] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid was prepared was made following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the acid was done following the same procedure as described for (±)-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid

^{1}H-NMR ($CDCl_3$) δ 1 1 (3H, d), 1 1 (1H, m), 2.0 (3H, s), 2.1 (2H, m), 2.3 (1H, m), 2.5 (2H, m), 3.9 (2H, m), 4.7 (1H, m), 5.6 (1H, m),), 6.5 (1H, d), 6 7 (2H, d), 6.9 (1H, t), 7 1-7.3 (7H, m), 7.4 (1H, d)
MS m/z: 522 (M+2)

[00740] (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-3)

[00741] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-[1-(4-dimethylamino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-dimethylaminobenzoyl chloride for 4-fluorobenzoyl chloride

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1 14 – 1 33 (m, 4 H), 2 13 (s, 3 H), 2 24 – 2 39 (m, 1 H), 2 94 (s, 6 H), 4 75 (ddd, 1 H), 5 61 (br s, 1 H), 6 44 (d, 2 H), 6 63 (d, 1 H), 6 96 (dd, 1 H), 7 07 – 7 36 (m, 6 H), 7.40 (d, 2 H)
MS m/z 420 (M + 1).

[00742] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-isopropoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-4)

[00743] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-isopropoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-isopropoxybenzoyl chloride for 4-fluorobenzoyl chloride.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1 14 (d, 3 H), 1.23 – 1 31 (m, 7 H), 2 03 (s, 3 H), 2 23 – 2.35 (m, 1 H), 4 48 (sept., 1 H), 4 74 (ddd, 1 H), 5 61 (br s, 1 H), 6.55 (d, 1 H), 6.64 (d, 2 H), 6 92 (dd, 1 H), 7.09 – 7.24 (m, 5 H), 7 29 (d, 1 H), 7.34 – 7.41 (m, 2 H)
MS m/z 477 (M + 1)

[00744] (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(6-morpholin-4-yl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-5)

[00745] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(6-morpholin-4-yl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 2-chloronicotinoyl chloride for 4-fluorobenzoyl chloride. Prior to removal of the benzyl carbamate, the chloronicotinamide was converted to the 2-morpholinonicotinamide as follows. A solution of the (2*S*,4*R*)-[1-(6-chloro-nicotinoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (525 mg, 1.20 mol) was dissolved in morpholine (5 mL) The resulting solution was heated at 70 °C over night. Upon completion of reaction (12 h), the solution was concentrated under reduced pressure; the crude residue was dissolved in ethyl acetate and washed with water and brine to remove remaining morpholine The extracts were dried over sodium sulfate, filtered and concentrated to

afford the crude morpholinonicotinate (639 mg, > 100%) The resulting product was carried on to fully elaborated (2S,4R)-N-(4-chloro-phenyl)-N-[2-methyl-1-(6-morpholin-4-yl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide as described in general procedure C

^{1}H-NMR (300 MHz, $CDCl_3$) δ. 1 11 -1.22 (m, 4 H), 2.03 (s, 3 H), 2.24 – 2.38 (m,1 H), 3.48 – 3 56 (m, 4 H), 3 74 – 3 80 (m, 4 H), 4.73 (ddd, 1 H), 5.56 (br s, 1 H), 6 30 (d, 1 H), 6.66 (d, 1 H), 7.02 (dd, 1 H), 7 12 (dd, 1 H), 7.16 – 7 25 (m, 3 H), 7 32 (d, 1 H), 7.40 (d, 2 H), 8.24 (br s, 1 H).

MS m/z 505 (M + 1).

[00746] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-6)

[00747] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 3-ethylisoxazole carbonyl chloride for 4-fluorobenzoyl chloride

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.06 – 1 23 (m, 7 H), 2.02 (s, 3 H), 2 21 – 2.37 (m, 1 H), 2.52 – 2.66 (m, 2 H), 4 72 (ddd, 1 H), 5 34 – 5 56 (br s, 1 H), 5 88 (s, 1 H), 6 80 (d, 1 H), 7.11 (dd, 1 H), 7.20 (d, 2 H), 7.28 – 7.43 (m, 4 H)

MS m/z. 438 (M + 1).

[00748] (2*S*,4*R*)-N-[1-(3-Benzyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (C-7)

[00749] (2*S*,4*R*)-N-[1-(3-Benzyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide was prepared following general procedure C, substituting 3-benzylisoxazole carbonyl chloride for 4-fluorobenzoyl chloride.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.06 – 1.43 (m, 4 H), 2.01 (s, 3 H), 2.16 – 2.35 (m, 1 H), 3.81 – 4.01 (m, 2 H), 4 70 (ddd, 1 H), 5 40 (br s, 1 H), 5.83 (s, 1 H), 6.75 (d, 1 H), 7.02 (dd, 1 H), 7.10 (m, d, 2 H), 7 14 – 7 22 (m, 2 H), 7.22 – 7.34 (m, 5 H), 7.38 (d, 2 H)

MS m/z· 500 (M + 1)

[00750] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-methoxymethyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-8)

[00751] 2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-methoxymethyl-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 3-methoxymethyl ether isoxazole carbonyl chloride for 4-fluorobenzoyl chloride.

^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.11 – 1.24 (m, 4 H), 2.02 (s, 3 H), 2.22 – 2.39 (m, 1 H), 3.28 (s, 3 H), 4.42 (s, 2 H), 4.73 (ddd, 1 H), 5.46 (br s, 1 H), 6 09 (s, 1 H), 6.79 (d, 1 H), 7.10 (d, 1 H), 7 10 (d, 2 H), 7.27 – 7.42 (m, 4 H)
MS m/z· 454 (M + 1)

[00752] (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-piperidine-1-carboxylic acid ethyl ester (C-9)

[00753] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-piperidine-1-carboxylic acid ethyl ester was prepared following general procedure C, substituting 4-(4-chlorocarbonyl-phenoxy)-piperidine-1-carboxylic acid ethyl ester for 4-fluorobenzoyl chloride.
^{1}H-NMR ($CDCl_3$) δ· 1.1 (3H, d), 1.1 (1H, m), 1.2 (3H, t), 1.7 (2H, m), 1.9 (2H, m), 2.0 (3H, s), 2.3 (1H, m), 3.3 (2H, m), 3.7 (2H, m), 4.1 (2H, q), 4.4 (1H, m), 4.8 (1H, m), 5.6 (1H, m), 6.5 (1H, d), 6.7 (2H, d), 6.9 (1H, t), 7.1-7.3 (7H, m), 7.4 (1H, d).
MS m/z 590 (M)

[00754] (2*S* ,4*R*)- 2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetamide (C-10)

[00755] (2*S*,4*R*)-2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetamide was made from (2S,4R)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the amide was done following the same procedure as described for (±)-N-[1-(4-carbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide
^{1}H-NMR ($CDCl_3$) δ 1.1(3H, m), 1.8(1H, s), 2.0 (3H, s), 2.3 (1H, m), 4.4 (2H, s), 4.7 (1H, m), 5.6 (1H, br), 5.9 (2H, brs) 6.5 (2H, d), 6.7 (2H, d), 6.9 (1H, t), 7.2-7.4(7H, m)
MS m/z 492 (M+1).

[00756] (2*S* ,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (C-11)

[00757] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was made from (2S,4R)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was

prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride Further elaboration to the morpholine was done following the same procedure as described for (±)-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide

^{1}H-NMR ($CDCl_3$) δ: 1 1 (3H, d), 1.1 (1H, m), 2.0 (3H, s), 2.3 (1H, m), 2.6 (4H, m), 2.8 (2H, m), 3.7 (4H, m), 4.1 (2H, m), 4 7 (1H, m), 5 6 (1H, m), 6.5 (1H, d), 6.7 (2H, d), 6.9 (1H, t), 7 1-7.3 (7H, m), 7.4 (1H, d)

MS m/z 549 (M+2)

[00758] (2*S* ,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid (C-13)

[00759] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid was made from (2S,4R)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the acid was done following the same procedure as described for {(±)-4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic.

^{1}H-NMR ($CDCl_3$) δ· 1.1 (3H, d), 1.1 (1H, m), 2 0 (3H, s), 2.3 (1H, m), 4.3 (2H, s), 4.6 (1H, m), 5.6 (1H, m), 6.4-6.9 (5H, m), 7.0-7.4 (7H, m)

MS m/z: 494 (M+2)

[00760] (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (C-14)

[00761] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was made from (2S,4R)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the tetrazole was done following the same procedure as described for (±)-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-propionamide.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.1 (1H, m), 2.0 (3H, s), 2.3 (1H, m), 4 8 (1H, m), 5.2 (2H, dd), 5.6 (1H, m), 6.4 (1H, m), 6.5 (1H, d), 7.0 (2H, m), 7.1-7.4 (8H, m).

MS m/z. 517 (M+1).

[00762] (2*S* ,4*R*)-N-{1-[4-(1-Acetyl-piperidin-4-yloxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (C-15)

[00763] (2*S*,4*R*)-N-{1-[4-(1-Acetyl-piperidin-4-yloxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide was prepared from (2S,4R)-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-piperidine-1-carboxylic acid ethyl ester, followed by removal of the ethoxy carbamate using basic hydrolysis and then acetylation

^{1}H-NMR ($CDCl_3$) δ 1 1 (3H, d), 1.1 (1H, m), 1.6-2.1 (4H, m), 2 0 (6H, s), 2.3 (1H, m), 3.4 (1H, m), 3 5-3 8 (3H, m), 4.4 (1H, m), 4.7 (1H, m), 5.6 (1H, m), 6.5 (1H, d), 6 7 (2H, d), 6.9 (1H, t), 7 1-7.3 (7H, m), 7.4 (1H, d)

MS m/z 560 (M+1).

[00764] (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(pyridin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (C-16)

[00765] (2*S* ,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(pyridin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (2S,4R)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was made from (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide.

(2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in dichloromethane and a solution of BBr_3 (1.0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for until no starting material remained The reaction was washed with sat $NaHCO_3$ carefully and brine. The organics were dried over $MgSO_4$, filtered and concentrated down. The residue was purified by Biotage flash chromatography using 100 % EtOAc to give a white solid.

[00766] The phenol was dissolved in DMF (5 mL) at room temperature Sodium hydride (60 % in oil) was added and the mixture allowed to stir 30 min. 4-Bromomethyl-pyridine was added and the reaction was allowed to stir over night. Ethanol was added and the reaction was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (2/98 methanol / dichloromethane – 5/95 methanol/dichloromethane gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.1 (1H, m), 2 0 (3H, s), 2 3 (1H, m), 4.7 (1H, m), 5.0 (2H, s), 5.6 (1H, m), 6.5 (1H, d), 6.7 (2H, d), 6.9 (1H, t), 7.0-7.4 (10H, m), 8 6 (2H, d).

MS m/z. 526 (M+1).

[00767] (2*S* ,4*R*)- 4-(3-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid (C-17)

[00768] (2*S*,4*R*)-4-(3-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid was prepared following general procedure C, substituting 3-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the acid was done following the same procedure as described for (±)-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1 1 (1H, m), 1 8-2 0 (2H, m), 2.0 (3H, s), 2.3 (1H, m), 2 4 (2H, m), 3.8 (2H, m), 4.8 (1H, m), 5.7 (1H, m), 6 4 (1H, m), 6.5 (1H, d), 6.8 (1H, m), 7.0 (1H, t), 7.1-7 4 (7H, m), 7 5 (1H, m)

MS m/z 521 (M+1).

[00769] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-18)

[00770] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared was made following general procedure C, substituting 3-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. Further elaboration to the phenol was done following the same procedure as described for (±)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide

^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, d), 1.1 (1H, m), 2 0 (3H, s), 2.3 (1H, m), 4 7 (1H, m), 5 6 (1H, m), 6.4 (2H, d), 6.5 (1H, d), 6 9 (3H, m), 7.1-7.3 (4H, m), 7.4 (2H, m), 8 0 (1H, br).

MS m/z 435 (M+1)

[00771] (2*S*, 4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-1-carboxylic acid ethyl ester (C-19)

[00772] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-1-carboxylic acid ethyl ester was prepared following general procedure C, substituting 4-(4-chlorocarbonyl-phenyl)-piperidine-1-carboxylic acid ethyl ester for 4-fluorobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (4 H, m), 1.3 (3 H, m), 1 5 (2 H, m), 1 7 (2 H, m), 2.0 (3 H, s), 2.3 (1 H, m), 2 6 (1 H, m), 2.8 (2 H, t), 4.1 (2 H, m), 4 2 (2 H, m), 4.8 (1 H, m), 5.6 (1 H, br), 6.5 (1 H, d), 6.9 (1 H, m), 7 0 (2 H, d), 7.1 (2 H, d), 7.3 (5 H, m), 7.4 (2H, m).

MS m/z. 474 (M+1)

[00773] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-20)

[00774] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 3-ethoxybenzoyl chloride for 4-fluorobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.2 (3 H, m), 1 3 (4 H, m), 2 0 (3 H, s), 2.2 (1 H, m), 3 9 (2 H, m), 4.8 (1 H, m), 5 6 (1H, br), 6.5 (1 H, d), 6.7 (1 H, d), 6.8 (2 H, m), 6 9 (1 H, m), 7.0 (1 H, m), 7.1-7.3 (4 H, m), 7 4 (2 H, d)

MS m/z: 463 (M+1).

[00775] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-carbamic acid ethyl ester (C-22)

[00776] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-carbamic acid ethyl ester was prepared following general procedure C, substituting (4-chlorocarbonyl-phenyl)-carbamic acid ethyl ester for 4-fluorobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ. 1.1 (3 H, m), 1 3 (4 H, m), 2.0 (3 H, s), 2 3 (1 H, m), 4 2 (2 H, m), 4 8 (1 H, m), 5 6 (1 H, br), 6.5 (1H, d), 6.9 (1 H, m), 7.1-7.3 (8 H, m), 7.4 (2 H, d).

MS m/z 506 (M + 1)

[00777] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-oxazol-5-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-24)

[00778] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-oxazol-5-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-oxazol-5-yl-benzoyl chloride for 4-fluorobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1 2 (3 H, m), 1.3 (1 H, m), 2.1 (3 H, s), 2.3 (1 H, m), 4.8 (1 H, m), 5.6 (1 H, br), 6.5 (1 H, d), 6.9 (1 H, m), 7.1-7.3 (8 H, m), 7.4 (1 H, d), 7.5 (2 H,d), 7 9 (1H, s).

MS m/z 486 (M+1)

[00779] (2*S*,4*R*)-N-(3,4-Dichloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-25)

[00780] (2*S*,4*R*)-N-(3,4-Dichloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure C, substituting 3,4-dichlorophenylboronic acid for 4-chlorophenylboronic acid and 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ: 1.2 (3 H, m), 1 3 (1 H, m), 2.0 (3 H, s), 2 3 (1 H, m), 3 7 (3 H, s), 4.8 (1 H, m), 5.6 (1 H, br), 6.6 (1 H, d), 6 7 (2 H, d), 7.0 (1 H, m), 7.2 (3 H, m), 7.3 (2 H, d), 7.4 (1 H, s), 7 5 (1 H, d).
MS m/z: 483 (M+1)

[00781] (2*S*,4*R*)-N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-26)

[00782] (2*S*,4*R*)-N-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure C, substituting 2,3-dihydro-benzo[1,4]dioxine-6-carboxylic acid for 4-chlorophenylboronic acid and 4-methoxyphenylbenzoyl chloride for 4-fluorobenzoyl chloride.
^{1}H-NMR ($CDCl_3$) δ: 1.2 (3 H, m), 1.3 (1H, m), 2 0 (3 H, s), 2.4 (1 H, m), 3.7 (3 H, s), 4 3 (4 H, s), 4.8 (1 H, m), 5 6 (1 H, br), 6.5 (1 H, d), 6.68 (2 H, d), 6.7-6 9 (3 H, m), 7.10-7.3 (5 H, m).
MS m/z: 474 (M+2)

[00783] (2*S*,4*R*)- N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-p-tolyl-acetamide (C-27)

[00784] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-p-tolyl-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride and 4-toluene boronic acid for 4-chlorophenylboronic acid
^{1}H-NMR (CDCl3) δ 1.15 (3H, d, overlapping 1H, t), 2 01 (3H, s), 2.33-2.36 (overlapping 1H, m, 1H,s), 3 73(3H,s), 4 70 (1H, m), 5.65 (1H, m), 6.50 (1H, d), 6.68 (2x1H, d), 6.95 (1H, t), 7.00-7 40 (8H, m)
MS m/z: 429 (M + 1).

[00785] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-28)

[00786] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-pyrrolidin-1-yl-benzoyl chloride for 4-fluorobenzoyl chloride
^{1}H-NMR ($CDCl_3$) δ. 1.11-1.15 (4H, m), 1.94-1 98 (4H, m), 2.03 (3H, s), 2 24-2.34 (1H, m), 3.21-3.25 (4H, m), 4 68-4.75 (1H, m), 5.61-5.65 (1H, br), 6.30 (2H, d), 6.63 (1H, d), 6 92-7 52 (9H, m).
MS m/z: 488 (M+1).

[00787] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-29)

[00788] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure C, substituting 1-isopropyl-1H-benzotriazole-5-carbonyl chloride for 4-fluorobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.19-1 27 (4 H, m), 1 68 (6 H, d), 2.04 (3 H, s), 2.30-2 40 (1 H, m), 4.83 (1 H, q), 4.98 (1 H, q) 5.45-5.55 (1 H, br), 6 48 (1 H, d), 6.83 (1 H, t), 7.10-7 41 (8 H, m), 8.13 (1 H, br)

MS m/z. 503 (M+1).

[00789] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(1-hydroxy-1-methyl-ethyl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (C-30)

[00790] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(1-hydroxy-1-methyl-ethyl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was prepared from (2*S*, 4*R*)-N-[1-(4-acetyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide. (2*S*,4*R*)-N-[1-(4-Acetyl-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (112 mg, 124 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. Methyl magnesium bromide (1.4 M in ether, 2 mL, 2.4 mmol) was added and the mixture stirred at 0 °C for 2 h The reaction was warmed to rt and stirred an additional 2 h. The reaction was poured into saturated aqueous ammonium chloride. The phases were separated and the aqueous was extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate, filtered, dried and concentrated. The crude alcohol was purified by silica gel chromatography to afford pure product (20 mg, 24 %)

^{1}H-NMR ($CDCl_3$) δ 1 12-1.21 (4 H, m), 1.48 (6 H, d), 2.02 (3 H, s), 2.25-2 34 (1 H, m), 4.70-4.80 (1 H, m), 5.45-5.54 (1 H, br), 6 50 (1 H, d), 6.88 (1 H, t), 7.11-7 38 (10 H, m)

MS m/z· 478 (M+1)

[00791] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethoxy-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-31)

[00792] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(3-ethoxy-isoxazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 3-ethoxy-isoxazole-5-carbonyl chloride for 4-fluorobenzoyl chloride

^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d), 1.33 (3H, t), 1.69 (1H, br s), 2.00 (3H, s), 2.21-2.38 (1H, m), 4 21 (2H, q), 4 66-4 73 (1H, m), 5.65 (1H, s), 6.86 (1H, d), 7.13-7 39 (8H, m)

MS m/z 454 (M).

[00793] (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-propionic acid (C-32)

[00794] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-propionic acid was prepared from (2*S*,4*R*)- 3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid. A solution of (2*S*,4*R*)-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid (50 mg, 0.102 mmol) in EtOH (2 ml) and CH_2Cl_2 (10 drops for solubility) was subjected to Pd-C (10%, *ca* 50 mg) and 1 atm H_2 gas After 1 hour, the mixture was filtered, concentrated and subjected to silica gel chromatography (2% MeOH in EtOAc to 10% MeOH in EtOAc), to afford the title compound (50 mg, 99 %).

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.09 (3H, d), 1.17-1.18 (1H, m), 2 00 (3H, s), 2.20-2.35 (1H, m), 2.46-2.60 (2H, m), 2.80-2.90 (2H, m), 4.65-4.80 (1H, m), 5.40-5.71 (1H, m), 6.48 (1H, d), 6.89 (1H, t), 7.0 (2H, d), 7 12 (2H, d), 7 20-7.48 (5H, m), 7.72 (1H, d).

MS m/z. 322 (M – C_8H_7NO).

[00795] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid (C-33)

[00796] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid was prepared following general procedure C, substituting 3-(4-chlorocarbonyl-phenyl)-acrylic acid methyl ester for 4-fluorobenzoyl chloride The ester was hydrolyzed as follows To a solution of (2*S*,4*R*)- 3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid methyl ester (112 mg, 0 239 mmol) in THF/MeOH (2 ml, 2 ml) was added LiOH (4 ml: 1.0 M in H_2O). Upon consumption of the starting unit (1 hour), the mixture was neutralized with aq. HCl (1.0 M), partioned with EtOAc (10 ml) and separated The organic layer was separated and concentrated whereby the resulting oil was subjected to silica gel chromatography (2% MeOH in EtOAc to 10% MeOH in EtOAc) to afford the title compound (110 mg, 99 %)

^{1}H-NMR (MeOD, 300 MHz) δ 0.85-0 95 (1H, m), 1.12 (3H, d), 2.04 (3H, s), 2.40-2.53 (1H, m), 4 70-4.80 (1H, m), 5.50-5.71 (1H, m), 6.46 (1H, d), 6.57 (1H, d), 6.96 (1H, t), 7.20-7.55 (8H, m), 7.60 (2H, d), 7.81 (1H, d).

MS m/z 320 (M – C_8H_7NO).

[00797] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-methoxy-phenyl)-acetamide (C-34)

[00798] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-methoxy-phenyl)-acetamide was prepared following general procedure C, substituting 4-

methoxybenzoyl chloride for 4-fluorobenzoyl chloride and 4-methoxyphenylboronic acid for 4-chlorophenylboronic acid.

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1 12 (3H, d), 1.20-1 23 (1H, m), 2.09 (3H, s), 2.30-2.42 (1H, m), 3 71 (3H, s), 3.81 (3H, s) 4 70-4 81 (1H, m), 5 50-5 80 (1H, m), 6.52 (1H, d), 6.67 (2H, d), 6 80-6.94 (4H, m), 7.10-7.40 (5H, m).

MS m/z 280 (M- $C_9H_{10}NO_2$).

[00799] (2*S*,4*R*)-N-(4-Isopropyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-35)

[00800] (2*S*,4*R*)-N-(4-Isopropyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride and 4-isopropylphenylboronic acid for 4-chlorophenylboronic acid

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.21 (6H, d), 1.20-1.23 (1H, m), 1.23 (3H, d), 2.09 (3H, s), 2.30-2 42 (1H, m), 2.80-2 95 (1H, m), 3.74 (3H, s), 4.65-4.83 (1H, m), 5.50-5.80 (1H, m), 6 53 (1H, d), 6 67 (2H, d), 6.72 (2H, d), 6.92 (1H, t), 7.02-7.12 (3H, m), 7 21 (2H, d), 7.38 (1H, d).

MS m/z· 280 (M- $C_{11}H_{14}NO$).

[00801] (2*S*,4*R*)-N-(4-Bromo-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-36)

[00802] (2*S*,4*R*)-N-(4-Bromo-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride and 4-bromophenylboronic acid for 4-chlorophenylboronic acid

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1 12 (3H, d), 1 20-1.24 (1H, m), 2.05 (3H, s), 2 20-2.38 (1H, m), 3 72 (3H, s), 4.66-4 81 (1H, m), 5.50-5.75 (1H, m), 6 52 (1H, d), 6.67 (2H, d), 6 92 (1H, t), 7.10-7 18 (5H, m), 7 26 (1H, t), 7.48-7 58 (2H, m).

MS m/z 493 (M + 1)

[00803] (2*S*,4*R*)-4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid (C-37)

[00804] (2*S*,4*R*)-4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid was made from (2*S*,4*R*)- 4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid methyl ester (2*S*,4*R*)- 4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid methyl ester prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride

and 4-phenylboronic acid methyl ester for 4-chlorophenylboronic acid (2*S*,4*R*)- 4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid methyl ester was converted to the acid using the following procedure. To a solution of 4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-benzoic acid methyl ester (10 mg, 0.038 mmol) in 4 ml methanol was added 100 mg K_2CO_3 (0 72 mmol, in 0.5 ml water). The resulting reaction mixture was stirred at room temperature overnight. The methanol was removed under vacuum. 1M HCl was added until the mixture is acidic Dichloromethane (20 ml) and 5 ml water was added Organic layer was dried with magnesium sulfate. Dichloromethane was removed under vacuum to give the title compound (15 mg, 86%)

^{1}H-NMR ($CDCl_3$) δ· 1 1 (3H, d), 1.1 (1H, m), 2.0 (3H, s), 2.3 (1H, m), 3.8 (3H, s), 4.8 (1H, m), 5 6 (1H, m), 6.5 (1H, d), 6.6 (2H, d), 6 9 (1H, t), 7 1-7 4 (6H, m), 8.1 (2H, d)

MS m/z 460 (M+2).

[00805] (2*S*,4*R*)-N-(3-Aminomethyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-38)

[00806] (2*S*,4*R*)-N-(3-Aminomethyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared from (2*S*, 4*R*)-N-(3-cyano-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. (2*S*, 4*R*)-N-(3-cyano-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following standard procedure C, substituting 3-cyanophenylboronic acid for 4-fluorobenzoyl chloride To a mixture of (2*S*, 4*R*)-N-(3-cyano-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (48mg,0.11mmol) in 2ml ethanol was added cobalt chloride (14 mg, 0.11mmol). Sodium borohydride (12 mg, 0.33 mmol) was added at 0 °C, and the temperature was held at 0 ° for 30 min. The mixture was then warmed to rt, and stirred overnight The reaction was quenched by adding saturated aqueous ammonium chloride. The separated aqueous layer was extracted with ethyl acetate The combined extracts were washed with water and brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure The crude oil was purified by HPLC to give the title compound (10mg, 10%).

^{1}H-NMR ($CDCl_3$) δ: 1.1-1.2 (4 H, m), 2.0 (3 H, s), 2.3 (1 H, m), 3.4 (2 H, br), 3 8 (3 H, s), 4 3 (1 H, d), 4.8 (2 H, d), 5.6 (1 H, br), 6 4 (1 H, m), 6.6 (2 H, m), 6.9 (1 H, m), 7.1-7.4 (8H, m).

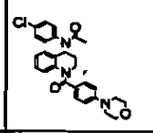
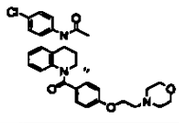
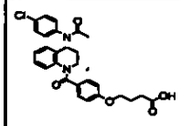
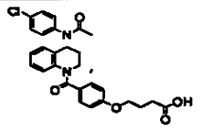
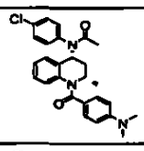
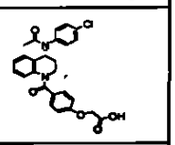
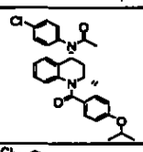
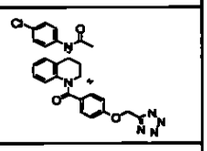
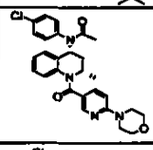
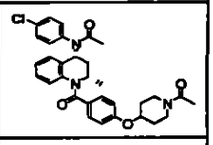
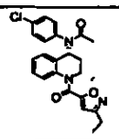
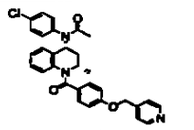
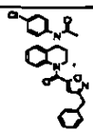
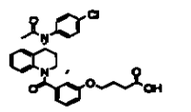
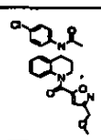
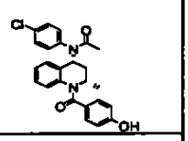
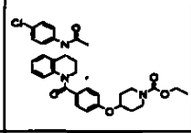
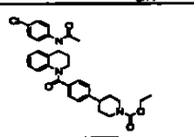
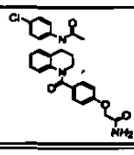
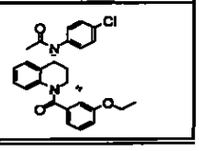
MS m/z 444 (M+1)

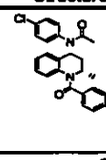
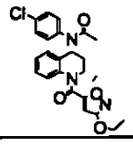
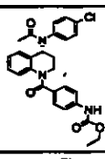
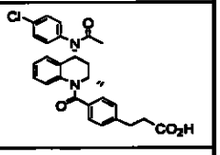
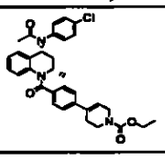
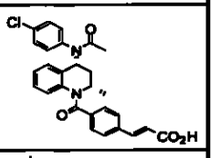
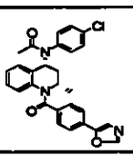
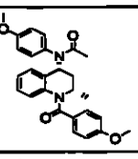
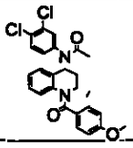
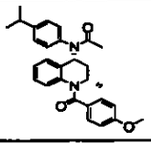
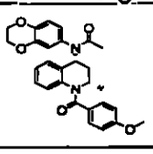
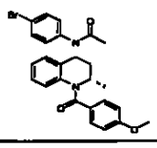
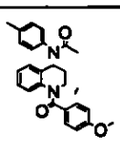
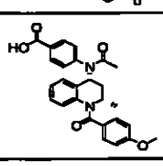
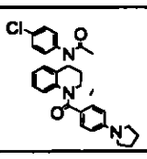
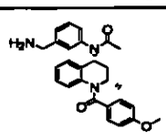
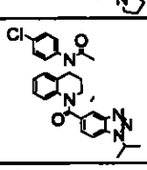
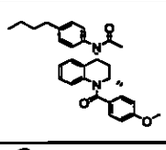
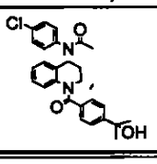
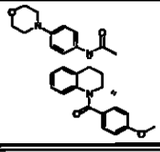
[00807] (2*S*,4*R*)-N-(4-Butyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (C-39)

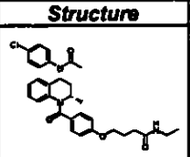
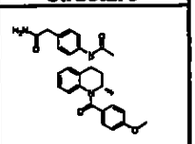
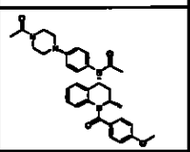
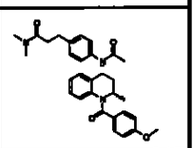
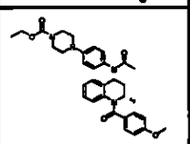
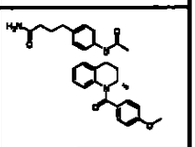
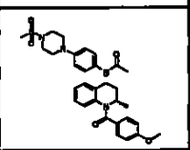
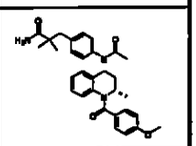
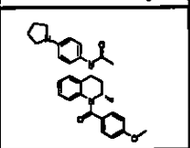
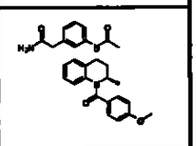
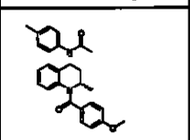
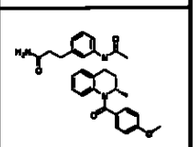
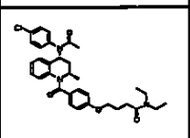
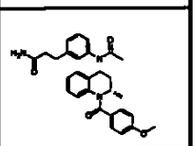
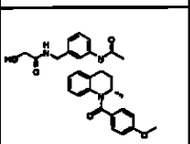
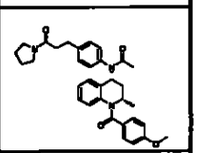
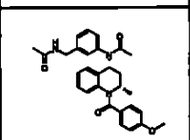
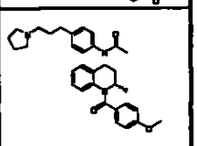
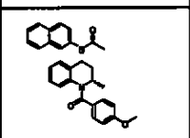
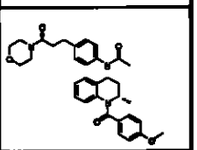
[00808] (2*S*,4*R*)-N-(4-Butyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure C, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride and 4-butylphenylboronic acid for 4-chlorophenylboronic acid ^{1}H-NMR ($CDCl_3$) δ 0 9 (3 H, m), 1 2 (3 H, d), 1.4 (3 H, m), 1 6 (2 H, m), 2 0 (3 H, s), 2 4 (1 H, m), 2 6 (2 H, m), 3.8 (3 H, s), 4.8 (1 H, m), 5 6 (1 H, br), 6 5 (1 H, d), 6 7 (2 H, d), 7 0 (1 H, m), 7 1-7 2 (7 H, m), 7 4 (1 H, d)
MS m/z 471 (M+1).

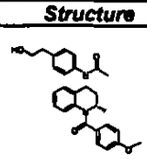
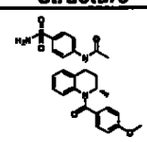
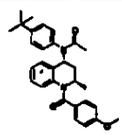
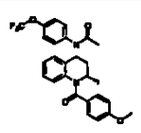
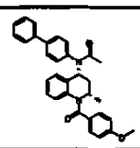
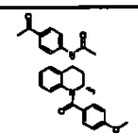
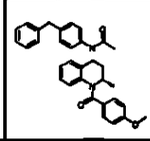
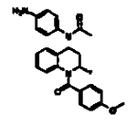
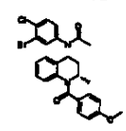
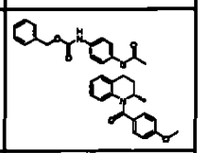
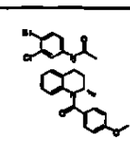
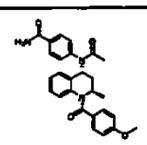
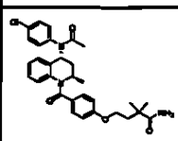
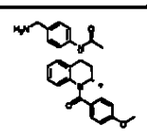
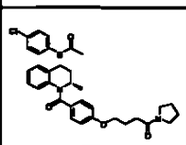
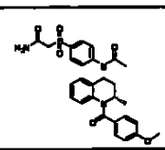
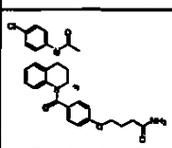
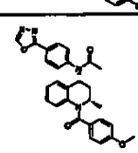
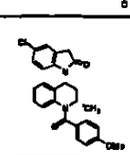
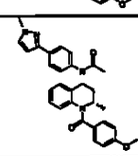
[00809] Compounds **C-40- C-147** can be prepared by the schemes set forth in Schemes 15-16 and by the general procedures C and others described herein. Those skilled in the art will be able to recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein.

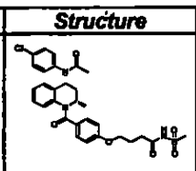
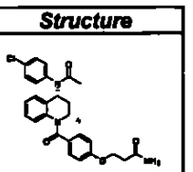
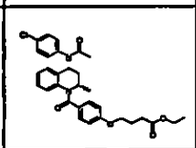
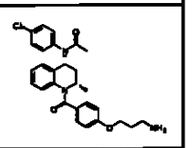
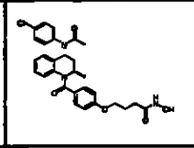
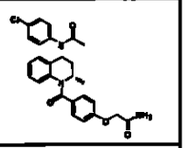
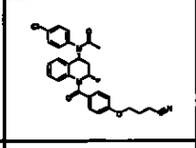
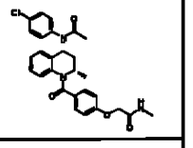
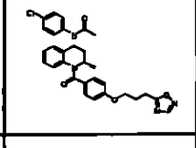
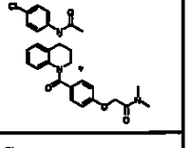
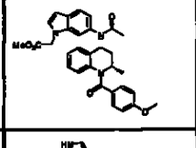
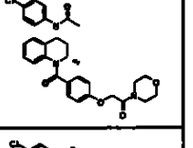
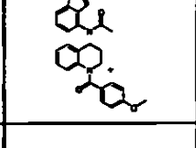
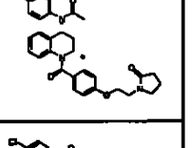
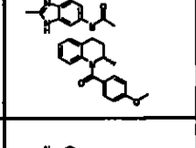
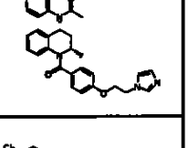
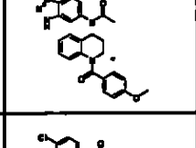
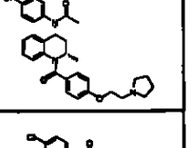
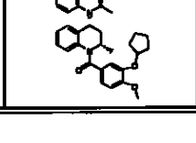
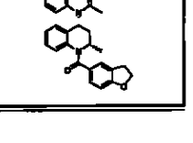
Table 3: Compounds Derived from General Procedure C

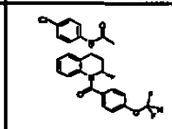
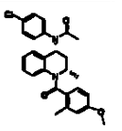
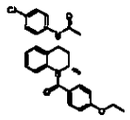
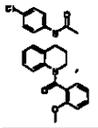
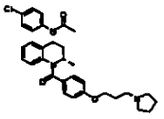
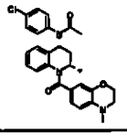
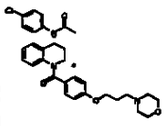
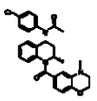
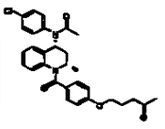
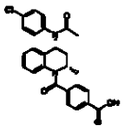
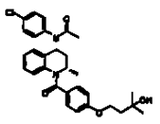
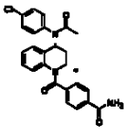
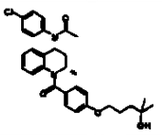
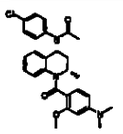
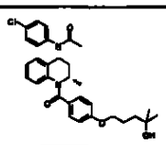
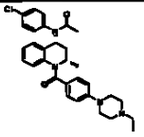
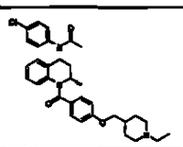
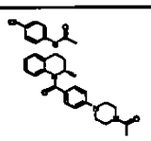
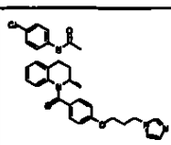
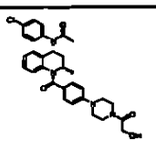
No.	Structure	No.	Structure
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C-3		C-13	
C-4		C-14	
C-5		C-15	
C-6		C-16	
C-7		C-17	
C-8		C-18	
C-9		C-19	
C-10		C-20	

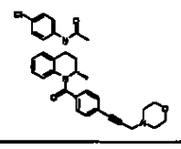
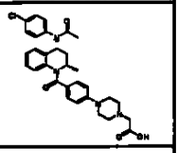
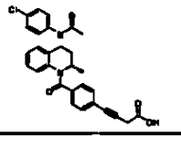
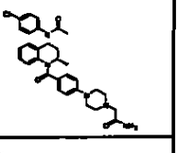
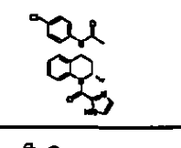
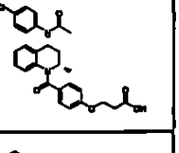
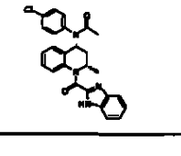
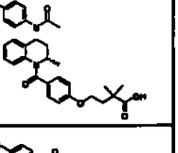
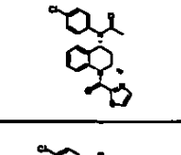
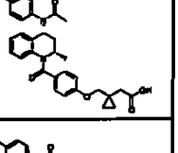
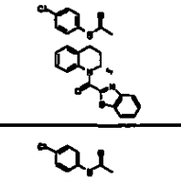
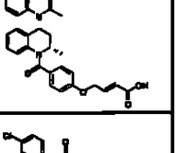
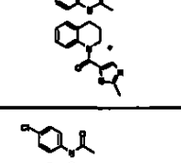
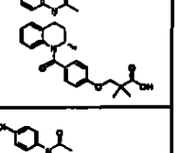
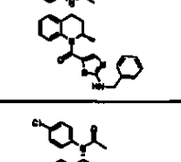
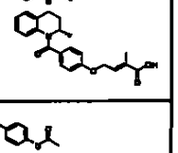
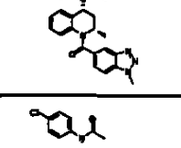
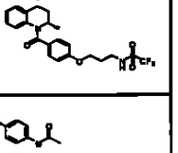
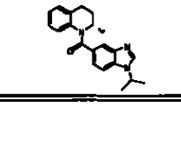
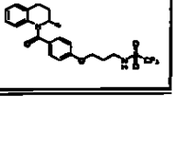
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C-22		C-32	
C-23		C-33	
C-24		C-34	
C-25		C-35	
C-26		C-36	
C-27		C-37	
C-28		C-38	
C-29		C-39	
C-30		C-40	

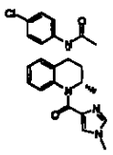
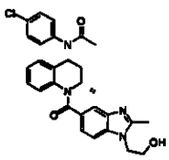
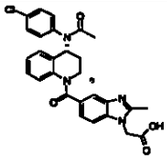
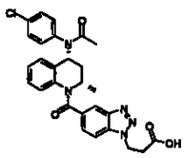
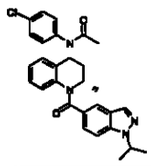
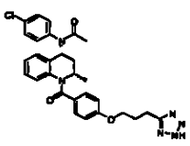
No.	Structure	No.	Structure
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C-42		C-52	
C-43		C-53	
C-44		C-54	
C-45		C-55	
C-46		C-56	
C-47		C-57	
C-48		C-58	
C-49		C-59	
C-50		C-60	

No.	Structure	No.	Structure
C-61		C-71	
C-62		C-72	
C-63		C-73	
C-64		C-74	
C-65		C-75	
C-66		C-76	
C-67		C-77	
C-68		C-78	
C-69		C-79	
C-70		C-80	

No.	Structure	No.	Structure
C-81		C-91	
C-82		C-92	
C-83		C-93	
C-84		C-94	
C-85		C-95	
C-86		C-96	
C-87		C-97	
C-88		C-98	
C-89		C-99	
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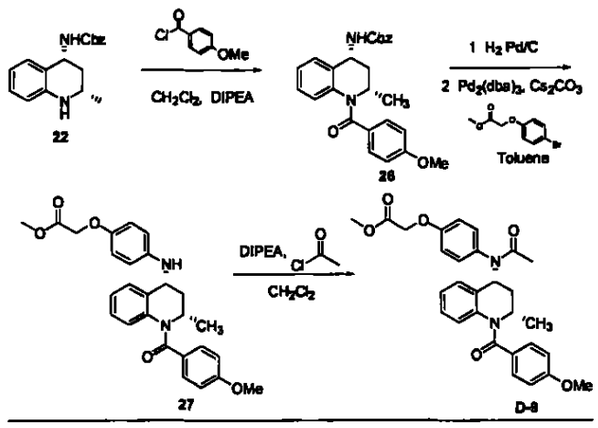
No.	Structure	No.	Structure
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C-103		C-113	
C-104		C-114	
C-105		C-115	
C-106		C-116	
C-107		C-117	
C-108		C-118	
C-109		C-119	
C-110		C-120	

No.	Structure	No.	Structure
C-121		C-131	
C-122		C-132	
C-123		C-133	
C-124		C-134	
C-125		C-135	
C-126		C-136	
C-127		C-137	
C-128		C-138	
C-129		C-139	
C-130		C-140	

No.	Structure	No.	Structure
C-141			
C-142			
C-143			
C-144			
C-145			
C-146			

General Procedure D

Scheme 15



[00810] **(2*S*,4*R*)-((4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenoxy)-acetic acid methyl ester (D-9)**

[00811] (2*S*,4*R*)-((4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenoxy)-acetic acid methyl ester was prepared from (2*S*,4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester as shown below (2*S*,4*R*)-(2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (7.6 g, 25 65 mmol) was dissolved in dichloromethane (50 mL) and the resulting solution was cooled to 0 °C. Triethylamine (14 3 mL) followed by freshly distilled anisoyl chloride (8.75 mL, 51 3 mmol) dissolved in dichloromethane (15 mL) were added dropwise to this solution. The resulting reaction mixture was allowed to warm to room temperature and stir over night. The mixture was partitioned between dichloromethane and 1 M sodium hydroxide. The extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated. The crude amide was purified by silica gel chromatography (2:1 hexane:ethyl acetate) to afford pure product (10 g, 91 %)

[00812] The (2*S*,4*R*)-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester thus formed (10 g) was dissolved in ethanol (400 mL). Palladium (10 % on Carbon) was added. The black suspension was stirred under an atmosphere of hydrogen for 3 h. The mixture was filtered and concentrated The crude amine was purified by filtration through a short silica plug (elution with ethyl acetate to 90/10 ethyl acetate/methanol gradient) to afford pure amine (5 17 g, 72 %)

[00813] (2*S*,4*R*)-(4-Amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxyphenyl)-methanone (100 mg, 0.34 mmol), methyl-2-(4-bromophenoxy)-acetate (91 mg, 0.37 mmol), $Pd_2(dba)_3$

(17 mg, 0 02 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (8 mg, 0 00002 mol) and cesium carbonate (0.163 g, 0.0005 mol) were taken in a round bottom flask which was then flushed with nitrogen gas through a rubber septum Toluene (2 mL) was injected into the flask through the rubber septum and the reaction mixture was stirred at 100 °C for 24 h. After cooling to room temperature the reaction mixture was filtered through Celite® and evaporated to give the crude product (0.236g) This crude product was purified by silica gel chromatography eluting with 100% hexanes to 50/50 hexanes/ethyl acetate gradient give the title compound (37mg, 24%).

[00814] Freshly distilled acetyl chloride (0.5 mL) was added to a solution of the aniline thus prepared (0.037g, 0.00008 mol) followed by diisopropylethylamine (0.0114g, 0.015 mL, 0.088 mmol) in dichloromethane (0.5 mL), the mixture was stirred at room temperature for 2 days. The reaction mixture was neutralized with 1 M sodium bicarbonate. The organic layer was separated, washed thrice with water, brine, dried over magnesium sulfate and evaporated. The resulting crude product was purified by silica gel chromatography eluting with (0% to 70% ethyl acetate in hexanes to afford the titled compound (15mg, 38%).

^{1}H- NMR ($CDCl_3$) δ 1.12-1.14 (4 H, m), 2 02 (3 H, s), 2 18 - 2 43(1 H, m), 3.75 (3 H, s) 3.82 (3 H, s), 4 65 (2 H, s), 4 67 - 4.82 (1 H, m), 5 45 - 5.73 (1 H, broad), 6.52 (1 H), 6.68 (2 H, d), 6 89 - 6.95 (3 H, m), 7 13 - 7.21 (5 H, m), 7 32 (1 H, d)

MS m/z 504 (M + 1).

[00815] (2*S*,4*R*)-(4-{Acetyl-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-amino}-phenoxy)-acetic acid (D-10)

[00816] (2*S*,4*R*)-(4-{Acetyl-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-amino}-phenoxy)-acetic acid was prepared from (2*S*,4*R*)-(4-{acetyl-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-amino}-phenoxy)-acetic acid methyl ester (15 mg, 0.03 mmol). The methyl ester was dissolved in methanol (1 mL), sodium hydroxide (1 mL, 0.1 M in water) was added and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was acidified with hydrochloric acid (1 M) and concentrated under reduced pressure The residue was extracted with ethyl acetate and the extract was washed thrice with water, brine, dried over sodium sulphate, filtered and concentrated to yield the title compound (13 mg, 89%).

^{1}H- NMR ($CDCl_3$) δ 1 07 (4 H, m), 1 99 (3 H, s), 2 12 - 2.38(1 H, broad), 3.7 (3 H, s), 4.61(2 H, s), 4.66 - 4.78(1 H, m), 5.47 - 5 75 (1 H, broad), 6 49 (1 H, d), 6 64(2 H, d), 6.86 - 6.9(3 H,m), 7 09 - 7.16(5 H, m), 7.27 (1 H,d).

MS m/z 489 (M^+), 490(M+1)

[00817] (2*S*,4*R*)-2-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-2-methyl-propionic acid (D-1)

[00818] (2*S*,4*R*)-2-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-2-methyl-propionic acid was prepared via saponification of 2-(4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-2-methyl-propionic acid methyl ester, as described in the synthesis of (2*S*,4*R*)-(4-{acetyl-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-amino}-phenoxy)-acetic acid The methyl ester was prepared following general procedure D, substituting 2-(4-bromo-phenyl)-2-methyl-propionic acid for methyl-2-(4-bromophenoxy)-acetate.

^{1}H-NMR (300 MHz, CD_3OD) δ. 1.07- 1 18 (m, 4 H), 1.58 (s, 6 H), 2.02 (s, 3 H), 2.42 – 2 56 (m, 1 H), 3.76 (s, 3 H), 4.74 (ddd, 1 H), 5 55 (br s, 1 H), 6.56 (d, 1 H), 6 75 (d, 2 H), 6.97 (dd, 1 H), 7.13 – 7.27 (m, 3 H), 7.36 (d, 2 H), 7.42 – 7 55 (m, 3 H)

[00819] **(2*S*,4*R*)-4-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-2-chloro-phenyl)-4-oxo-butyric acid (D-2)**

[00820] (2*S*,4*R*)-4-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-2-chloro-phenyl)-4-oxo-butyric acid was prepared from the corresponding methyl ester following the procedure above for the synthesis of (2*S*,4*R*)-(4-{acetyl-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-amino}-phenoxy)-acetic acid. The corresponding methyl ester was prepared following general procedure D, substituting 4-(4-bromo-2-chloro-phenyl)-4-oxo-butyric acid methyl ester for methyl-2-(4-bromophenoxy)-acetate

^{1}H-NMR (300 MHz, CD_3OD) δ. 1.10 – 1 19 (m, 4 H), 2 08 (br s, 3 H), 2 41 – 2 56 (m, 1 H), 2 69 – 2.74 (m, 2 H), 3.20 – 3 26 (m, 2 H), 3.75 (s, 3 H), 4 74 (ddd, 1 H), 5.45 – 5.62 (br s, 1 H), 6 57 (d, 1 H), 6 74 (d, 2 H), 6.98 (dd, 1 H), 7.16 (d, 2 H), 7 20 – 7.27 (m, 1 H), 7.42 – 7.49 (m, 2 H), 7 60 (br s, 1), 7.73 (d, 1 H)

MS m/z. 549 (M + 1).

[00821] **(2*S*,4*R*)-N-(4-Dimethylsulfamoyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (D-3)**

[00822] (2*S*,4*R*)-N-(4-Dimethylsulfamoyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure D, substituting 4-bromo-N,N-dimethyl-benzenesulfonamide for methyl-2-(4-bromophenoxy)-acetate.

^{1}H-NMR ($CDCl_3$) δ. 1 1 (3 H, d), 1.1 (1H, m), 2.0 (3 H, s), 2 3 (1 H, m), 2.8 (6 H, s), 3.8 (3 H, s), 4 8 (1 H, m), 5.6 (1 H, m), 6.6 (1 H, d), 6.7 (2 H, d), 6.9 (1 H, t), 7.2 (3 H, m), 7.3 (1 H, m), 7 5 (2 H, d), 7.8 (2 H, d).

MS m/z: 522 (M+1)

[00823] **(2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide (D-4)**

[00824] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-[4-(pyrrolidine-1-sulfonyl)-phenyl]-acetamide was prepared following general procedure D, substituting 1-(4-bromo-benzenesulfonyl)-pyrrolidine for methyl-2-(4-bromophenoxy)-acetate.

^{1}H-NMR ($CDCl_3$) δ: 1 1 (3 H, d), 1.1 (1 H, m), 1.7 (4 H, m), 2.0 (3 H, s), 2 3 (1 H, m), 3 3 (4 H, m), 3 7 (3 H, s), 4.7 (1 H, m), 5 6 (1 H, m), 6.5 (1 H, d), 6 6 (2 H, d), 6.9 (1 H, t), 7 3 (4 H, m), 7.4 (2 H, d), 7 9 (2 H, d).

MS m/z. 548 (M+1)

[00825] **(2*S*,4*R*)-N-(4-Methanesulfonyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (D-5)**

[00826] (2*S*,4*R*)-N-(4-Methanesulfonyl-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure D, substituting 1-bromo-4-methanesulfonyl-benzene for methyl-2-(4-bromophenoxy)-acetate.

^{1}H-NMR ($CDCl_3$) δ: 1 1 - 1 2 (3 H, m), 2 0 - 2 2 (4 H, m), 2.3 (1 H, m), 3.1 (3 H, s), 3.7 (3 H, s), 4.8 (1 H), 5.6-5.8 (1 H, br), 6 5 (1 H, d), 6 6 (2 H, d), 6.9 (1 H, t), 7.1-7.3 (4 H, m), 7.4 (2 H, d), 8.0 (2 H, d)

MS m/z 493 (M+1).

[00827] **(2*S*,4*R*)-3-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionic acid (D-6)**

[00828] (2*S*,4*R*)-3-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionic acid was prepared from (2*S*,4*R*)- N-(4-bromo-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. (2*S*,4*R*)- N-(4-Bromo-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was converted to the acrylic acid using the same procedure described in the synthesis of (±)-3-[4-[(4-chloro-phenyl)-propionyl-amino]-1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-6-yl]-acrylic acid. The reduction and saponification were carried out as in the procedure describing the preparation of (2*S*,4*R*)-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-propionic acid.

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.12 (3H, d), 1 20-1.24 (1H, m), 2 00 (3H, s), 2.22-2.38 (1H, m), 2.52 (2H, t), 3.00 (2H, t), 3.72 (3H, s), 4 64-4.79 (1H, m), 5.44-5.70 (1H, m), 6.50 (1H, d), 6 65 (2H, d), 6.90 (1H, t), 7.10-7.28 (7H, m), 7.32 (1H, d)

[00829] (2*S*,4*R*)-3-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionamide (D-7)

[00830] (2*S*,4*R*)-3-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionamide was prepared from (2*S*,4*R*)-3-(4-{Acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionic acid To a solution of 3-(4-{acetyl-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-amino}-phenyl)-propionic acid (21 mg, 0.042 mmol) in dimethylformamide (200 µl) was added HATU (24 mg, 0.063 mmol), HOBt (8.5 mg, 0.063 mmol), NH_4Cl (4.5 mg, 0.084 mmol) and DIPEA (29 µl, 0 168 mmol). Upon consumption of the starting unit (2.5 hours), the mixture was diluted with EtOAc (10 ml) and washed with sat. $NaHCO_3$ (4 X 10 ml) The EtOAc layer was collected, dried over Na_2SO_4, filtered, and concentrated to afford the title compound (17 2 mg, 82 %).

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.09 (3H, d), 1 20-1.24 (1H, m), 2.02 (3H, s), 2.22-2.38 (1H, m), 2.52 (2H, t), 3.00 (2H, t), 3.73 (3H, s), 4 64-4.79 (1H, m), 5.30-5.70 (3H, m), 6.50 (1H, d), 6.68 (2H, d), 6 91 (1H, t), 7.10-7 28 (7H, m), 7.32 (1H, d).

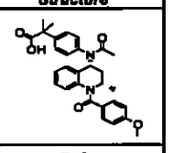
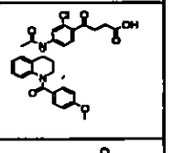
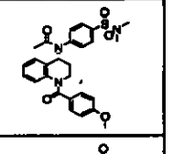
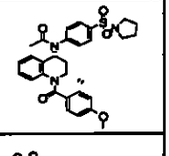
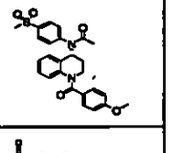
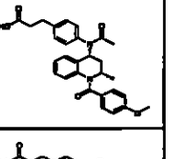
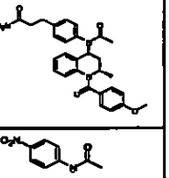
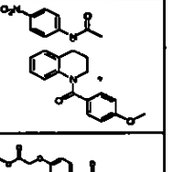
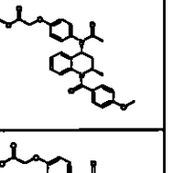
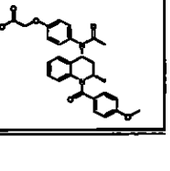
[00831] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-nitro-phenyl)-acetamide (D-8)

[00832] (2*S*,4*R*)-N-[1-(4-Methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-nitro-phenyl)-acetamide was made following general procedure D, substituting 4-bromonitrobenzene for methyl-2-(4-bromophenoxy)-acetate.

^{1}H-NMR ($CDCl_3$ 300 MHz) δ 1.12 (3H, d), 1 20-1 24 (1H, m), 2 07 (3H, s), 2.20-2 35 (1H, m), 3 73 (3H, s), 4 66-4.81 (1H, m), 5 50-5.78 (1H, m), 6 55 (1H, d), 6.68 (2H, d), 6.96 (1H, t), 7.10-7.32 (4H, m), 7.46 (2H, d), 8.28 (2H, d)

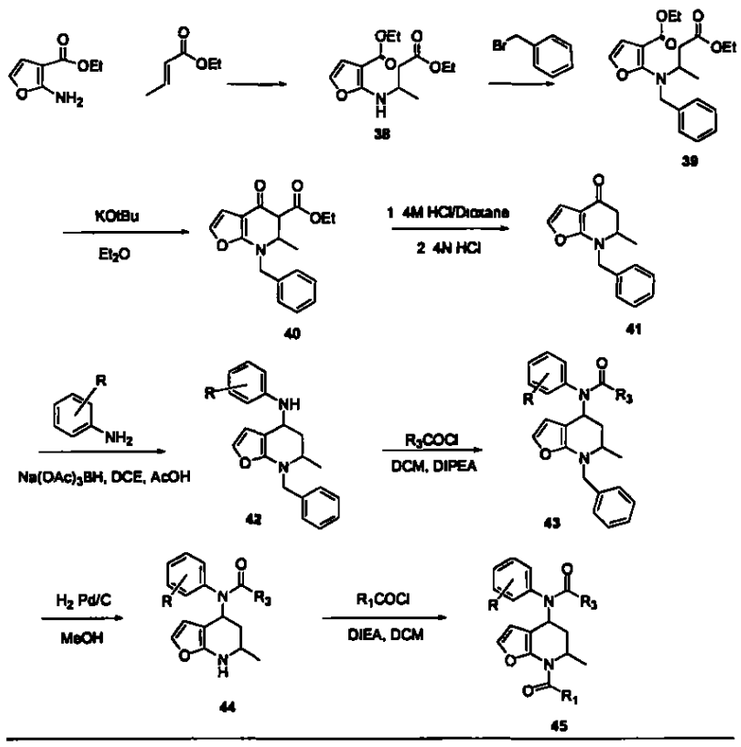
MS m/z 460 (M + 1).

Table 4: Compounds Derived from General Procedure D

No	Structure
D-1	
D-2	
D-3	
D-4	
D-5	
D-6	
D-7	
D-8	
D-9	
D-10	

General procedure E

Scheme 16



[00833] (±)-N-(7-acetyl-6-methyl-4,5,6,7-tetrahydrohetero[2,3-b]pyridin-4-yl)-N-substituted phenylacetamides (45)

[00834] 2-(2-Ethoxycarbonyl-1-methyl-ethylamino)-furan-3-carboxylic acid ethyl ester (38)

[00835] 2-Amino-furan-3-carboxylic acid ethyl ester and but-2-enoic acid ethyl ester is dissolved in ethanol and heat to reflux in the presence of Al_2O_3, until no starting material remains and filter and concentrate down The residue is purified by flash chromatography to afford the corresponding diketone

[00836] 2-[Benzyl-(2-ethoxycarbonyl-1-methyl-ethyl)-amino]-furan-3-carboxylic acid ethyl ester (39)

[00837] The synthesis is accomplished using the alkylation described for the synthesis of A-164, substituting benzyl bromide for the 3-methoxybenzyl bromide.

[00838] 7-Benzyl-6-methyl-4-oxo-4,5,6,7-tetrahydro-furo[2,3-b]pyridine-5-carboxylic acid ethyl ester (40)

[00839] To a solution of the diester in ethyl ether at room temperature is added potassium tert-butoxide and the mixture is allowed to stir for 1 hour The mixture is filtered to remove any hydrolyzed material The solvent was removed in vacuo to afford the potassium salt of the bicyclic ester.

[00840] 7-Benzyl-6-methyl-6,7-dihydro-5H-furo[2,3-b]pyridin-4-one (41)

[00841] The α-keto-ester is dissolved in 4M HCl in dioxane and stirred for 2 hours at room temperature. Then 4 N HCl is added and the mixture was heated in a 100 °C oil bath for 12 hours. The mixture is then cooled to room temperature and neutralize with 1N NaOH The aqueous layer is extracted with ethyl acetate, dried over magnesium sulfate and filter Evaporate the solvent *in vacuo* and purify the residue by flash chromatography to afford the corresponding ketone

[00842] (±)- (7-Benzyl-6-methyl-4,5,6,7-tetrahydro-furo[2,3-b]pyridin-4-yl)-substituted phenyl-amine (42)

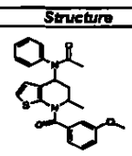
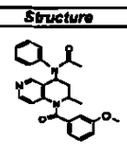
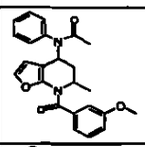
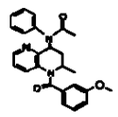
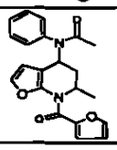
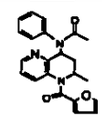
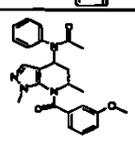
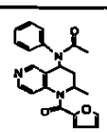
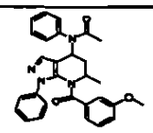
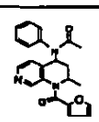
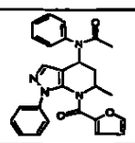
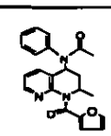
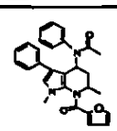
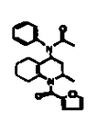
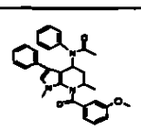
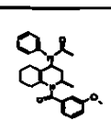
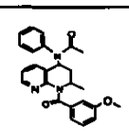
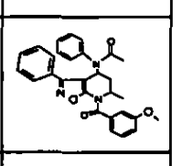
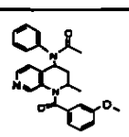
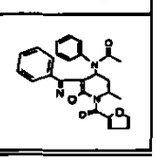
[00843] Synthesis of the substituted phenyl amine is accomplished using the procedure described for **F-1**, substituting aniline for the corresponding aniline.

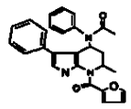
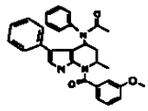
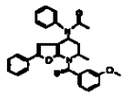
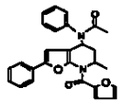
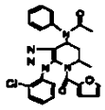
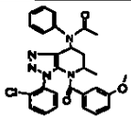
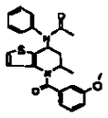
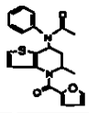
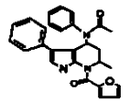
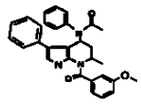
[00844] (±)-N-(7-Benzyl-6-methyl-4,5,6,7-tetrahydro-furo[2,3-b]pyridin-4-yl)-N-substituted phenyl-substituted amide (45)

[00845] Synthesis of the corresponding phenyl amide is accomplished using the hydrogenation and acylation procedures described in general procedure B with the corresponding acid chlorides Representative examples of compound **45** are shown in the table below

[00846] Compounds **E-1 – E-30** can be prepared by the schemes set forth in Schemes 18 and by the general procedures E 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

Table 5: Examples using General Procedure E

No	Structure	No.	Structure
E-1		E-11	
E-2		E-12	
E-3		E-13	
E-4		E-14	
E-5		E-15	
E-6		E-16	
E-7		E-17	
E-8		E-18	
E-9		E-19	
E-10		E-20	

No	Structure	No	Structure
E-21			
E-22			
E-23			
E-24			
E-25			
E-26			
E-27			
E-28			
E-29			
E-30			

General Procedures F

[00847] N-[1-(3-Methoxy-benzoyl)-2,2-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (F-1)

[00848] N-[1-(3-Methoxy-benzoyl)-2,2-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide from 4-(hydroxy-2,2-dimethyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone which was synthesized according to reference Hamann, L G , Higuchi, R. I. , Zhi, L , Edwards, J P ; Wang, X ; Marrschke, K B ; Kong, J. W.; Farmer, L J., Jones, T. D. *J Med Chem* 1998, *41*, 623 This was further elaborated to N-[1-(3-methoxy-benzoyl)-2,2-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide using an in-situ formation of the iodide and displacement with the aniline according to the following procedure

[00849] To a chilled solution of (4-hydroxy-2,2-dimethyl-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone (500 mg, 1.6mmol) in 10 ml dichloromethane was added slowly 0.8 ml iodotrimethylsilane (5 6mmol) at 0 °C The resulting reaction mixture was stirred at 0 °C for 6 hours. Then the mixture was concentrated under vacuum. The residue was dissolved in 12 ml THF. $BaCO_3$ (630mg, 3.2mmol) and aniline (0 17 ml, 1.92mmol) was added The mixture was stirred at RT overnight The mixture was filtered and the filtrate was concentrated under vacuum The residue was purified by silica gel chromatography, eluting with ethyl acetate-hexane (1:4) to give (2,2-dimethyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone (150 mg, 24%)

[00850] To a solution of (2,2-dimethyl-4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone in methylene chloride (5 mL) was added diisopropylethylamine followed by acetyl chloride. The mixture was stirred at room temperature over night The mixture was poured into water and extracted with dichloromethane The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered, dried and concentrated. The crude residue was purified by silica gel chromatography (50% hexanes/50% ethyl acetate) to afford N-[1-(3-methoxy-benzoyl)-2,2-dimethyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide.

^{1}H-NMR ($CDCl_3$) δ· 1 5 (1H, m), 1.6 (3H, s), 1 7 (3H, s), 1.9 (1H, m), 2 0 (3H, 3), 3 7 (3H, m), 5 8 (1H, m), 6 5 (1H, d), 6.6-7 1 (8H, m), 7 2 (1H, m), 7 3-7.5 (3H, d)

MS m/z: 429 (M+1).

[00851] (2*S*,4*R*)-4-Chloro-N-ethyl-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-benzamide (F-2)

[00852] (2*S*,4*R*)-4-Chloro-N-ethyl-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-benzamide was synthesized as described in general procedure C, except following benzyl carbamate removal the amine was modified in the following manner To a solution of (2*S*,4*R*)-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxy-phenyl)-methanone (200 mg,

0 68mmol) in 20 ml dichloromethane was added acetaldehyde (0.042 mL, 0 75mmol). The reaction mixture was stirred 30 min at room temperature Then sodium triacetoxyborohydride (0 156 g, 0 75mmol) was added and the resulting reaction mixture was stirred at room temperature for 6 hours *N,N*-diisopropylethylamine (0 3 mL, 2.3mmol) and 4-chlorobenzoyl chloride (0 4 mL, 3 1mmol) was added and stirred at room temperature overnight Dichloromethane (40 ml) was added. The mixture was washed with 30 ml sodium hydroxide (1N). The organic layer was dried with magnesium sulfate, filtered and concentrated *in vacuo* The residue was purified by silica gel chromatography, eluting with ethyl acetate-dichloromethane (1:4) to give 80 mg (24 %) title compound

^{1}H-NMR ($CDCl_3$) δ. 1.2-1 4 (7H, m), 1.7 (1H, m), 2.7 (1H, m), 3.1 (1H, m), 3.8 (3H, s), 4.2 (1H, m), 4 8 (1H, m), 6.5 (1H, d), 6.6 (2H, d), 6 8 (2H, m), 6.9 (1H, m), 7.1-7.5 (6H, m)

MS m/z 463 (M+1).

[00853] N-[1-(3-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide (F-3)

[00854] N-[1-(3-Methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide was made from 1-(4-methoxy-benzoyl)-2,3-dihydro-1H-quinolin-4-one which was synthesized according to reference Bellassou-Fargeau, M C.; Graffe, B., Sacquet, M C., Maitte, P. *J of Heter Chem* **1985**, 22(3), 713. This was further elaborated to (4-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone by reduction of the ketone to the alcohol and in-situ formation of the iodide and displacement with the aniline according to the following procedure the following procedure. To a solution of 1-(3-methoxy-benzoyl)-2,3-dihydro-1H-quinolin-4-one (310 mg, 1 1mmol) in 5 ml methanol was added 410 mg sodium borohydride (4.4mmol). The resulting reaction mixture was stirred at room temperature for 3 hours. The mixture was concentrated under vacuum and the residue was purified by silica gel chromatography, eluting with ethyl acetate-hexane (1.2) to give (4-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone (215 mg, 69%) This was further elaborated to (3-methoxy-phenyl)-(4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-methanone using the following procedure To a chilled solution of (4-hydroxy-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxy-phenyl)-methanone in dichloromethane was added slowly iodotrimethylsilane at 0 °C. The resulting reaction mixture was stirred at 0 °C for 6 hours. Then the mixture was concentrated under vacuum The residue was dissolved in THF. $BaCO_3$ and aniline was added The mixture was stirred at room temperature overnight. The mixture was filtered and the filtrate was concentrated under vacuum The residue was purified by silica gel chromatography, eluting with ethyl acetate-hexane (1·4) to give (4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-(3-methoxy-phenyl)-methanone

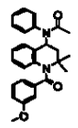
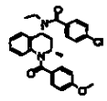
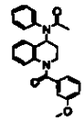
[00855] To a solution of (4-phenylamino-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxy-phenyl)-methanone in methylene chloride was added diisopropylethylamine followed by acetyl chloride The

mixture was stirred at room temperature over night The mixture was poured into water and extracted with dichloromethane. The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (50% hexanes/50% ethyl acetate) to afford (±)-N-[1-(3-methoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide

^{1}H-NMR ($CDCl_3$) δ 1 2 (1H, m), 1.9 (3H, s), 2 1 (1H, m), 2.3 (1H, m), 3 5 (1H, m), 3 7 (3H, m), 4.1 (1H, m), 6.4 (2H, m), 6.6 (1H, m), 6.8-7 3 (6H, m), 7 4 (3H, m), 7.5 (1H, d)

MS m/z: 401 (M+1).

Table 6: Structurally Diverse Series

No.	Structure	No	Structure
F-1			
F-2			
F-3			

[00856] The Disclosed Compounds Inhibit Binding of PGD_2 to CRTH2

[00857] This radioligand membrane binding assay evaluates the ability of compounds to inhibit [^{3}H] Prostaglandin D_2 (PGD_2) binding to the cloned human CRTH2 receptor stably expressed in HEK-293 cells (expressing human CRTh2 receptor and α subunit or the heterotrimeric G protein 16 were prepared by Biosignal Company) using Scintillation Proximity Assay.

[00858] A binding buffer containing 50mM Tris-HCl (pH 7.5), 5mM $MgCl_2$ and 1mM EDTA was 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 [^{3}H] PGD_2 at twotimes the final assay concentration were prepared and stored on ice before adding to wells. Cold PGD_2 at twenty times the final assay concentration was prepared and stored on ice before adding to wells defining non-specific binding (NSB) coming plates #3653 were used for this assay.

[00859] 10 mM stock concentrations of compounds in 100% DMSO were prepared and stored at room temperature. A 10 point concentration response curve was then constructed for each compound, starting at 10 μM (final assay concentration). The compounds were prepared at 40 times final assay concentrations with nine consequent-3-fold dilutions.

[00860] 0.1 μl of each concentration of compound were added to the appropriate well of the 384 plate and 2 μl of cold PGD_2 was added into the wells defining NSB 20 μl of [^{3}H] PGD_2 and then 20 μl of 2x of bead/membrane solution were then added to each well.

[00861] The plates were allowed to incubate at room temperature for approximately 2 hours and then counted on Packard Topcount using SPA tritium protocol for 1 minute/well

[00862] The percent inhibition of PGD_2 binding (PGD_2 used at the K_D value or lower) to the HEK-293 cell membranes was determined, the assay was always run as duplicate for n=1 for a total of n=2

[00863] Compounds A-3, A-11, A-16, A-17, A-20, A-24, A-35, A-49, A-51, A-54, A-55, A-67, A-70, A-72, A-73, A-81, A-82, A-120, A-130, A-131, A-132, A-143, A-144, A-147, A-153, A-156, A-157, A-159, B-7, B-9, B-11, B-13, B-18, B-20, B-26, B-28, B-34, B-39, B-40, B-47, B-51, B-58, B-59, B-63 to B-66, B-68, B-70, B-73, B-74, B-84, B-86, B-97, B-101 to B-112, C-33, C-37, C-38, D-1, D-2, D-6, D-10, F-3 have K_i <10 uM

[00864] Compounds A-8, A-53, A-58, A-124, A-126, A-154, B-53, B-100, F-1 have K_i <60 uM

[00865] All remaining compounds have K_i <1 uM

Ammonium acetate-standard conditions:

% A (Water)	95.0
% B (Acetonitrile)	5.0
% Ammonium acetate	0 1
Flow (ml/mın)	2 500
Stop Tıme (mıns)	3 8
Mın Pressure (bar)	0
Max Pressure (bar)	400
Oven Temperature Left(°C)	10.0
Oven Temperature Right(°C)	10.0

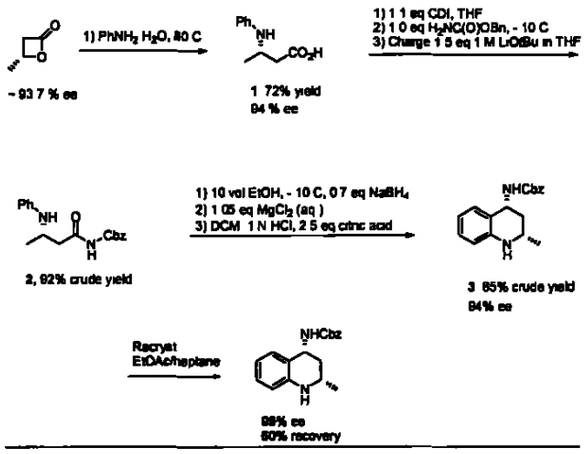
HP1100 LC Pump Gradient Tımetable

The gradıent Tımetable contaıns 4 entries which are:

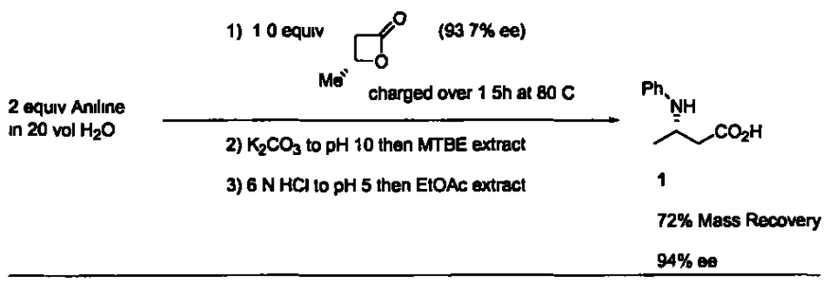
Time	A%	B%	C%	D%	Flow	Pressure
0.00	95.0	5.0	0.0	0 0	2.500	400
2.00	0.0	100.0	0.0	0.0	2.500	400
3.00	0.0	100.0	0.0	0.0	2.500	400
3.05	95.0	5.0	0.0	0 0	2.000	400

LC-MS data were acquired usıng the "Ammonıum acetate-standard" method unless otherwıse noted.

Scheme 17



Scheme 18



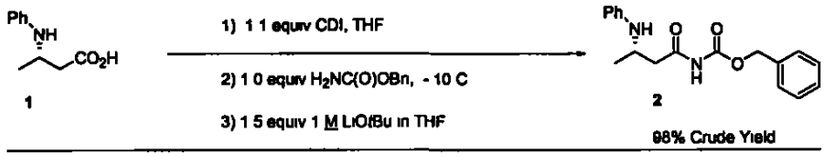
[00866] (S)-3-Phenylamino-butyric acid (1)

[00867] A jacketed 30-L 3-neck bottom-valve cylındrical reactor equıpped wıth overhead stırrer, reflux condenser, addıtıon funnel, and N_2 ınlet was flushed wıth N_2 Water (8.7 L) was charged

followed by aniline (423 L, 4 9 mol). Stirring was initiated and the internal temperature set for 80 °C After the internal temperature reached 77 °C, (R)-β-butyrolactone was charged over 1 5 h via addition funnel. The internal temperature was maintained between 80 – 81 7 °C during the course of addition Once addition was completed, reaction was cooled to 20 °C over 1 h. K_2CO_3 (250 g, 1.8 mol, 0 75 equiv) was charged as a solid, and the aqueous pH was determined to be 10. The aqueous phase was extracted with MTBE (3 x 2 L), and the extracts were discarded. After adjusting the pH of the aqueous phase to 5 with 6 N HCl (225 mL), it was extracted with EtOAc (3 x 2 L). After each extraction, the pH was checked and was readjusted to 5 with 6 N HCl as necessary. The combined EtOAc extracts were washed with saturated brine (2 L), dried with $MgSO_4$, and concentrated via rotary evaporation to produce a pink oil Recovery 300 g (72 %) Enantiomeric excess was determined by chiral HPLC to be 94%.

^{1}H-NMR ($CDCl_3$) δ. 7.24 (t, 2 H); 6 81 (t, 1 H); 6.73 (d, 2 H), 3 93 (m, 1 H); 2,68 (dd, 1 H); 2.51 (dd, 1 H); 1.30 (d, 3 H).

Scheme 19

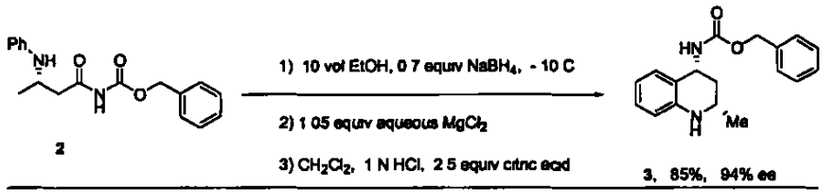


[00868] (S)-(Phenylamino-butyryl)-carbamic acid benzyl ester (2)

[00869] A 5-L, jacketed, glass reactor equipped with overhead stirrer, addition funnel and thermocouple was flushed with N_2. A solution of (S)-3-phenylaminobutyric acid (1, 100g, 558 mmol) in 800 mL THF (8 volumes relative to amino acid) was charged to the reactor. The internal temperature of the reaction mixture was set to 20 °C 1,1'-Carbonyldiimidazole (99.5 g, 614 mmol) was charged to the stirred solution to produce a clear solution along with a mild exotherm (5 °C) and much gas evolution. After 1 h, benzyl carbamate (84 3 g, 558 mmol) was charged, and the internal temperature was set for -15 °C At -15 °C, a 1 M solution of LiOt-Bu in THF (837 mL, 837 mmol) was charged to the reaction via addition funnel in 30 min so as to maintain the internal temperature between -10 and -15 °C. The solution becomes opaque pale brown and more viscous The internal temperature is maintained at about -10 °C for another 15 min and then allowed to warm to ambient temperature. After 16 h, the reaction was quenched by the addition of 1000 mL EtOAc (10 volumes) followed by the 280 mL 1N HCl and 1000 mL H_2O (10 volumes). The resulting aqueous phase was pH 9. The phases were separated, and the aqueous phase was extracted with another 600 mL EtOAc (6 volumes). The organic phases were combined and washed with 1000 mL 10% brine (10 volumes) The resulting organic solution of crude product is distilled down to a minimal volume of 500 to 700 mL at 170 to 200 torr and a pot temperature of 35 to 40 °C. This crude product was partitioned between 2.0 L 1N HCl (20 volumes) and 1.0 L MTBE. An amber oily phase formed which was the HCl salt of the product and was kept with the aqueous acid phase. The MTBE phase was extracted with another 1000 mL 1N HCl (10 volumes), and the combined HCl phases were backwashed with another 500 mL MTBE. The pH of the aqueous solution was adjusted to 9-10 by the addition of 495 mL saturated aqueous K_2CO_3 The aqueous basic solution was extracted twice with 800 mL EtOAc (8 volumes), and the organic phases were combined, washed with 500 mL brine, dried over Na_2SO_4 and evaporated to produce 161 g (92 %) of crude amber oil

^{1}H-NMR ($CDCl_3$) δ 7.35 (m, 5 H); 7 15 (t, 2 H); 6.72 (t, 1 H); 6.61 (d, 2 H), 5 15 (s, 2 H), 4 03 (m, 1 H), 3 02 (dd, 1 H); 2 84 (dd, 1 H), 1.28 (d, 3 H)

Scheme 20

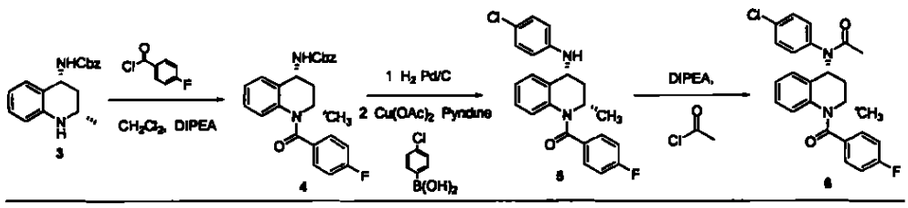


[00870] (2*S*,4*R*)- (2-Methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (3)

[00871] A 5-L, jacketed, glass reactor equipped with overhead stirrer, addition funnel and thermocouple was flushed with N_2. A solution of (S)-(Phenylamino-butyryl)-carbamic acid benzyl ester (2) (160g, 512 mmol) in EtOH (960 mL, 6 volumes) was charged to the reactor, and the internal temperature was set to -15 °C The $NaBH_4$ (13 6g, 359 mmol) was charged to the stirred solution in 3 portions. An aqueous solution of $MgCl_2$ $6H_2O$ (109g, 538 mmol in 110 mL water) was charged to the reactor via addition funnel over 1 h to maintain the internal temperature between -10 to -5 °C After the addition was complete, the internal temperature was adjusted to 0 °C and the mixture was allowed to stir another 30 min. The reactor was charged with 960 mL CH_2Cl_2 (6 volumes), citric acid (246g, 1280 mmol), and 960 mL 1N HCl (6 volumes) The internal temperature was set for 20 °C and the mixture was allowed to stir for 16 h The reaction mixture was diluted with 960 mL EtOAc and the aqueous pH was adjusted to 9 by the addition of 470 mL saturated aqueous K_2CO_3. The phases were separated and the organic phase washed twice with 640 mL water and then 640 mL brine. The organic phase was dried over Na_2SO_4 and evaporated to provide 130 g of a solid (86% yield). The crude product was recrystallized from 20 volumes of a 9/1, heptane/EtOAc mixture. The solid was slurried with 260 mL EtOAc (2 volumes) and 780 mL heptane (6 volumes) and heated to 75 °C to provide a clear solution At 75 °C, another 260 mL heptane (2 volumes) was slowly added followed by gradual cooling. Crystallization usually begins around 58 to 68 °C. At ambient temperature, another 1300 mL heptane (10 volumes) was slowly added. After stirring at ambient another 2 hr, the solids are filtered and washed with 4 volumes of 9/1 heptane/EtOAc. The solids were dried in a vacuum oven to provide 90 g (60% recovery). The product had an enantiomeric excess of 99.2% as determined by chiral HPLC

^{1}H-NMR ($CDCl_3$) δ: 7 38 (m, 5H); 7 22 (d, 1H); 7.07 (t, 1 H), 6 78 (t, 1 H); 6.69 (d, 1 H); 5.17 (s, 2 H), 5 07 (m, 1 H); 4.94 (d, 1 H); 3 58 (m, 1 H), 2 33 (m, 1 H); 1.60 (q, 1 H); 1.30 (d, 3 H)

Scheme 21



[00872] General Procedure G: (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (6)

[00873] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (1 0 g, 3.38 mmol) in methylene chloride (50 mL) at room temperature was added diisopropylethylamine (650 uL, 3.72 mmol) followed by 4-fluorobenzoyl chloride The reaction was stirred over night at room temperature. The mixture was poured into water and extracted with ethyl acetate The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford the pure amide (720 mg, 51 %)

[00874] (2*S*,4*R*)-[1-(4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (720 mg, 1 73 mmol) was dissolved in ethanol (30 mL). The vessel in which resided the resulting solution was evacuated and backfilled with argon A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen Reaction was complete after 4 h. The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution was filtered through an Celite ® and concentrated to afford the crude amine.

[00875] To a solution of (2*S*, 4*R*)- (4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-fluoro-phenyl)-methanone (1.0 g, 3.5 mmol) in DMF (20 mL, dry) was added 4-chlorophenylboronic acid (1.1 g, 7.0 mmol), pyridine (850 uL, 10.5 mmol) and copper(II)acetate (1.27 g, 7.0 mmol) The heterogeneous green mixture was stirred open to air for 1 h and then warmed to 60 °C and stirred over night (14 h). The mixture was then cooled to rt, poured into rapidly stirred ethyl acetate (150 mL), solids were removed by filtration through Celite ®. The extracts were washed several times with water and then once with brine. The extracts were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford the aniline product (250 mg, 18 %) as a yellow oil.

[00876] To a solution of (2*S*, 4*R*)- [4-(4-chloro-phenylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(4-fluoro-phenyl)-methanone (250 mg, 0 636 mmol) in acetyl chloride (5 mL) was added diisopropylethylamine (120 uL, 0.70 mmol) The mixture was stirred at rt 4 h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure N-(4-chloro-phenyl)-N-[1-(4-fluoro-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (200 mg, 71 %).

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.1 (m, 1H), 2.0 (d, 3H), 2.3 (m, 1H), 4.7 (m, 1H), 5 6 (m, 1H), 6.5 (d, 1H),6.7-7 0 (m, 3H), 7.1-7 4 (m, 8H)

MS m/z 436 (M+1).

[00877] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid ethyl ester (G-1)

[00878] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid ethyl ester was made following general procedure G, substituting 4-(4-chlorocarbonyl-phenyl)-piperazine-1-carboxylic acid ethyl ester for 4-fluorobenzoyl chloride The rest of the procedure is followed as indicated in general procedure G to yield (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid ethyl ester.

[00879] 4-(4-Chlorocarbonyl-phenyl)-piperazine-1-carboxylic acid ethyl ester was prepared by the following procedure. Piperdine and 4-fluoro-benzoic acid methyl ester were heated at 65°C in DMSO for 48 h (US Patent 6069143) The reaction was quenched with $NaHCO_3$ and extracted 3x ethyl acetate was dried over $MgSO_4$, filtered and concentrated down. The ester was used directly. 4-Piperazin-1-yl-benzoic acid methyl ester was acetylated with ethyl chloroformate and DIEA in CH_2Cl_2 to give 4-(4-methoxycarbonyl-phenyl)-piperazine-1-carboxylic acid ethyl ester. The methyl ester was hydrolyzed with to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature 2 hours The mixture was cooled to 0 °C, acidified to form a white precipitate. The solid was filtered to give 4-(4-methoxycarbonyl-phenyl)-piperazine-1-carboxylic acid. The acid was converted to the acid chloride by reaction with oxalyl chloride.

^{1}H-NMR ($CDCl_3$) δ· 1.10 (d, 3H), 1.24 (m, 4H), 2 00 (s, 3H), 2.27 (m, 1H), 3.13 (t, 4H), 3.55 (t, 4H), 4.12 (q, 2H), 4.70 (m, 1H), 5.56 (brs, 1H), 6.54 (d, 1H), 6.62 (d, 2H), 6 91 (t, 1H), 7 09 (d, 2H), 7.14 (d, 2H), 7.27 (m, 2H), 7 36 (d, 2H).

MS m/z 575.16 (M+1).

[00880] N-{3-[(glycoloylamino)methyl]phenyl}-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-2)

[00881] N-{3-[(glycoloylamino)methyl]phenyl}-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride, and (3-cyanophenyl)boronic acid for 4-chlorophenylboronic acid The rest of the procedures were followed as indicated in general procedure A to afford N-(3-cyanophenyl)-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.

[00882] N-(3-cyanophenyl)-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was further treated with cobalt(II) chloride and sodium

borohydride (1eq, 3 eq) to afford N-[3-(aminomethyl)phenyl]-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

[00883] N-[3-(aminomethyl)phenyl]-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was then further coupled with glycolic acid using coupling reagent such as EDCI with HOBt to afford N-{3-[(glycoloylamino)methyl]phenyl}-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

^{1}H -NMR (CDCl3) δ: 1.1-1 2 (m, 4H), 2 0 (s, 3H), 2.3 (m, 1H), 3 8 (s, 3H), 4.2 (m, 1H), 4.5 (m, 2H), 4 7 (m, 2H), 5 6 (br, 1H), 6.5 (m, 1H), 6 6 (m, 2H), 6.9 (m, 1H), 7.1-7.4 (m, 8H)

MS m/z: 502 (M + 1)

[00884] ***N*-(4-chloro-2-fluorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-3)**

[00885] *N*-(4-chloro-2-fluorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride The amine-aryl coupling was performed differently to what is described in procedure G. Therefore (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (obtained from the hydrogenation step, 200 mg, 0 6 mmol, 1 equ.) was dissolved in ethylene glycol dimethyl ether (1 mL) in a Schlenk tube To this solution was added sequentially 1-bromo-4-chloro-2-fluorobenzene (105 uL, 0.84 mmol, 1.4 equ.), cesium carbonate (274 mg, 0.84 mmol, 1.4 equ.), palladium acetate (16 mg, 0.024 mmol, 0.04 equ.) and 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (23 mg, 0 048 mmol, 0.08 equ) The reaction mixture was flushed with nitrogen and heated to 95°C in the Schlenk tube for 48 h Reaction mixture was concentrated to leave a residue 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 black oil The crude product was purified by silica gel chromatography (methylene chloride/methanol 100/0 to 99/1 gradient) to provide (2*S*,4*R*)-*N*-(4-chloro-2-fluorophenyl)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (60 mg, 24 %)

[00886] To a solution of (2*S*,4*R*)-*N*-(4-chloro-2-fluorophenyl)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (60 mg, 0 14 mmol, 1 equ) in acetyl chloride (0 5 mL) was added diisopropylethylamine (25 uL, 0 14 mmol, 1 equ). The mixture was stirred at room temperature for 16 h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (methylene chloride/methanol 99.5/0.5) to afford pure *N*-(4-chloro-2-fluorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (140 mg, 92 %).

^{1}H-NMR (CDCl3) δ 1.15 (d, 3H), 2.05 (s, 3H), 2 30 (m, 1H), 3 75 (s, 3H), 4.75 (m, 1H), 5.65 (m, 1H), 6.50 (d, 1H), 6 70 (d, 2H), 7.00 (t, 1H), 7 15-7 20 (m, 4H), 7.25-7 40 (m, 3H).
MS m/z: 467 (M+1)

[00887] 4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzamide (G-4)

[00888] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-cyanobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (143 mg, 0.33 mmol) and potassium hydroxide (55 mg, 1 00 mmol)) were dissolved in water (150 mL), ethanol (3 mL) and heated to 70 °C for 4h. The slurry was portioned between 1N HCl (until acidic) and methylene chloride The organic layer was collected, concentrated and subjected to flash chromatography (EtOAc to 20% MeOH, EtOAc) to afford the title compound as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.15-1 25 (m, 1H), 1 17 (d, 3H), 2.11 (s, 3H), 2.20-2.34 (m, 1H), 4 70-4.84 (m, 1H), 5.50-5 80 (m, 1H), 5 80-6.00 (m, 1H), 6 40-6 60 (m, 1H), 6.40 (d, 1H), 6.83 (t, 1H), 7 08-7.30 (m, 8H), 7 60 (d, 2H).
MS m/z. 462 (M +1)

[00889] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-2-fluoro-phenoxy)-2,2-dimethyl-butyric acid methyl ester (G-5)

[00890] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester in methylene chloride at room temperature was added diisopropylethylamine followed by 3-fluoro-4-methoxy-benzoyl chloride. The reaction was stirred over night at room temperature The mixture was poured into water and extracted with ethyl acetate The extracts were washed with 1 M (aq) NaOH and brine, dried over $MgSO_4$, filtered dried and concentrated The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford the pure amide

[00891] (2*S*,4*R*)-[1-(3-Fluoro-4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester was dissolved in ethanol (30 mL). The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen. Reaction was complete after 4 hours The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution was filtered through an Celite ® and concentrated to afford the crude amine.

[00892] To a solution of (2*S*,4*R*)-(4-Amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(3-fluoro-4-methoxy-phenyl)-methanonein in DMF (dry) was added 4-chlorophenylboronic acid, pyridine and copper(II)acetate. The heterogeneous green mixture was stirred open to air for 1 hour and then warmed to 60 °C and stirred over night (14 h). The mixture was then cooled to room temperature,

poured into rapidly stirred ethyl acetate (150 mL); solids were removed by filtration through Celite ® The extracts were washed several times with water and then once with brine. The extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford the aniline product as a yellow oil

[00893] To a solution of (2*S*,4*R*)-[4-(4-chloro-phenylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(3-fluoro-4-methoxy-phenyl)-methanone in methylene chloride was added diisopropylethylamine followed by acetyl chloride. The mixture was stirred at rt 4 h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aq. $NaHCO_3$, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure the final product.

[00894] N-(4-Chloro-phenyl)-N-[1-(3-fluoro-4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (115 mg, 0.256 mmol) was dissolved in DMF (5 mL) at room temperature. K_2CO_3 (175 mg, 1.28 mmol) and 5-bromo-2,2-dimethyl-pentanoic acid ethyl ester (100 mg, 0.511 mmol) was added and the reaction mixture was allowed to stir over night. The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (2/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1 2 (s, 6H), 1.2 (m, 1H), 2.0 (s, 3H), 2.0 (t, 1H), 2 3 (m, 1H), 3.8 (s, 3H), 4.0 (t, 2H), 4.7 (m, 2H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (t, 1H), 6.7 (d, 1H), 6.9 (t, 1H), 7 2 (m, 5H), 7 4 (d, 2H)
MS m/z: 581 (M+1)

[00895] (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(3,4-dihydro-2H-benzo[1,4]oxazine-6-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (G-6)

[00896] 6-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester was dissolved in methylene chloride (3 mL) and iodotrimethylsilane (1 mL) After 4 days, the reaction was quenched with sat. aq $NaHCO_3$ The residue was partitioned between methylene chloride and water, then extracted three times with methylene chloride, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate) to afford the product.
^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (m, 1H), 2.0 (s, 3H), 2.3 (m, 1H), 3 3 (m, 2H), 4.2 (m, 2H), 4 7 (m, 1H), 5.5 (m, 1H), 6.4 (d, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6.96 (t, 1H), 7.2 (m, 5H), 7 4 (d, 2H).
MS m/z· 476 (M+1).

[00897] N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (G-7)

[00898] N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide was prepared following general procedure A, substituting 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl chloride for 4-fluorobenzoyl chloride (4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl chloride was prepared in one step from 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoic acid . 4-[3-(Trifluoromethyl)-1H-pyrazol-1-yl]benzoic acid was treated with oxalyl chloride in DCM and catalytic DMF to afford 4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl chloride in decent yield) The rest of the procedures were followed as indicated in general procedure A to afford N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

^{1}H-NMR (CDCl3) δ. 1 20 (d, 3H ; t, 1H), 2.03 (s, 3H), 2.33 (m, 1H), 4 80 (m, 1H), 5 62 (m, 1H), 6 47 (d, 1H), 6.77 (d, 1H), 6.90 (t, 1H), 7.00-7 40 (m, 10H)., 7 66 (d, 1H)

MS m/z 553 (M + 1).

[00899] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (G-8)

[00900] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (400 mg, 1.36 mmol) in methylene chloride (4 mL) at room temperature was added triethylamine (0 320 mL, 2 3 mmol) followed by 4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl chloride (1.5 mmol) The reaction was stirred over night at room temperature. The mixture was poured into water and extracted with ethyl acetate. The extracts were washed with 1 M (aq) NaOH and brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford the pure amide

[00901] (2*S*,4*R*)-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (300 mg) was dissolved in ethanol The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen. Reaction was complete after 4 hours. The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution was filtered through an Celite ® and concentrated to afford the crude amine

[00902] To a solution of (2*S*, 4*R*)-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-methanone (662 mg, 1.87 mmol) in methylene chloride (8 mL) was added 4-chlorophenylboronic acid (583 mg, 3.74 mmol), triethylamine (1.81 ml, 13.09 mmol) and copper(II)acetate (681 mg, 3.74 mmol). The heterogeneous green mixture was stirred open to air for 1 hour and then warmed to 60 °C and stirred over night (14 h) The mixture was then

cooled to room temperature, poured into rapidly stirred ethyl acetate (150 mL), solids were removed by filtration through Celite ® The extracts were washed several times with water and then once with brine The extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford the aniline product as a yellow oil.

[00903] To a solution of (2*S*,4*R*)-[4-(4-Chloro-phenylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazin-7-yl)-methanone (540 mg, 1 25 mmol) in methylene chloride (5 mL) was added diisopropylethylamine (0.240 mL, 1 37 mmol) followed by acetyl chloride (2 mL). The mixture was stirred at room temperature 4 hours The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aq. $NaHCO_3$, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford the final product.

^{1}H-NMR ($CDCl_3$) δ 1.1 (d, 3H), 1.1 (m, 1H), 2 0 (d, 3H), 2.3 (m,·1H), 2.8 (s, 3H), 3 2 (t, 2H), 4 2 (t, 2H), 4 7 (m, 1H), 5 6 (m, 1H), 6 3 (d, 1H), 6.5 (d, 1H), 6.6 (d, 1H), 6 8 (s, 1H), 6.9 (t, 1H), 7.2 (m, 5H), 7.4 (d, 2H).

MS m/z: 490 (M+1).

[00904] (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(2,2-difluoro-benzo[1,3]dioxole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (G-9)

[00905] (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(2,2-difluoro-benzo[1,3]dioxole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure G, substituting 2,2-difluoro-1,3-benzodioxole-5-carbonyl chloride for 4-fluorobenzoyl chloride. The rest of the procedures were followed as indicated in general procedure G to afford (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(2,2-difluoro-benzo[1,3] dioxole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide.

^{1}H-NMR (CDCl3) δ: 1.15 (3H, d, overlapping 1H, t), 2.02 (3H, s), 2.33(1H, m), 4.78(1H, m), 5 60(1H, m), 6.44 (1H, d), 6.68 (1H, d), 6.95 (1H, t), 7 00-7.40 (8H, complex.

MS m/z 499 (M + 1).

[00906] 5-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)pentanamide (G-10)

[00907] Benzyl [(2S,4R)-1-(4-iodobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate was prepared following general procedure G, substituting 4-iodo-benzoyl chloride for 4-fluorobenzoyl chloride.

[00908] To a solution of benzyl [(2S,4R)-1-(4-iodobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate (0 6 g, 1 14 mmol) in DMF (15 mL) at room temperature was added pent-4-enoic acid ethyl ester (0.292 g, 2 28 mmol), potassium acetate (0 67 g, 6.84 mmol), palladium acetate (0 05 g, 0.228 mmol), tetrabutylammonium chloride (0 32 g, 1.14 mmol), and triphenylphosphine (0 06 g, 0.228 mmol). The mixture was stirred at room temperature for 1 hour and then heated to 70 °C for 3 hours The mixture was concentrated and ethyl acetate was added. The solution was washed with water, dried and concentrated. The residue was purified by silica gel chromatography (70 % CH_2Cl_2 /30%EtOAc) to afford ethyl (4E)-5-(4-{[(2S,4R)-4-{[(benzyloxy)carbonyl]amino}-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)pent-4-enoate (0.5 g, 83%), which was further converted into ethyl 5-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)pentanoate following general procedure G

[00909] Ethyl 5-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)pentanoate (0.135 g, 0.25 mmol) was hydrolyzed to the acid by dissolving in 6 ml methanol and potassium carbonate (0 2 g in 4 ml water) was added. The mixture was heated to 40 °C for 24 hours and methanol was removed in vacuo. The mixture was acidified to form a white precipitate. The solid was filtered to give the acid To a solution of the acid in DMF (10 mL) at room temperature was added HATU (0.143 g, 0 375 mmol), DIEA (0.18 mL, 1 mmol), HOBt (0.057 g, 0.375 mmol), and ammonium chloride (0 027 g, 0.5 mmol) was added The mixture was stirred for 18 hours and concentrated. The residue was dissolved in CH_2Cl_2 and washed with water The organic layer was concentrated and purified by silica gel chromatography (87 % CH_2Cl_2 /13%methanol) to afford 5-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)pentanamide.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, 3H), 1 18 (m, 1H), 1 56 (m, 3H), 1.98 (s, 3H), 2.05 (m, 1H), 2 14 (m, 2H), 2.26 (m, 1H), 2.53 (m, 2H), 4.74 (m, 1H), 5.59 (br, 2H), 5.76 (m, 1H), 6 48 (d, 1H), 6 88 (t, 1H), 6 94 (m, 2H), 7 19 (m, 6H), 7.32 (d, 2H).

MS m/z: 519 (M+1)

[00910] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-[1-(2,3-dihydro-benzofuran-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (G-11)

[00911] (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(2,3-dihydro-benzofuran-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was made following general procedure G, substituting 2,3-dihydro-benzofuran-5-carbonyl chloride for 4-fluorobenzoyl chloride. The rest of the procedure is followed as indicated in general procedure G to yield (2*S*,4*R*)- N-(4-chloro-phenyl)-N-[1-(2,3-dihydro-benzofuran-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide.

^{1}H-NMR ($CDCl_3$) δ 1 09 (d, 3H), 1.22 (t, 1H), 1.99 (s, 3H), 2 25 (s, 1H), 3.04 (m, 2H), 4.49 (t, 2H), 4 70 (m, 1H), 5 61 (bs, 1H), 6.50 (m, 2H), 6 88 (m, 2H), 7.10 (d, 2H), 7.18 (d, 2H), 7 26 (d, 1H), 7.34 (d, 2H)

MS m/z 461 2 (M+1).

[00912] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(pyridin-3-ylcarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-12)

[00913] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(pyridin-3-ylcarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure G, substituting nicotinoyl chloride hydrochloride for 4-fluorobenzoyl chloride. The rest of the procedures were followed as indicated in general procedure G to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(pyridin-3-ylcarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide in decent yield.

^{1}H-NMR ($CDCl_3$, 300MHz) δ 1 07-1.09 (d, 3H), 2 01 (s, 3H), 2.21-2 33 (m, 2H), 4.05-4.12 (q, 1H), 4.76-4.81 (m, 1H), 6.54-6 74 (d, 1H), 6.93-7 38 (m, 9H), 8.49-8 56 (d, 2H).

MS m/z: 420 (M+1).

[00914] *N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-phenylacetamide (G-13)

[00915] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. The rest of the procedures were followed as indicated in general procedure G to afford (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was obtained in decent yield

[00916] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (200 mg, 0 36 mmol) was dissolved in MeOH and a catalytic amount of Palladium on Carbon (10%) was added The round bottom flask in which resided the resulting solution was evacuated and backfilled with hydrogen. The reaction was stirred under the hydrogen atmosphere overnight. The mixture was carefully filtered through a Celite ® plug and concentrated to afford crude product. The crude product was purified by silica gel chromatography (hexanes/ethyl acetate system) to afford *N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-phenylacetamide (142 mg, 95%).

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1.60 (s, 1H), 2 02 (s, 3H), 2.30 (m, 1H), 3.74 (s, 3H), 4.75 (m, 1H), 5.45 (b, 1H), 6.50 (d, 1H), 6 67 (d, 2H), 6.92 (t, 1H) 7.13-7.18 (m, 3H), 7.28 (d, 1H), 7 32-7.40 (m, 5H).

MS m/z: 415 (M+1)

[00917] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-2-fluoro-phenoxy)-2,2-dimethyl-butyric acid (G-14)

[00918] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-2-fluoro-phenoxy)-2,2-dimethyl-butyric acid methyl ester (100 mg) was dissolved in methanol/THF (1:1, 5 mL), and lithium hydroxide (1.0N, 1 mL) was added. After 1 hour, the reaction was acidified (HCl) and extracted from with methylene chloride. The organic layer was dried, filtered, and concentrated. The crude residue was purified by silica gel chromatography ethyl acetate – 5%MeOH/ethylacetate gradient) to afford the product

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1 2 (s, 6H), 1.2 (m, 1H), 2 0 (s, 3H), 2.0 (t, 1H), 2 3 (m, 1H), 4.0 (t, 2H), 4.7 (m, 2H), 5.6 (bs, 1H), 6.5 (d, 1H), 6 6 (t, 1H), 6.7 (d, 1H), 6 9 (t, 1H), 7.2 (m, 5H), 7.4 (d, 2H), 11.1 (bs, 1H)

MS m/z 567 (M+1).

[00919] (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (G-15)

[00920] (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure G, substituting 1-Isopropyl-1H-indazole-5-carbonyl chloride for 4-fluorobenzoyl chloride (1-Isopropyl-1H-indazole-5-carbonyl chloride was prepared in three steps from 1H-Indazole-5-carboxylic acid ethyl ester. 1H-Indazole-5-carboxylic acid ethyl ester was alkylated using 2-bromopropane in presence of sodium hydride in DMF at room temperature to yield the desired 1-isopropyl-1H-indazole-5-carboxylic acid ethyl ester. Ester hydrolysis using 1N sodium hydroxide in ethanol at 80°C gave 1-Isopropyl-1H-indazole-5-carboxylic acid and subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded 1-isopropyl-1H-indazole-5-carbonyl chloride in decent yield) The rest of the procedures were followed as indicated in general procedure G to afford (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. (The first exception being in the deprotection of the benzyloxycarbonyl group by treatment with 30% HBr in AcOH substituting for palladium on carbon(10%) and the other in the step of N-arylation of (2S,4R)-(4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(1-isopropyl-1H-indazol-5-yl)-methanone with 4-chlorophenylboronic acid, in presence of copper acetate, triethylamine was substituted for pyridine, and the reaction was carried out in dichloromethane at room temperature to afford the (2S,4R)-N-(4-chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide).

^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, d; overlapping 1H, t), 1 60 (2x3H, d), 2.02 (3H, s), 2.33(1H, m), 4.78(2x1H, m, overlapping), 5.60(1H, m), 6.44 (1H, d), 6.95 (1H, t), 7.00-7.40 (9H, complex)

ESI-MS m/z· 501 (M + 1).

[00921] ***N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-2-methylpropanamide (G-16)**

[00922] *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-2-methylpropanamide was synthesized according to general procedure G by replacing 4-fluorobenzoyl chloride with 4-methoxybenzoyl chloride and by substituting acetyl chloride with 2-methyl propanoyl chloride. The rest of the procedure was followed as indicated in general procedure G to yield *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-2-methylpropanamide.

^{1}H-NMR ($CDCl_3$) δ: 1 12-1 26 (m, 10H), 2.20-2 28 (m, 1H), 2.61 (sp, 1H), 3 72 (s, 3H), 4.69-4.79 (m, 1H), 5.61 (br s, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6.92 (t, 1H), 7.11-7.41 (m, 8H).

MS m/z· 477 (M+1).

[00923] ***N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (G-17)**

[00924] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following the procedure for *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide substituting 1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chloride for 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride. (1,3-Dimethyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl chloride was prepared from commercially available 1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid by treatment with oxalyl chloride and catalytic DMF in dichloromethane).

^{1}H-NMR ($CDCl_3$) δ. 1 15 (d, 3H), 1.17 (t, 1H), 2 02 (s, 3H), 2.25 (s, 3H), 2 25(m, 1H), 3 80 (s, 3H), 4.62-4 74 (m, 1H), 5.48 -5 60 (m, 1H), 6.55 (s, 1H), 7 00-7.40 (m, 8H).

MS m/z. 493 (M + 1).

[00925] ***N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (G-18)**

[00926] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure G, substituting 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride for 4-fluorobenzoyl chloride. (1-Isopropyl-1H-pyrazole-4-carbonyl chloride was prepared from commercially available 1-isopropyl-1H-pyrazole-4-carboxylic acid by treatment with oxalyl chloride and catalytic DMF in dichloromethane). Other modifications to general procedure A were inclusive of the deprotection of the benzyloxycarbonyl group via treatment with 30% HBr in acetic acid instead of palladium on carbon (10%) and the use of

triethylamine instead of pyridine using dichloromethane as solvent at room temperature during the *N*-arylation sequence.

^{1}H-NMR ($CDCl_3$) δ. 1.11 (d, 3H), 1 13 (t, 1H), 1.36 (d, 6H), 2.00 (s, 3H), 2.21-2.28 (m, 1H), 4 25-4.34 (m, 1H), 4.65-4.76 (m, 1H), 5 36-5 56 (br, 1H), 6.95 (d, 1H), 7 00-7 40 (m, 9H).

MS m/z 451 (M + 1)

[00927] *N*-1*H*-indol-4-yl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-19)

[00928] *N*-1*H*-indol-4-yl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride.

[00929] A mixture of (2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (0.12 g, 0 4 mmol) (obtained after the hydrogenation step),

tert-butyl 4-bromo-1H-indole-1-carboxylate (0.099 g, 0.39 mmol), palladium dba (0.018 g, 0 02 mmol), biphenyl-2-yl(di-tert-butyl)phosphine (0.006 g, 0.02 mmol) and cesium carbonate (0.13 g, 0 4 mmol) in dimethoxy ethane (3 mL) was stirred at 80C under nitrogen for 15 h The reaction mixture was filtered The filtrate was evaporated to yield the crude product (0 222 g) which was then cleaned by silica gel chromatography (10% ethyl acetate: hexane) to give desired *tert*-Butyl 4-{[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1*H*-indole-1-carboxylate (0.054 g, 32%)

^{1}H-NMR ($CDCl_3$) δ: 1.32 (d, 3H), 1.47-1.57 (m, 1H), 1.71 (s, 9H), 2.87-2.96 (m, 1H), 3 81 (s, 3H), 4 63-4 69 (m, 1H), 4 88-5 01 (m, 1H), 6.46 (d, 1H), 6.56-6.63 (m, 2H), 6 75-6 78 (m, 2H), 6.94-7.09 (m, 2H), 7.2-7.36 (m, 4H), 7 59-7 66 (m, 2H).

MS m/z· 512 (M+1)

[00930] A mixture of methyl tert-butyl 4-{[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1H-indole-1-carboxylate (0.054 g, 0 1 mmol), freshly distilled acetyl chloride (0.5 mL) , diisopropylethylamine (0.015 g, 0.12 mmol) and 4-N.N-dimethylaminopyridine (catalytic amount) was stirred at room temperature for 43 h. Ice was added to the reaction mixture and stirred for 1 h The reaction mixture was neutralized with solid sodium bicarbonate and extracted with ethyl acetate The ethyl acetate extract was washed twice with water, brine, dried over sodium sulphate and evaporated. The crude product (0.055 g) thus obtained was cleaned by silica gel chromatography (ethyl acetate: hexane) to give clean *tert*-butyl 4-{acetyl[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1*H*-indole-1-carboxylate (0.035 g, 60%)

^{1}H-NMR ($CDCl_3$) δ: 1.04 (d, 3H), 1.47-1.57 (m, 1H), 1 69 (s, 9H), 1.97 (s, 3H), 2.87-2 96 (m, 1H), 3.75(s, 3H), 4 64-4 77 (m, 1H), 4.88-5.01 (m, 1H), 6 53 (d, 1H), 6 66 (d, 1H), 6.69 (d, 2H), 6 92-6.97 (m, 1H), 7 14-7 29 (m, 5H), 7 45 (d, 1H), 7.73 (d, 1H), 8 21 (d, 1H).
MS m/z: 411, 280.

[00931] tert-Butyl 4-{acetyl[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-1H-indole-1-carboxylate (0.035 g, 0 068 mmol) was stirred in 4 N HCl in dioxane (1 mL) for 24 h and then evaporated to dryness. The residue was dissolved in ethyl acetate, washed with 1N NaOH, water, brine, dried over sodium sulphate and evaporated to dryness to give the crude product (0.023 g). The crude was cleaned by silica gel chromatography to give clean *N*-1*H*-indol-4-yl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (0.008 g, 28%).
^{1}H-NMR ($CDCl_3$) δ 1.03 (d, 3H), 2 01 (s, 3H), 3.75(s, 3H), 4.08-4 16 (m, 1H), 4.61-4 79 (m, 1H), 6 52-6 55 (m, 2H), 6.67-6 7 (m, 2H), 6.92-7 51 (m, 9H), 8.62 (bs, 1H)
MS m/z 454 (M+1).

[00932] 4-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoic acid (G-20)

[00933] Methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoate was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture heated to 40°C for 2 h The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoic acid
^{1}H-NMR ($CDCl_3$) δ: 1.09-1 12 (m, 1H), 1.11 (d, 3H), 1.22 (d, 6H), 1.69-1 74 (m, 2H), 2 01 (s, 3H), 2.24-2.31 (m, 1H), 2.83 (s, 3H), 3.27 (t, 2H), 4.65-4.76 (m, 1H), 5 60 (br s, 1H), 6.39 (d, 2H), 6 62 (d, 1H), 6.95 (t, 1H), 7.07-7.16 (m, 3H), 7.18-7.28 (m, 3H), 7.37 (d, 2H).
MS m/z 562 (M+1).

[00934] *N*-(4-chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-21)

[00935] *N*-(4-chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure G, substituting 4-

methoxybenzoyl chloride for 4-fluorobenzoyl chloride Procedure A was followed further substituting acetoxyacetylchloride for acetyl chloride in the last step to yield 2-{(4-chlorophenyl)[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-oxoethyl acetate

[00936] 2-{(4-Chlorophenyl)[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-oxoethyl acetate (496 mg, 0 98 mmol, 1 eq) was dissolved in methanol (12 ml). A solution of potassium carbonate (1.08 g, 7.84 mmol, 8 eq) in water (5 ml) was added and reaction mixture was stirred at room temperature for 4 h. The mixture was concentrated and the residue dissolved in ethyl acetate and washed with water, brine, and then dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (methylene chloride/methanol: 98/2) to afford *N*-(4-chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (380 mg, 84 %) ^{1}H-NMR (DMSO) δ: 1.05 (d, 3H), 2 45 (m, 1H), 3 70 (s, 3H), 3.80-3.95 (dd, 2H), 4.60 (m, 1H), 4 80 (m, 1H), 5.40 (m, 1H), 6.55 (d, 1H), 6.75 (d, 2H), 6 95 (t, 1H), 7.10 (d, 2H), 7 20 (t, 1H), 7.40-7 60 (m, 5H)

MS m/z: 465 (M+1).

[00937] (2*S*,4*R*)-6-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester (G-22)

[00938] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (990 mg, 3.49 mmol) in methylene chloride at room temperature was added triethylamine (1 21 mL, 8 71 mmol) followed by 6-chlorocarbonyl-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester (3 49 mmol). The reaction was stirred over night at room temperature. The mixture was poured into water and extracted with ethyl acetate The extracts were washed with 1 M (aq) NaOH and brine, dried over $MgSO_4$, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford the pure amide.

[00939] (2*S*,4*R*)-6-(4-Benzyloxycarbonylamino-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester (697 mmol) was dissolved in ethanol (30 mL) The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen Reaction was complete after 4 hours The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution was filtered through an Celite ® and concentrated to afford the crude amine

[00940] To a solution of (2*S*,4*R*)-6-(4-Amino-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl)-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester (470 mg, 1 18 mmol) in methylene chloride was added 4-chlorophenylboronic acid (368 mg, 2 36 mmol), triethylamine (1.31 mL, 9.42

mmol) and copper(II)acetate (429 mg, 2.36 mmol) The heterogeneous green mixture was stirred open to air for 1 hour and then warmed to 60 °C and stirred over night (14 hours) The mixture was then cooled to room temperature, poured into rapidly stirred ethyl acetate (150 mL); solids were removed by filtration through Celite ® The extracts were washed several times with water and then once with brine. The extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford the aniline product as a yellow oil.

[00941] To a solution of (2*S*, 4*R*)-6-[4-(4-Chloro-phenylamino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-2,3-dihydro-benzo[1,4]oxazine-4-carboxylic acid ethyl ester (343 mg, 0 673 mmol) in methylene chloride (2 mL) was added diisopropylethylamine (0.129 mL, 0.739 mmol) followed by acetyl chloride (2 mL). The mixture was stirred at room temperature 4 hours The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aq. sodium $NaHCO_3$, brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure product.

^{1}H-NMR ($CDCl_3$) δ. 1.1 (d, 3H), 1.2 (m, 1H), 1 3 (t, 3H), 2.0 (s, 3H), 2.3 (m, 1H), 3.3 (m, 2H), 4.0 (m, 2H), 4 3 (m, 2H), 4.7 (m, 1H), 5.5 (m, 1H), 6 4 (d, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6 96 (t, 1H), 7.2 (m, 4H), 7.4 (d, 2H)

MS m/z. 548 (M+1).

[00942] ***N*-[(2*S*,4*R*)-6-chloro-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (G-23)**

[00943] *N*-[(2*S*,4*R*)-6-chloro-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide was synthesized as described for (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester, substituting 4-chloroaniline for aniline. Further elaboration following general procedure A, substituting 4-methoxy-benzoyl chloride for 4-fluorobenzoyl chloride, yielded *N*-[(2*S*,4*R*)-6-chloro-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide.

^{1}H-NMR ($CDCl_3$) δ· 1.13 (d, 3H), 1 15 (t, 1H), 2.03 (s, 3H), 2.27 (m, 1H), 3 76 (s, 3H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.43 (d, 1H), 6.71 (d, 2H), 6 93 (d, 1H), 7.14-7 29 (m, 5H), 7.41 (d, 2H).

MS m/z 483 (M+1)

[00944] **[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]acetic acid (G-24)**

[00945] Ethyl [(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]acetate was prepared following the procedure for *N*-(4-

chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide substituting ethyl {[5-(chlorocarbonyl)isoxazol-3-yl]oxy}acetate for 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride (Ethyl {[5-(chlorocarbonyl)isoxazol-3-yl]oxy}acetate was prepared in 4 steps from methyl 3-hydroxy 5-isoxazole carboxylate. Methyl 3-hydroxy 5-isoxazole carboxylate (1.00 g, 6 95 mmol) was alkylated using ethyl bromoacetate (0 850 mL, 7.64 mmol) in presence of potassium carbonate (1 05 g, 7.64 mmol) and catalytic potassium iodide in DMF (3.00 mL) at room temperature overnight. Water was added to the reaction mixture and extracted with ethyl acetate The organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to yield the desired methyl 3-(2-ethoxy-2-oxoethoxy)isoxazole-5-carboxylate (60%) (Ref WO 03/063800 PCT/US03/03224) Methyl 3-(2-ethoxy-2-oxoethoxy)isoxazole-5-carboxylate was further treated with aqueous 5% sodium hydroxide in methanol to yield 3-(carboxymethoxy)isoxazole-5-carboxylic acid (86%). This diacid (0 700 g, 3 76 mmol) was selectively esterified in the presence of catalytic p-toluenesulfonic acid monohydrate (100 mg) in ethanol at room temperature. Water was added to the reaction and the mixture was extracted with ethyl acetate. The organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to give the desired 3-(2-ethoxy-2-oxoethoxy)isoxazole-5-carboxylic acid (90%). 3-(2-Ethoxy-2-oxoethoxy)isoxazole-5-carboxylic acid was treated with oxalyl chloride and catalytic DMF in dichloromethane to yield the desired ethyl {[5-(chlorocarbonyl) isoxazol-3-yl]oxy}acetate) Ethyl [(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]acetate was treated with a solution of lithium hydroxide monohydrate (aq) in methanol at room temperature overnight to afford [(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]acetic acid in 60% yield

^{1}H-NMR ($CDCl_3$) δ: 1 15 (d, 3H), 1.17 (t, 1H), 2.02 (s, 3H), 2.42-2.68 (m, 1H), 4.69 (s, 1H) 4.72-4.78 (m, 1H), 5 44-5.58 (br, 1H), 6.80 (d, 1H), 7.00-7.40 (m, 8H)

MS m/z: 484 (M + 1).

[00946] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-cyanobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-25)

[00947] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-cyanobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure G, substituting 4-cyanobenzoyl chloride for 4-fluorobenzoyl chloride. The rest of the procedure is followed as indicated in general procedure G to yield *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-cyanobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.

^{1}H-NMR ($CDCl_3$) δ· 1 10-1.20 (m, 1H), 1.16 (d, 3H), 2 03 (s, 3H), 2.20-2.36 (m, 1H), 4 70-4.84 (m, 1H), 5 48-5.70 (m, 1H), 6 40 (d, 1H), 6 91 (t, 1H), 7.16-7.32 (m, 6H), 7.38 (d, 2H), 7.47 (d, 2H).

MS m/z: 444 (M +1)

[00948] Ethyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]-2,2-dimethylbutanoate (G-26)

[00949] Ethyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]-2,2-dimethylbutanoate was prepared following the procedure for *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, substituting ethyl 4-{[5-(chlorocarbonyl)isoxazol-3-yl]oxy}-2,2-dimethylbutanoate for 1-isopropyl-1*H*-pyrazole-4-carbonyl chloride. (Ethyl 4-{[5-(chlorocarbonyl) isoxazol-3-yl]oxy}-2,2-dimethylbutanoate was prepared in three steps from methyl 3-hydroxy 5-isoxazole carboxylate Methyl 3-hydroxy 5-isoxazole carboxylate (1.00 g, 6 94 mmol) was alkylated using ethyl 4-bromo-2,2-dimethylbutanoate (1 59 g, 7 63 mmol) in the presence of potassium carbonate (1.05 g, 7 64 mmol) and catalytic potassium iodide in DMF (5.00 mL) at room temperature overnight. Water was added to the reaction mixture and the mixture was extracted with ethyl acetate The organics were washed with brine, dried over anhydrous sodium sulfate, filtered, concentrated in vacuo and purified on silica gel by flash chromatography using hexane/ethyl acetate (10-50% gradient) to afford methyl 3-(4-ethoxy-3,3-dimethyl-4-oxobutoxy)isoxazole-5-carboxylate in 35% yield. Selective hydrolysis of the methyl ester by subsequent treatment with lithium hydroxide (aq) (1.50 equiv.) in methanol at room temperature afforded 3-(4-ethoxy-3,3-dimethyl-4-oxobutoxy)isoxazole-5-carboxylic acid which was then treated with oxalyl chloride and catalytic DMF in dichloromethane to yield the desired ethyl 4-{[5-(chlorocarbonyl)isoxazol-3-yl]oxy}-2,2-dimethylbutanoate).

^{1}H-NMR ($CDCl_3$) δ· 1.18 (d, 3H), 1 18 (t, 1H), 1 19 (s, 6H), 1.20(t, 3H), 1 99-2.02 (s, 3H, m, 1H), 2 24-2.36 (m, 1H), 4.15 (q, 2H), 4 17-4 22 (m, 2H), 4 64-4.74 (m, 1H), 5.60-5.68 (br, 1H), 6.80 (d, 1H), 7 00-7 40 (m, 8H)

MS m/z. 568 (M + 1)

[00950] 4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid (G-27)

[00951] Methyl 4-((2S,4R)-4-(N-(4-chlorophenyl)acetamido)-2-methyl-1,2,3,4-tetrahydroquinoline-1-carbonyl)benzoate was made following general procedure G, substituting methyl 4-(chlorocarbonyl)benzoate for 4-fluorobenzoyl chloride The rest of the procedure is followed as indicated in general procedure A to yield Methyl 4-((2S,4R)-4-(N-(4-chlorophenyl)acetamido)-2-methyl-1,2,3,4-tetrahydroquinoline-1-carbonyl)benzoate, which was saponified with excess lithium hydroxide in MeOH/THF/H_2O (2:1:2). The slurry was acidified with 1N HCl and the crude product was extracted using methylene chloride. The organic portion was

concentrated, and the resulting slurry was subjected to preparatory HPLC to afford the title compound as a white solid.^{1}H-NMR ($CDCl_3$ δ· 1 15-1.22 (m, 1H), 1 16 (d, 3H), 2.06 (s, 3H), 2.20-2 36 (m, 1H), 3.50-4 05 (bs, 1H), 4.72-4.88 (m, 1H), 5 50-5.75 (m, 1H), 6 45 (d, 1H), 6 85 (t, 1H), 7.08-7 30 (m, 6H), 7.40 (d, 2H), 7 87 (d, 2H).
MS m/z: 463 (M +1)

[00952] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide (G-28)

[00953] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide was made following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride Procedure G was followed further substituting cyclopropane carbonyl chloride for acetyl chloride in the last step to yield *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide
^{1}H-NMR (CDCl3) δ: 0.75 (m, 2H), 1.00-1 20 (m, 5H), 1 45 (m, 1H), 2.30 (m, 1H), 3.75 (s, 3H), 4 75 (m, 1H), 5 60 (m, 1H), 6 50 (d, 1H), 6 60 (d, 2H), 6 90 (t, 1H), 7.10-7 45 (m, 8H)
MS m/z. 475 (M+1).

[00954] *N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-[4-(1*H*-pyrrol-1-yl)phenyl]acetamide (G-29)

[00955] *N*-(4-amino-phenyl)-*N*-[(2S,4R)-1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared similarly to General Procedure G: To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (1.00 equiv.) in methylene chloride at room temperature was added diisopropylethylamine (1.50 equiv) followed by 4-anisoyl chloride (1.15 equiv). The reaction was stirred over night at room temperature. The mixture was poured into water and extracted with ethyl acetate. The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered, dried and concentrated. The crude residue was purified by silica gel chromatography (75% hexanes / 25 % ethyl acetate) to afford 2*S*,4*R*)-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester

[00956] (2*S*,4*R*)-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-carbamic acid benzyl ester (1 00 equiv.) was dissolved in ethanol (30 mL). The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %, 0 10 equiv. by wt.) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 40 psi hydrogen Reaction was complete after 4 h. The mixture was carefully filtered and concentrated to 10% volume. The resulting concentrated solution

was filtered through a Celite ® and concentrated to afford the crude amine, (2*S*, 4*R*)- (4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxy-phenyl)-methanone

[00957] To a solution of (2*S*, 4*R*)- (4-amino-2-methyl-3,4-dihydro-2H-quinolin-1-yl)-(4-methoxy-phenyl)-methanone (1.00 equiv.) in DMF was added 4-nitrophenylboronic acid (2.00 equiv.), pyridine (2.50 equiv) and copper(II)acetate (2 00 equiv.). The heterogeneous green mixture was stirred open to air for 1 h and then warmed to 60 °C and stirred over night (14 h) The mixture was then cooled to rt, poured into rapidly stirred ethyl acetate (150 mL); solids were removed by filtration through Celite ® The extracts were washed several times with water and then once with brine. The extracts were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford (4-methoxy-phenyl)-[(2S,4R)-2-methyl-4-(4-nitro-phenylamino)-3,4-dihydro-2H-quinolin-1-yl]-methanone as a yellow solid.

[00958] To a solution of (2*S*, 4*R*)- [4-(4-nitro-phenylamino)-2-methyl-3,4-dihydro-2H-quinolin-1-yl]-(4-methoxy-phenyl)-methanone (1.00 equiv.) in methylene chloride was added diisopropylethylamine (1 05 equiv) followed by acetyl chloride (1.00equiv). The mixture was stirred at rt 48 h The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure *N*-(4-nitro-phenyl)-*N*-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide, which was reduced to *N*-(4-amino-phenyl)-*N*-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]- acetamide using excess NH_4CO_2H, catalyic Pt(sulfided), in ethanol at reflux for 30 m., followed by filtration and concentration. The amine was used without further purification due to inherent chemical instability.

[00959] *N*-(4-amino-phenyl)-*N*-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]- acetamide (22mg, 0.05 mmol) was dissolved in MeOH:THF (1 mL each) and cooled to 10 °C. 2,5-dimethoxy-tetrahydrofuran (1 25 equiv.) was dissolved in THF and catalytic H_2SO_4, and added drop wise to the aniline mixture. The mixture was poured into sat. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was dried, filtered and concentrated, and the crude residue was purified by preparative HPLC to afford the title compound as an off-white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.00-1 22 (m, 1H), 1.12 (s, 3H), 2 04 (s, 3H), 2.22-2.42 (m, 1H), 3.72 (s, 3H), 4 64-4 84 (m, 1H), 5 50-5.80 (m, 1H), 6.38 (s, 2H), 6 53 (d, 1H), 6.67 (d, 2H), 6 94 (t, 1H), 7 05-7 48 (m, 10H).

MS m/z. 480 (M +1)

[00960] Methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoate (G-30)

[00961] Methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoate was prepared according to procedure G substituting 4-nitrobenzoyl chloride for 4-fluorobenzoyl chloride in the first step and, to avoid complications, the CBZ protecting group was cleaved by treatment of a solution of the protected amine, benzyl [(2*S*,4*R*)-2-methyl-1-(4-nitrobenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]carbamate, in dichloromethane with hydrogen bromide in acetic acid (30 wt%) followed by precipitation of the product from the reaction mixture by the addition of hexanes. The rest of general procedure A was followed as indicated to yield *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(4-nitrobenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.

[00962] This material was reduced by exposure to sulfided platinum (10 wt%) and ammonium formate (4 0 equivalents) in ethanol at 70 °C until all starting material was consumed to afford *N*-[(2*S*,4*R*)-1-(4-aminobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide.

[00963] This material underwent reductive alkylation first with methyl 2,2-dimethyl-4-oxobutanoate then formaldehyde (Methyl 2,2-dimethyl-4-oxobutanoate was prepared in 3 steps from methyl 4,4-dimethoxybutanoate. Methyl 4,4-dimethoxybutanoate underwent lithium enolate formation with lithium diisopropyl amide (1.1 equivalents) in THF at -78 °C followed by quenching with methyl iodide (2 0 equivalents) and aqueous work up, repeating the same protocol yielded, after standard chromatography (5% ethyl acetate/hexanes), methyl 4,4-dimethoxy-2,2-dimethylbutanoate Subsequent treatment of this material with aqueous 6 normal hydrochloric acid in acetone afforded, after standard aqueous work up, methyl 2,2-dimethyl-4-oxobutanoate) A solution of methyl 2,2-dimethyl-4-oxobutanoate (1.0 equivalents), sodium triacetoxyborohydride (1.2 equivalents) and aniline in THF with acetic acid (1.0 equivalent) was stirred until all starting material had been consumed. The reaction was then diluted with methanol, acidified with concentrated hydrochloric acid (3 drops) and an excess formaldehyde (37 weight % in H_2O) and sodium cyanoborohydride (5 equivalents) were added. The reaction mixture stirred at room temperature until all starting material had been consumed, then standard aqueous work up followed by chromatography (50% ethyl acetate/hexanes) afforded methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoate.

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.14 (m, 1H), 1.13 (d, 3H), 1.20 (d, 6H), 1.71-1.79 (m, 2H), 1.98 (s, 3H), 2.24-2 28 (m, 1H), 3.02 (s, 3H), 3 30 (t, 2H), 3.57 (s, 3H), 4 69-4.76 (m, 1H), 5 51 (br s, 1H), 6.39 (d, 1H), 6 84 (t, 1H), 7.16 (d, 2H), 7.24-7 29 (m, 4H), 7.34 (d, 2H), 7.54 (d, 2H).

MS m/z 576 (M+1).

[00964] N-[3-(acetylamino)phenyl]-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-31)

[00965] N-[3-(acetylamino)phenyl]-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride, and 3-acetamidophenylboronic acid for 4-chlorophenylboronic acid. The rest of the procedures were followed as indicated in general procedure G to afford N-[3-(acetylamino)phenyl]-N-[(2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

^{1}H -NMR (CDCl3) δ 1 1-1 2 (m, 4H), 2.0 (s, 3H), 2 3 (m, 4H), 3.7 (s, 3H), 4.8 (m, 1H), 5 6 (br, 1H), 6.5 (d, 1H), 6 7 (m, 2H,), 6 9 (m, 1H,), 7 1-7 4 (m, 7H,), 7 5 (m, 1H)

MS m/z: 472 (M + 1).

[00966] ***N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-{4-[(methylsulfonyl)amino]phenyl}acetamide (G-32)**

[00967] *N*-(4-amino-phenyl)-*N*-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]- acetamide (32 mg, 0 075 mmol) was dissolved in methylene chloride (1 mL) and triethylamine (10 equiv.), then cooled to -30 °C. Methanesulfonyl chloride (5 equiv.) was added, after 30min, TLC showed complete consumption of the starting aniline. The mixture was poured into water and extracted with EtOAc. The organic layer was dried, filtered and concentrated to afford the corresponding *bis*-methanesulfonated adduct

[00968] The crude residue was dissolved in MeOH and ~20 equiv. of Cs_2CO_3 was added. After stirring for 5 min, the mixture was poured into sat. $NaHCO_3$ and EtOAc The organic layer was dried, filtered and concentrated The resulting crude material was subjected to flash chromatography (EtOAc) to afford the title compounds as a white solid

^{1}H-NMR ($CDCl_3$) δ. 1 00-1 22 (m, 1H), 1 11 (s, 3H), 1 20-1.28 (m, 1H), 2 01 (s, 3H), 2 20-2.40 (m, 1H), 3.01 (s, 3H) 3.72 (s, 3H), 4.64-4.82 (m, 1H), 5.45-5 75 (m, 1H), 6.51 (d, 1H), 6.63 (d, 2H), 6.91 (t, 1H), 7 10-7.35 (m, 7H), 7.38-7 44 (m, 1H)

MS m/z 508 (M +1)

[00969] ***N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-pyridin-4-ylacetamide (G-33)**

[00970] *N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-pyridin-4-ylacetamide was made following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. The amine-aryl coupling was performed differently to what is described in procedure G. Therefore (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (obtained from the hydrogenation step, 356 mg, 1.2 mmol, 1 equ.) was dissolved in ethylene glycol dimethyl ether (4 mL) in a Schlenk tube. To this solution was added sequentially 4-bromopyridine hydrochloride (280 mg, 1.44 mmol, 1.2 equ), cesium carbonate (940 mg, 2 88 mmol, 2 4 equ),

palladium acetate (32 mg, 0.048 mmol, 0.04 equ) and 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (48 mg, 0.096 mmol, 0 08 equ.). The reaction mixture was flushed with nitrogen and heated to 100°C in the Schlenk tube for 48 h Reaction mixture was concentrated to leave a residue 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 brown oil. The crude product was purified by silica gel chromatography (methylene chloride/methanol: 99/1 to 90/10 gradient) to provide (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-*N*-pyridin-4-yl-1,2,3,4-tetrahydroquinolin-4-amine (125 mg, 28 %)

[00971] To a solution of (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-*N*-pyridin-4-yl-1,2,3,4-tetrahydroquinolin-4-amine (90 mg, 0.24 mmol, 1 equ) in methylene chloride (0.8 mL) was added diisopropylethylamine (84 uL, 0 48 mmol, 2 equ) followed by acetyl chloride (340 uL, 4 80 mmol, 20 equ). The mixture was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (methylene chloride/methanol 97/3) to afford pure *N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-pyridin-4-ylacetamide (60 mg, 61 %).

^{1}H-NMR (CDCl3) δ: 1.20 (d, 3H), 2 20 (s, 3H), 2.30 (m, 1H), 3.75 (s, 3H), 4.80 (m, 1H), 5.65 (m, 1H), 6.60 (d, 1H), 6.70 (d, 2H), 7.05 (t, 1H), 7 10-7 20 (m, 4H), 7.25-7.40 (m, 2H), 8.70 (d, 2H)
MS m/z: 416 (M+1).

[00972] ***N*-(4-chloro-2-methylphenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (G-34)**

[00973] *N*-(4-chloro-2-methylphenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride The amine-aryl coupling was performed differently to what is described in procedure G. Therefore (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (obtained from the hydrogenation step, 500 mg, 1 5 mmol, 1 equ) was dissolved in ethylene glycol dimethyl ether (5 mL) in a Schlenk tube. To this solution was added sequentially 2-bromo-5-chlorotoluene (400 mg, 1.95 mmol, 1.3 equ.), cesium carbonate (684 mg, 2.10 mmol, 1 4 equ), palladium acetate (40 mg, 0.06 mmol, 0.04 equ.) and 2-(Dicyclohexylphosphino)-2',4',6'-tri-i-propyl-1,1'-biphenyl (60 mg, 0.12 mmol, 0.08 equ) The reaction mixture was flushed with nitrogen and heated to 90°C in the Schlenk tube for 48 h. Reaction mixture was concentrated to leave a residue 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 black oil The crude product was purified by silica gel

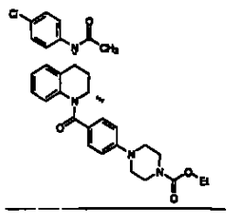
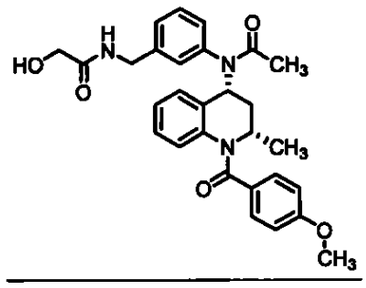
chromatography (methylene chloride/methanol. 99/1) to provide (2*S*,4*R*)-*N*-(4-chloro-2-methylphenyl)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (200 mg, 32 %)

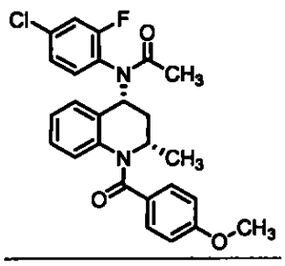
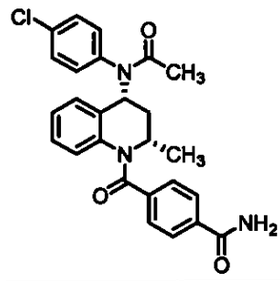
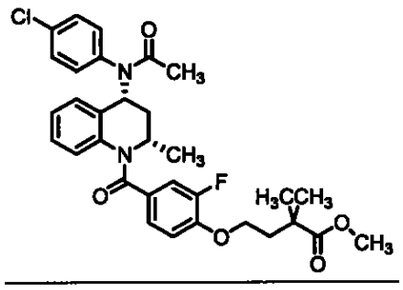
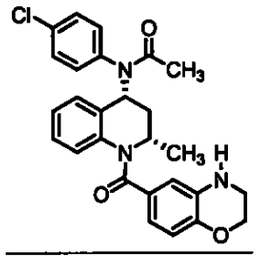
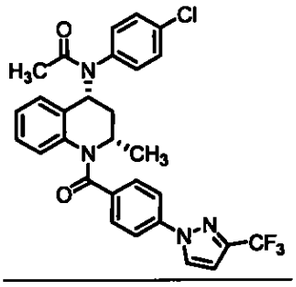
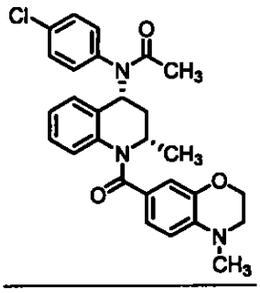
[00974] To a solution of (2*S*,4*R*)-*N*-(4-chloro-2-methylphenyl)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (140 mg, 0.33 mmol, 1 equ) in acetyl chloride (1.0 mL) was added diisopropylethylamine (58 uL, 0 33 mmol, 1 equ.). The mixture was stirred at room temperature for 5 h The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (methylene chloride/methanol 99/1) to afford pure *N*-(4-chloro-2-methylphenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (140 mg, 92 %).

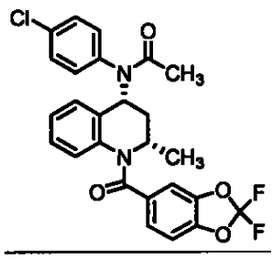
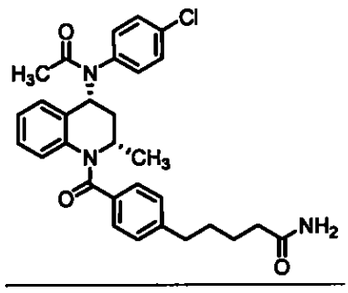
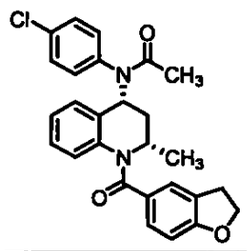
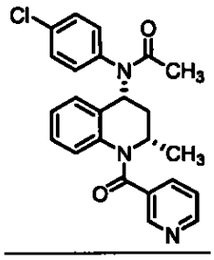
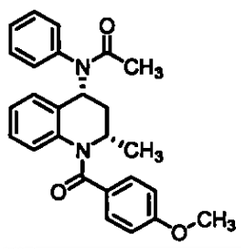
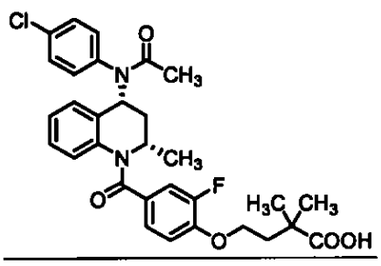
^{1}H-NMR (CDCl3) δ. 1 10 (d, 3H), 1.95 (s, 3H), 2.15 (m, 1H), 2.35 (s, 3H), 3 70 (s, 3H), 4.75 (m, 1H), 5.60 (m, 1H), 6 50 (d, 1H), 6.65 (d, 2H), 6.95 (t, 1H), 7.15-7.30 (m, 6H), 7.40 (s, 1H)

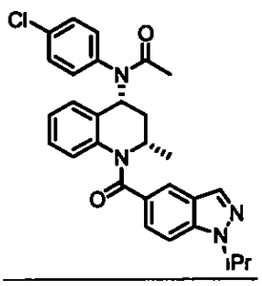
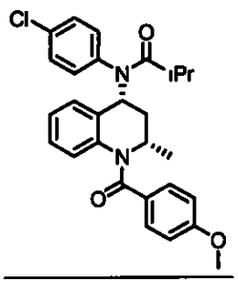
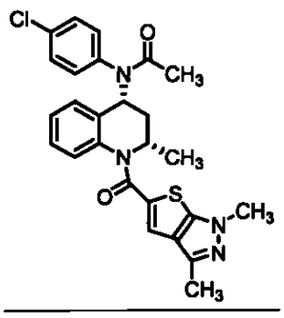
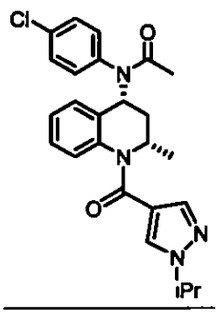
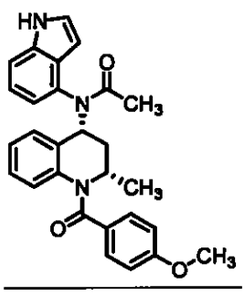
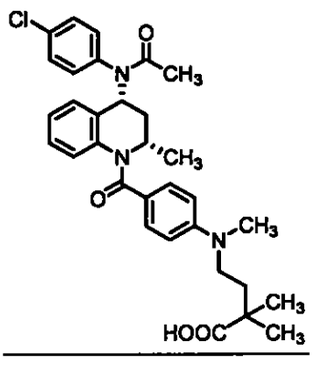
MS m/z· 463 (M+1)

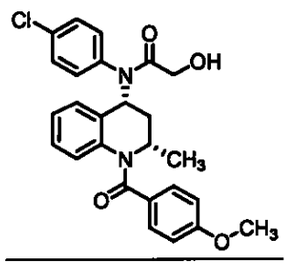
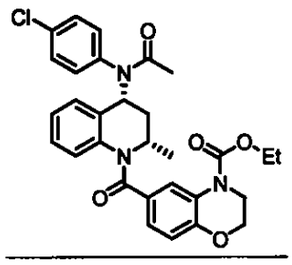
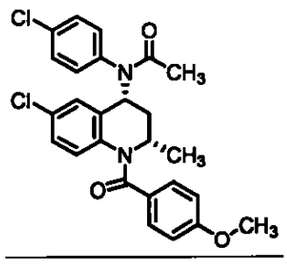
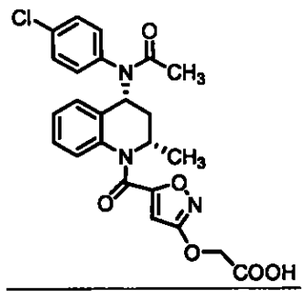
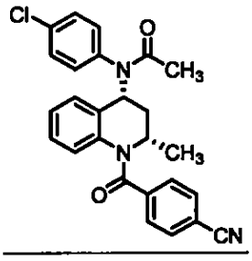
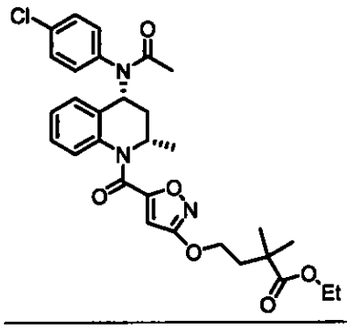
Table 7: Exemplary Compounds:

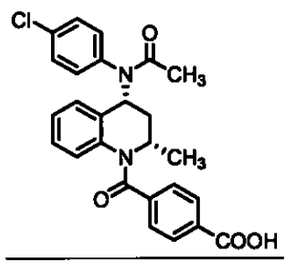
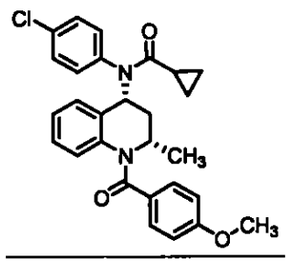
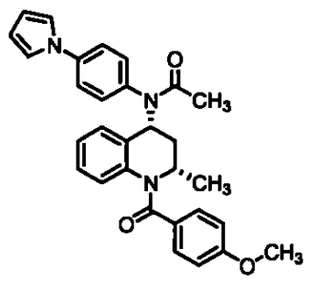
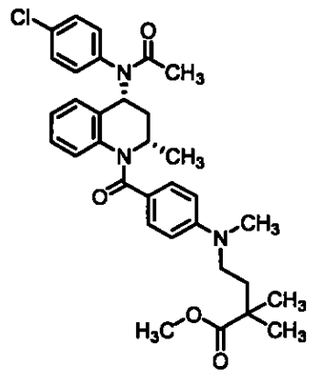
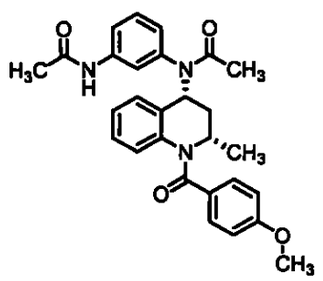
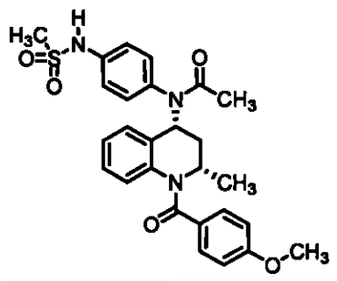
 G-1	 G-2

 G-3	 G-4
 G-5	 G-6
 G-7	 G-8

 G-9	 G-10
 G-11	 G-12
 G-13	 G-14

 G-15	 G-16
 G-17	 G-18
 G-19	 G-20

 G-21	 G-22
 G-23	 G-24
 G-25	 G-26

 G-27	 G-28
 G-29	 G-30
 G-31	 G-32

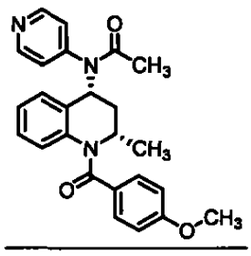
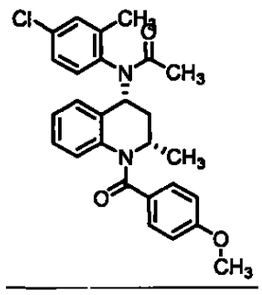
	
G-33	G-34

Table 8: Names of Compounds Exemplified in Table 7:

G-1 Ethyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperazine-1-carboxylate

G-2 *N*-{3-[(Glycoloylamino)methyl]phenyl}-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-3 *N*-(4-Chloro-2-fluorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-4 4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzamide

G-5 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate

G-6 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,4-dihydro-2*H*-1,4-benzoxazin-6-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-7 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

G-8 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

G-9 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(2,2-difluoro-1,3-benzodioxol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

G-10 5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pentanamide

G-11 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(2,3-dihydro-1-benzofuran-5-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-12 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(pyridin-3-ylcarbonyl)-1,2,3,4-

tetrahydroquinolin-4-yl]acetamide

G-13 *N*-[(2*S*,4*R*)-1-(4-Methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-phenylacetamide

G-14 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoic acid

G-15 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-indazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

G-16 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-2-methylpropanamide

G-17 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

G-18 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(1-isopropyl-1*H*-pyrazol-4-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

G-19 *N*-1*H*-Indol-4-yl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-20 4-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoic acid

G-21 *N*-(4-Chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-22 Ethyl 6-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2,3-dihydro-4*H*-1,4-benzoxazine-4-carboxylate

G-23 *N*-[(2*S*,4*R*)-6-Chloro-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide

G-24 [(5-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]acetic acid

G-25 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-cyanobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-26 Ethyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}isoxazol-3-yl)oxy]-2,2-dimethylbutanoate

G-27 4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid

G-28 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide

G-29 *N*-[(2*S*,4*R*)-1-(4-Methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-

[4-(1*H*-pyrrol-1-yl)phenyl]acetamide

G-30 Methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]-2,2-dimethylbutanoate

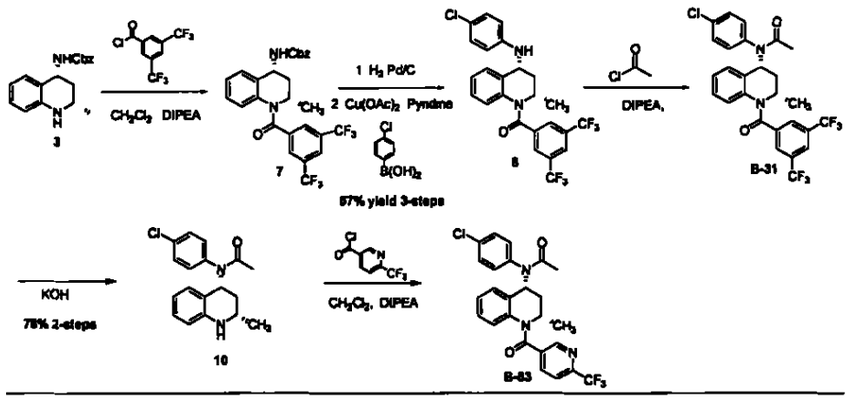
G-31 *N*-[3-(Acetylamino)phenyl]-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

G-32 *N*-[(2*S*,4*R*)-1-(4-Methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-{4-[(methylsulfonyl)amino]phenyl}acetamide

G-33 *N*-[(2*S*,4*R*)-1-(4-Methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-pyridin-4-ylacetamide

G-34 *N*-(4-Chloro-2-methylphenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

Scheme 22



[00975] General Procedure H:

[00976] *N*-(4-chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]carbonyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (H-83)

[00977] To a solution of (2*S*, 4*R*)-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-carbamic acid benzyl ester (20.0 g, 0 067 mol) in methylene chloride (150 mL) at room temperature was added diisopropylethylamine (40.2 mL, 0 288 mol) at 0 °C followed by addition of 3,5-bis(trifluoromethyl)benzylchloride (24 2 g, 15 8 mL, 0 087 mol) A catalytic amount of 4-dimethylaminopyridine was added and the reaction turned a dark brown and was allowed stir overnight at room temperature. The mixture was partitioned between sodium bicarbonate (saturated) and methylene chloride The organic layer was separated and dried over sodium sulfate, filtered and concentrated to a brown solid. The crude material was taken up in 150 mL of methanol and stirred with 15 g of cesium carbonate for 20 min. 160 mL of methylene chloride and 150 mL of water was

added to the solution and separated. The aqueous layer was extracted 2 additional times with methylene chloride The organics were collected together and dried over sodium sulfate, filtered and concentrated down to give a light orange solid (36 g, quant.).

[00978] Benzyl (2S,4R)-1-(3,5-bis(trifluoromethyl)benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-ylcarbamate (36 g, 0.067 mol) was dissolved in ethanol (135 mL). The vessel in which resided the resulting solution was evacuated and backfilled with argon. A catalytic amount of Palladium on Carbon (10 %) was added. The vessel was once again evacuated and this time was backfilled with hydrogen and shaken in a Parr bottle at 10 psi hydrogen. Reaction was allowed to shake until no starting material remained (1 day). The mixture was carefully filtered through a Celite ® pad and concentrated to afford the crude amine (26.6g, 99 %).

[00979] (3,5-bis(trifluoromethyl)phenyl)((2S,4R)-4-amino-2-methyl-3,4-dihydroquinolin-1(2H)-yl)methanone (26 6 g, 0.066 mol) was dissolved in 1.0 L of dry methylene chloride. To the solution was also added 4-chlorophenylboronic acid (20.7 g, 0 132 mol, 2 equ.), triethylamine (71 2 mL, 0.496mol, 7.5 equ) and copper(II)acetate (24 g, 0 132 mol, 2 equ.). Finally 20 gm of molecular sieves was added. The heterogeneous green mixture was stirred open to air for 1 h, an additional 2 equivalent of 4-chlorophenylboronic acid (20.7 gm, 0 132 mol) was added. The mixture was allowed to stir at room temperature overnight and was then filtered through Celite ®. The filtrate was diluted with ethyl acetate to precipitate the copper salts, the mixture was filtered a second time through Celite ® to give a brown solution which was concentrated down The residue was purified by flash chromatography (95 % methylene chloride / 5 % ethyl acetate) to afford 19 54 g of the product in 57 % yield as a white solid.

[00980] A solution of (3,5-bis(trifluoromethyl)phenyl)((2S,4R)-4-(4-chlorophenylamino)-2-methyl-3,4-dihydroquinolin-1(2H)-yl)methanone (19.44 g, 0 037 mol) in acetyl chloride (5 mL) was cooled to 0 °C and triethylamine (6 59 mL, 0.037 mol) was added dropwise over ~30 min, a precipitate forms during this time An additional 250 mL of methylene chloride was added to completely dissolve all the precipitate The reaction was allowed to stir overnight at room temperature The mixture was concentrated under reduced pressure, partitioned between ethyl acetate and 1N sodium hydroxide while cooled to 0 °C. The aqueous layer was extracted 3 times with ethyl acetate washed with sat. aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (25/75 hexanes/ethyl acetate gradient) to afford pure N-((2S,4R)-1-(3,5-bis(trifluoromethyl)benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-N-(4-chlorophenyl)acetamide (H-31) (18 2 g, 86 %)

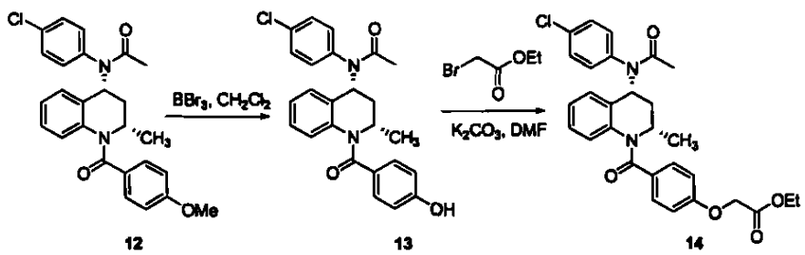
^{1}H-NMR ($CDCl_3$) δ: 1.20 (d, 3H), 1.10-1.20 (m, 1H), 2.03 (s, 3H), 2 24-2.40 (m, 1H), 4 72-4.86 (m, 1H), 5.40-5.70 (m, 1H), 6.41 (d, 1H), 6.94 (t, 1H), 7.18-7.28 (m, 4H), 7 37 (t, 2H), 7 59 (s, 2H), 7 76 (s, 1H).

MS m/z 555 (M +1).

[00981] To a solution of N-((2S,4R)-1-(3,5-bis(trifluoromethyl)benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-N-(4-chlorophenyl)acetamide (5.5 g, 9.9 mmol) in ethanol (60 mL) and water (10 mL) was added potassium hydroxide (3 00g, 53.5 mmol) The mixture was heated to 70 °C. After 1 hour, an additional portion of potassium hydroxide (3.00g, 53.5 mmol) was added and the reaction was stirred for an additional 30m. The mixture was partitioned between ethyl acetate and sodium bicarbonate (sat aq.). The organic layer was separated, washed twice with brine, dried over sodium sulfate, filtered and concentrated. The crude material was subjected to flash chromatography (2/1 hexanes/ethyl acetate gradient), resulting in pure N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide as a white solid (2.85 g, 91%).
^{1}H-NMR (CDCl3) δ: 1 10 (d, 3H), 1.30 (m, 1H), 1.80 (m, 1H), 1.90 (s, 3H), 3.50 (m, 1H), 3.60 (m, 1H), 6 30 (s broad, 1H), 6 45 (d, 1H), 6 70 (t, 1H), 6.90 (d, 2H), 7.00 (t, 1H), 7.15-7 25 (m, 3H). MS m/z 315 (M+1).

[00982] To a solution of N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (104 mg, 0 33 mmol, 1 equ) in methylene chloride (2 0 mL) at room temperature was added diisopropylethylamine (86 uL, 0.49 mmol, 1 50 equ.) followed by 6-trifluoromethyl nicotinyl chloride (104 mg, 0 49 mmol, 1 50 equ.). The reaction was stirred over night at room temperature. The mixture was concentrated, then poured into water and extracted with ethyl acetate. The extracts were washed with 1 M (aq) NaOH and brine, dried over magnesium sulfate, filtered, dried and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate/hexane 1 1) to afford the pure *N*-(4-chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]carbonyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (140 mg, 87 %)
^{1}H-NMR ($CDCl_3$) δ: 1.16-1.18 (m, 1H), 1.17 (d, 3H), 1.99 (s, 3H), 2.20-2 28 (m, 1H), 4 77 (sextet, 1H), 5.50 (bs, 1H), 6.44 (d, 1H), 6.93 (t, 1H), 7.16-7 22 (m, 3H), 7 45-7 30 (m, 5H), 8.65 (s, 1H)
MS m/z = 465 (M+1).

Scheme 23



12 13 14

[00983] General Procedure I:

[00984] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (13)

[00985] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was prepared following general procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride. (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-methoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in dichloromethane and a solution of BBr_3 (1.0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for until no starting material remained The reaction was washed with sat $NaHCO_3$ carefully and brine. The organics were dried over $MgSO_4$, filtered and concentrated down The residue was purified by Biotage flash chromatography using 100 % EtOAc to give (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide

[00986] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid ethyl ester (14)

[00987] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.147 g) was dissolved in DMF at room temperature and K_2CO_3 was added Ethyl 4-bromoacetate (0 065 g) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (80/20 hexanes/ethyl acetate – 50/50 hexanes ethyl acetate gradient) to afford the product in 130 mg, 73 %.

[00988] (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionamide (H-1)

[00989] (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionamide was prepared from (2*S*,4*R*)- 3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionic acid. The acid (0 060 g, 0.118 mmol) was dissolved in DMF (1 5 mL) at room temperature and HOBt (0.024 g, 0.177 mmol), HATU (0 068 g, 0 177 mol), and diisopropylethylamine (0.082 mL, 0.472 mmol) was added followed by ammonium chloride (0.014 g, 0.236 mmol) and stirred at room temperature for 18 h. The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1 23 (m, 1H), 1.64 (br, 1H), 2.01 (s, 3H), 2.27 (m, 1H), 2 44 (t, 2H), 3.37 (t, 2H), 4.69 (m, 1H), 5.40 (br, 1H), 5 61 (brs, 1H), 5.80 (br, 1H), 6 31 (d, 2H), 6 59 (d, 1H), 6.94 (t, 1H), 7 02 (d, 2H), 7.10-7.23 (m, 4H), 7 36 (d, 2H).

MS m/z: 505 3 (M+1).

[00990] 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoic acid (H-2)

[00991] To the solution of methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate (176mg, 0 30 mmol) in MeOH/THF (1 mL/1mL) was added excessive LiOH (1N aqueous solution) The reaction mixture was stirred at r t overnight The reaction was quenched by adding 6N HCl to PH 2. The mixture was concentrated under reduced pressure to remove MeOH and THF. DCM (30 mL) was added The reaction mixture was washed with brine (30 mL) The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford slightly yellow solid product (120 mg, 70%)

^{1}H-NMR ($CDCl_3$, 300MHz) δ· 1.11-1.13 (d, 3H), 1 25 (s, 6H), 2.02-2.08 (m, 5H), 2 22-2.40 (m, 2H), 3.99-4 04 (t, 2H), 4.71-4 76 (q, 1H), 5.46 (b, 1H), 6.51-6.75 (m, 3H), 6 92-7 06 (m, 2H), 7 16-7 38 (m, 5 H).

MS m/z: 567 (M+1).

[00992] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-fluoro-acetic acid ethyl ester (H-3)

[00993] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (202 mg, 0 46 mmol) was dissolved in DMF (2 mL) at room temperature. Cs_2CO_3 (760 mg, 2.33 mmol) was added followed by bromo-fluoro-acetic acid ethyl ester (0 070 mL, 0 583 mmol) and the reaction was allowed to stir overnight The mixture was partitioned between methylene chloride and water; the organic layer was dried over Na_2SO_4, filtered and concentrated The crude residue was purified by silica gel chromatography (2/1 hexanes/ ethyl acetate) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (m, 1H), 1.3 (t, 3H), 2.0 (s, 3H), 2 3 (m, 1H), 4 3 (q, 2H), 4.8 (m, 1H), 5.6 (bs, 1H), 5.9 (d, 1H), 6 5 (d, 1H), 6.9 (m, 3H), 7.2 (m, 6H), 7 4 (d, 2H).

MS m/z: 539 (M+1)

[00994] **(2*S*,4*R*)- 2-[4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetamide (H-4)**

[00995] (2*S*,4*R*)- 2-[4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetamide was made from (2*S* ,4*R*)- [4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetic acid. The acid (0 120 g, 0.21 mmol) was dissolved in DMF (2 mL) at room temperature and HOBt (0.043 g, 0.32 mmol), HATU (0.122 g, 0.32 mol), and diisopropylethylamine (0 15 mL, 0.64 mmol) was added followed by ammonium chloride (0.023 g, 0.42 mmol) and stirred at room temperature for 18 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down The crude residue was purified HPLC purification

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1.20 (m, 1H), 2.00 (s, 3H), 2 24 (m, 1H), 3.04 (t, 4H), 3 50 (m, 6H), 4.70 (m, 1H), 5.40(br, 1H), 5 56 (brs, 1H), 5.80 (br, 1H), 6.51 (d, 1H), 6.63 (d, 2H), 6 89 (t, 1H), 7 07-7 25 (m, 6H), 7 35 (d, 2H).

MS m/z 560 (M+1)

[00996] **4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-5)**

[00997] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture stirred at 40 °C overnight. The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

^{1}H-NMR ($CDCl_3$) δ: 1.11-1 21 (m, 10H), 1 25 (s, 6H), 2.03 (t, 2H), 2.21-2.29 (m, 1H), 2 61 (sp, 1H), 3.95 (t, 2H), 4.69-4 76 (m, 1H), 5 60 (br s, 1H), 6.51 (d, 1H), 6 62 (d, 2H), 6 91 (t, 1H), 7.11-7.43 (m, 8H)

MS m/z· 577 (M+1)

[00998] **{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]amino}acetic acid (H-6)**

[00999] {[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]amino}acetic acid was prepared from (2*S*,4*R*)-N-{1-[4-(3-amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide

(2*S*,4*R*)-N-{1-[4-(3-amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (0.032g, 0 065 mmol) was dissolved in dimethylformamide, ethyl bromoisobutyrate (0.05mL, 0.26 mmol) and potassium carbonate (0.018g, 0.13 mmol) were added The reaction was heated to 50°C for 17h. The reaction was concentrated down and purified using 50%ethyl acetate/ 50% hexane to 100% ethyl acetate to give 0 007g, 12% yield of {[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl] amino}acetic ethyl ester.

[001000]

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.17 (t, 3H), 1.23 (m, 1H), 1 55 (s, 6H), 2 02 (s, 3H), 2.06 -2.12 (m, 1H), 2.28 (m, 1H), 3.63 (q, 2H), 3 70-3 77 (m, 2H), 3.91 -3.95 (m, 1H), 4.13 (q, 2H), 4.74 (sextet, 1H), 5.58 (bs, 1H), 6.49-6.68 (m, 3H), 6 92 (t, 1H), 7 05-7 28 (m, 6H), 7.37 (d, 1H) MS m/z = 606 1 (M+1)

[001001] {[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl] amino}acetic ethyl ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature overnight. The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give {[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]amino}acetic acid 0 005g, 75% yield.
MS m/z . 578 3 (M+1).

[001002] *N*-[(2*S*,4*R*)-1-(4-*tert*-butylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (H-7)

[001003] *N*-[(2*S*,4*R*)-1-(4-*tert*-Butylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide was synthesized according to general procedure H substituting 4-*tert*-butylbenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. The rest of the procedure was followed as indicated in general procedure H to yield *N*-[(2*S*,4*R*)-1-(4-*tert*-butylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide.

^{1}H-NMR ($CDCl_3$) δ: 1 13-1.22 (m, 1H), 1.14 (d, 3H), 1.22 (s, 9H), 2.03 (s, 3H), 2.24-2 35 (m, 1H), 4 72-4.80 (m, 1H), 5.61 (br s, 1H), 6 52 (d, 1H), 6.89 (t, 1H), 7.10-7.29 (m, 8H), 7.37 (d, 2H).
MS m/z. 475 (M+1)

[001004] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{1-[4-(3-hydroxy-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-8)

[001005] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF (5 mL) at room temperature. K_2CO_3 was added

followed by 4-bromo-2-methyl-butan-2-ol and the reaction was allowed to stir at 90°C over night. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by HPLC to afford the product.

[001006] 4-bromo-2-methyl-butan-2-ol was prepared from 3-bromo-propionic acid ethyl ester. 3-Bromo-propionic acid ethyl ester (1 0 g, 5.5 mmol) was dissolved in 10 mL of ether and 3.7 mL of methyl magnesium bromide (3 0 M in ether) was added at 0°C. The raction was stirred at 0°C until no starting material remained The reaction was quenched with a sat'd ammonium chloride solution and extracted 3 x with ether The organic were collected together and dried over $MgSO_4$, filtered and concentrated down to give 4-bromo-2-methyl-butan-2-ol.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (d, 3H), 1 24 (s+m,7H), 1 90 (t, 2H), 2.01 (s, 3H), 2.22 (m, 2H), 4.07 (t, 2H), 4.72 (m, 1H), 5.60 (brs, 1H), 6.50 (d, 1H), 6.65 (d, 2H), 6 90 (t, 1H), 7.10-7 20 (m, 5H), 7 25 (t, 1H), 7 35 (d, 2H)

MS m/z· 521 (M+1).

[001007] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-iodobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-9)

[001008] Purification of crude material in the last step of the synthesis of 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid also allowed to isolate *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-iodobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide as a by-product in the synthesis (45 mg).

^{1}H-NMR (MeOD) δ: 1 15 (d, 3H), 2.05 (s, 3H), 2.45 (m, 1H), 4.75 (m, 1H), 5.55 (m, 1H), 6.55 (d, 1H), 6 95 (t, 1H), 7 25 (m, 5H), 7.30-7 55 (m, 5H).

MS m/z: 545 (M+1).

[001009] (2*S*,4*R*)-N-{1-[4-(3-Acetylamino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (H-10)

[001010] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (99 mg, 0.202 mmol) was dissolved in methylene chloride (2 mL) and triethylamine (0.056 mL, 0 404 mmol) and cooled to -40 °C Acetyl chloride (15 drops via pipet) was added and the mixtrue was warmed to 0 °C for 30 minutes. The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated The crude residue was purified by silica gel chromatography (1/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (s, 3H), 1.2 (m, 1H), 1 9 (s, 3H), 2.0 (m, 2H), 2 0 (s, 3H), 2 3 (m, 1H), 3.4 (q, 2H), 4.0 (t, 2H), 4.7 (m, 1H), 5.6 (bs, 1H), 5 7 (bs, 1H), 6.5 (d, 1H), 6 6 (d, 2H), 6 9 (t, 1H), 7.2 (m, 6H), 7.4 (d, 2H).
MS m/z: 534 (M+1)

[001011] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(4,4,4-trifluoro-3-hydroxy-3-trifluoromethyl-butoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-11)

[001012] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF (5 mL) at room temperature. K_2CO_3 was added followed by toluene-4-sulfonic acid 4,4,4-trifluoro-3-hydroxy-3-trifluoromethyl-butyl ester and the reaction was allowed to stir at 90 °C over night. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by HPLC to afford the product.

[001013] Toluene-4-sulfonic acid 4,4,4-trifluoro-3-hydroxy-3-trifluoromethyl-butyl ester was prepared from 4,4,4-trifluoro-3-hydroxy-3-trifluoromethyl-butyric acid 4,4,4-trifluoro-3-hydroxy-3-trifluoromethyl-butyric acid (1.74g, 7 0 mmol) was dissolved in THF (2 mL) at 0°C and BH_3 SMe_3 (2.6 mL, 26 mmol) was added dropwise (Ref· Tetrahedron, **2002**, 9839). The reaction was allowed to warm to room temperature and stir for 16h. The reaction was quenched with methanol and the solvent was removed to give the crude 4,4,4-trifluoro-3-trifluoromethyl-butane-1,3-diol. The alcohol was converted to the tosylate by addition of 4,4,4-trifluoro-3-trifluoromethyl-butane-1,3-diol dissolved in pyridine (2 mL) to tosyl chloride (1 39 mL) in 2 mL of CH_2Cl_2 and a catalytic amount of DMAP The reaction was stirred at room temperature for 2 h and quenched
^{1}H-NMR ($CDCl_3$) δ: 1 12 (m, 4H), 2.01 (s, 3H), 2.24 (m, 1H), 2.25 (t, 2H), 3 94 (t, 2H), 4.70 (m, 1H), 5.53 (brs, 2H), 6.48 (d, 1H), 6 61 (d, 2H), 6.93 (t, 1H), 7 09-7.27 (m, 6H), 7 37 (d, 2H).
MS m/z· 629 (M+1).

[001014] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid amide (H-12)

[001015] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid (0 070g, 0.125 mmol) was converted to the amide by dissolving in THF (1 mL) at room temperature. HOBt (0 025 g), EDCI (0 035 g), and ammonium chloride (0.014 g, 0 25 mmol) was added along with 2 drops of DMF and stirred at room temperature for 11 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by

silica gel chromatography (50% ethyl acetate/50% methanol) to afford the product as a white powder in a 71% yield

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 4H), 1 19-1 60 (m, 7H), 2 01 (s, 4H), 2 20-2 39 (m, 2H), 4 72 (sextet, 1H), 5 60 (bs, 1H), 6.54 (d, 1H), 6.63 (d, 2H), 6.91 (t, 1H) 7.11-7.38 (m, 8H).

MS m/z 560 (M+1).

[001016] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(1H-tetrazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-13)

[001017] The nitrile was prepared from (2*S*,4*R*)- N-(4-chloro-phenyl)-N-{1-[4-(3-cyano-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide by dissolving in toluene, sodium azide and triethylammonium hydrochloride were added and the mixture was heated to 80 °C over night. Reaction was cooled to room temperature and water was added, followed by hydrochloric acid (1 N) until acidic. The aqueous solution was extracted three times with dichloromethane. The combined extracts were dried over magnesium sulfate, filtered, dried and concentrated. The crude product was triturated with ethyl ether/hexanes to yield a white solid in 63% yield

^{1}H-NMR ($CDCl_3$) δ. 1.02 (d, 3H), 1.19 (m, 1H), 1.89 (s, 3H), 1.96 (m, 2H), 2.11 (m, 1H), 2.79 (m, 2H), 3.63 (m, 2H), 4.59 (sextet, 1H), 5.42 (bs, 1H), 6 35 (m, 3H), 6.77 (t, 1H), 6 91-7.08 (m, 7H), 7.22 (d, 1H).

MS m/z· 545 (M+1).

[001018] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (H-14)

[001019] To a solution of *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide (200 mg, 0.42 mmol, 1 equ.) in methylene chloride (0.3 mL) was added a 1 M solution of boron tribromide in methylene chloride (1.2 mL, 1 26 mmol, 3 equ.). The reaction mixture was stirred at room temperature for 4 h, then the reaction was quenched with methanol and concentrated. The residue 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 *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide as a beige powder (190 mg, 98 %).

[001020] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was made from *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]cyclopropanecarboxamide following general procedure I, substituting methyl 4-bromo-2,2-dimethylbutanoate for ethyl 4-bromoacetate to yield methyl 4-(4-{[(2*S*,4*R*)-4-[(4-

chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

^{1}H-NMR (CDCl3) δ: 0.75 (m, 2H), 1.10 (m, 2H), 1.20 (d, 3H), 1 25 (s, 6H), 1 45 (m, 1H), 2.05 (t, 2H), 2.30 (m, 1H), 3.65 (s, 3H), 3.95 (t, 2H), 4.75 (m, 1H), 5 60 (m, 1H), 6.50 (d, 1H), 6.60 (d, 2H), 6.90 (t, 1H), 7 10-7 45 (m, 8H)

MS m/z 589 (M+1)

[001021] Methyl 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoate (H-15)

[001022] Methyl 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoate was prepared following general procedure B, substituting methyl 5-[4-(chlorocarbonyl)-2-fluorophenyl]-2,2-dimethylpentanoate for 6-trifluoromethyl nicotinyl chloride. (Methyl 5-[4-(chlorocarbonyl)-2-fluorophenyl]-2,2-dimethylpentanoate was prepared in five steps from 4-bromo-3-fluorobenzoic acid To a solution of 3-bromo-3-fluorobenzoic acid in toluene/methanol was added dropwise a 2M solution of trimethylsilyl diazomethane until slight yellow coloration persists indicating reaction had gone to completion. Reaction mixture was concentrated to give methyl-3-bromo-3-fluorobenzoate. To a solution of methyl-3-bromo-3-fluorobenzoate in dimethylformamide was added sequentially palladium acetate, triphenylphosphine, tetrabutylammonium chloride, potassium acetate and methyl 2,2-dimethylpent-4-enoate Reaction mixture was heated under microwave irradiation at 130°C for 10 m to give methyl 3-fluoro-4-[(1*E*)-5-methoxy-4,4-dimethyl-5-oxopent-1-en-1-yl]benzoate. Hydrogenation of this diester gave methyl 3-fluoro-4-(5-methoxy-4,4-dimethyl-5-oxopentyl)benzoate which benzoic ester was selectively hydrolyzed using lithium hydroxide to give 3-fluoro-4-(5-methoxy-4,4-dimethyl-5-oxopentyl)benzoic acid. Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded methyl 5-[4-(chlorocarbonyl)-2-fluorophenyl]-2,2-dimethylpentanoate in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford methyl 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoate.

^{1}H-NMR (CDCl3) δ. 1.15 (d, 3H), 1.45 (m, 4H), 2.05 (s, 3H), 2 30 (m, 1H), 2.55 (m, 2H), 3.65 (s, 3H), 4 80 (m, 1H), 5 60 (m, 1H), 6.55 (d, 1H), 6 75 (d, 1H), 6.90-7.05 (m, 3H), 7 15-7.25 (m, 3H), 7 30-7 40 (m, 3H).

MS m/z 579 (M+1).

[001023] (2*S*,4*R*)-N-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid (H-16)

[001024] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 32 g, 0.74 mmol) was dissolved in 10 ml DMF at room temperature and K_2CO_3 (0 51 g, 3.7 mmol) was added. 3-Chloro-2,2-dimethyl-propionic acid ethyl ester (0 25 g, 1.52 mmol) was added and the reaction was allowed to heat to 90°C for 6 days. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (60% EtOAc/ 40% Hexane) to afford the (2*S*,4*R*)-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid ethyl ester (0.13 g, 32%)

[001025] The ester was hydrolyzed to the acid by dissolving in 8 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.052 g in 2.5 ml water) was added. The mixture was heated to 40 °C for 3 hours. The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give the product (0.098 g, 79%).

^{1}H-NMR ($CDCl_3$) δ: 1 13 (d, 3H), 1.15 (t, 1H), 1.31 (s, 6H), 2 03 (s, 3H), 2.27 (m, 1H), 3.88 (q, 2H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6.52 (d, 1H), 6 69 (d, 2H), 6 83 (t, 2H), 7.08-7.35 (m, 6H), 7.38 (d, 2H).

MS m/z· 535 (M+1)

[001026] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propane-1-sulfonic acid (H-17)

[001027] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (207 mg, 0.481 mmol) was dissolved in DMF (5 mL) at room temperature NaH (58 mg, 2.40 mmol) was added followed by 3-chloro-propane-1-sulfonic acid (sodium salt, 135 mg, 0.60 mmol) and the reaction was allowed to stir over night The mixture was partitioned between methylene chloride and HCl (1 0N/water), then extracted three times with methylene chloride, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by preparatory HPLC to afford the product

^{1}H-NMR ($CDCl_3$) δ 1.1 (d, 3H), 1 1 (m, 1H), 2.0 (s, 3H), 2.2 (m, 3H), 3 2 (t, 2H), 3.9 (t, 2H), 4 8 (d, 1H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6.9 (t, 1H), 7.2 (m, 6H), 7 4 (d, 2H), 10.6 (bs, 1H).

MS m/z· 557 (M+1).

[001028] Methyl 4-(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate (H-18)

[001029] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (476 mg, 1 05 mmol) was dissolved in DMF at room temperature and Cs_2CO_3 (854 mg, 2.63 mmol) was added. Methyl 4-bromo-2,2-dimethylbutanoate (702 mg, 1 58

mmol) was added and the reaction was stirred at r t. overnight. The reaction mixture was concentrated under reduced pressure The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford methyl 4-(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate (286 mg, 52%)

^{1}H-NMR ($CDCl_3$, 300MHz) δ 1 11-1.14 (d, 3H), 1.18-1 19 (d, 6H), 2.00 (s, 3H), 2 22-2.27 (m, 1H), 3 64 (s, 3H), 3.88-3.95 (m, 1H), 4.69-4.77 (m, 1H), 5 57 (b, 1H), 6.48-6.50 (d, 1H), 6.72-6.84 (m, 3 H), 6.91-6.96 (m, 1H), 7 12-7.37 (m, 6H).

MS m/z. 581 (M+1)

[001030] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-19)

[001031] *N*-[(2*S*,4*R*)-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (543 mg, 0 95 mmol) was dissolved in dichloromethane and a solution of TBAF (1 0 M in THF, 5.0 mL) was added, the reaction mixture was stirred at room temperature for until no starting material remained The reaction was washed with sat. $NaHCO_3$ and brine carefully The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using Hexanes-EtOAc system to give *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (477 mg, 100%).

^{1}H-NMR ($CDCl_3$) δ 1.15 (d, 3H), 1.25 (m, 2H), 2.07 (s, 3H), 2.30 (b, 1H), 4 75 (m, 1H), 6.55 (d, 1H), 6 68 (d, 1H), 6 62-6 70 (m, 3H) 7.15-7 25 (m, 4H), 7.35-7.42 (m, 2H)

MS m/z· 453 (M+1)

[001032] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N,N-diethyl-butyramide (H-20)

[001033] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N,N-diethyl-butyramide was prepared from (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (0.511 g, 0.93 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature 4 hours The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-1-ethylidene-pentG-2,4-dienyloxy)-butyric acid in 74% yield. The acid

(0.050g, 0.09mmol) was converted to the amide by dissolving in THF (2 mL) at room temperature. HOBt (0.019 g), EDCI (0.022 g), and diethylamine (0.010 mL) was added along with 2 drops of DMF and stirred at room temperature for 11 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% ethyl acetate/50% hexane to 100% ethyl acetate) to afford the product (0.023 mg, 54%)

^{1}H-NMR ($CDCl_3$) δ 0 91 (d, 3H), 0.96 (t, 6H), 1 06 (m, 1H), 1.58 (m, 2H), 1.86 (s, 3H), 2 11 (m, 1H), 2.29(m, 2H), 3.11-3.17 (m, 4H), 3 78 (m, 2H), 4.56 (sextet, 1H), 5.43 (bs, 1H), 6 34 (d, 1H), 6.48 (d, 2H), 6.76 (t, 1H), 6.59-7 19 (m, 8H).

MS m/z: 576 (M+1)

[001034] *N*-{(2*S*,4*R*)-6-chloro-2-methyl-1-[(3-methylisoxazol-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide (H-21)

[001035] *N*-{(2*S*,4*R*)-6-chloro-2-methyl-1-[(3-methylisoxazol-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide was prepared following the procedure described for *N*-{(2*S*,4*R*)-1-[3,5-bis(trifluoromethyl)benzoyl]-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide substituting 3-methylisoxazole-5-carbonyl chloride for 3,5-bistrifluoromethyl benzoyl chloride.

^{1}H-NMR ($CDCl_3$) δ 1.10 (d, 3H), 1.10 (1H, m), 2.02 (s, 3H), 2 20 (s, 3H), 2 24-2.32 (m, 1H), 4 68-4 74 (m, 1H), 5.45-5.50 (m, 1H), 5 80 (s, 1H), 6.80 (d, 1H), 7.10-7.40 (m, 7H)

MS m/z: 458 (M + 1)

[001036] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid (H-22)

[001037] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid ethyl ester (0.060, 0.10 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added. The mixture was stirred at room temperature 10 hours. The mixture was cooled to room temperature, acidified to form a white precipitate The solid was filtered to give (2*S*,4*R*)-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid as a white powder in 62% yield

^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 4H), 1.24-1 60 (m, 5H), 2 01 (s, 6H), 2.20-2.39 (m, 2H), 4 72 (sextet, 1H), 5.60 (bs, 1H), 6.53 (d, 1H), 6.64 (d, 2H), 6 91 (t, 1H) 7.11-7 38 (m, 8H).

MS m/z 561 (M+1).

[001038] Methyl 5-(4-{[(2*S*,4*R*)-4-[[(acetyloxy)acetyl](4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate (H-23)

[001039] Methyl 5-(4-{[(2*S*,4*R*)-4-[[(acetyloxy)acetyl](4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate was prepared following general procedure B, substituting acetoxyacetylchloride for acetyl chloride in step 3 to provide 2-[{(2*S*,4*R*)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}(4-chlorophenyl)amino]-2-oxoethyl acetate.

[001040] To a solution of 2-[{(2*S*,4*R*)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}(4-chlorophenyl)amino]-2-oxoethyl acetate (500 mg, 0.82 mmol, 1equ) in ethanol (6 mL) and water (1 mL) was added potassium hydroxide (229 mg, 4 1 mmol, 5 equ.) The mixture was heated to 70 °C for 4h. The mixture was neutralized with 1N aqueous HCl and extracted with ethyl acetate. The organic layer was separated, washed with a saturated aqueous solution of sodium bicarbonate and twice with brine, dried over sodium sulfate, filtered and concentrated to give crude *N*-(4-chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide used as such in the next step.

[001041] *N*-(4-Chlorophenyl)-2-hydroxy-*N*-[(2*S*,4*R*)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (300 mg, 0.91 mmol, 1 equ.) was dissolved in methylene chloride (3 mL). To this solution was added EDC (464 mg, 2.7 mmol, 3 equ.) and acetic acid (164 mg, 2 7 mmol, 3 equ.) and the reaction mixture was stirred at room temperature for 20h. Reaction mixture was concentrated and the residue dissolved in ethyl acetate and washed with water, brine, and then dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (methylene chloride/methanol: 99/1 to 98/2 gradient) to afford 2-{(4-chlorophenyl)[(2*S*,4*R*)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-oxoethyl acetate (240 mg, 84 %).

[001042] To a solution of 2-{(4-chlorophenyl)[(2*S*,4*R*)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}-2-oxoethyl acetate (170 mg, 0.45 mmol, 1 equ.) in methylene chloride (2.0 mL) at room temperature was added diisopropylethylamine (127 uL, 0.73 mmol, 1.60 equ.) followed by methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate (196 mg, 0 73 mmol, 1 60 equ.). The reaction was stirred over night at room temperature. The mixture was concentrated, then poured into water and extracted with ethyl acetate The extracts were washed with brine, dried over magnesium sulfate, filtered dried and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate/hexane 25/75 to 1.1 gradient) to afford the pure methyl 5-(4-{[(2*S*,4*R*)-4-[[(acetyloxy)acetyl](4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate (110 mg, 40 %).

^{1}H-NMR (CDCl3) δ· 1 10 (s, 6H), 1 15 (d, 3H), 1.45 (m, 4H), 2.15 (s, 3H), 2.35 (m, 1H), 2 50 (m, 2H), 3.65 (s, 3H), 4.40-4.55 (q, 2H), 4.80 (m, 1H), 5.55 (m, 1H), 6.55 (d, 1H), 6 90-7.0 (m, 3H), 7 05-7.20 (m, 3H), 7 30-7 55 (m, 5H)

MS m/z: 619 (M+1).

[001043] 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-1-methylpyrrolidine-2-carboxylic acid (H-24)

[001044] 4-Hydroxy-1-methyl-pyrrolidine-2-carboxylic acid (0 27 g, 1.85 mmol) was dissolved in 5 ml methanol at room temperature and (trimethylsilyl)diazomethane (2M solution in hexane) was added until solution become yellow. The mixture was concentrated down to afford crude 4-hydroxy-1-methyl-pyrrolidine-2-carboxylic acid methyl ester, which was converted to 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-1-methylpyrrolidine-2-carboxylic acid following the same procedure as for the preparation of (1*R*,2*R*)-2-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylic acid

[001045] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyramide (H-25)

[001046] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyramide was prepared from (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford pure (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide (63%).

^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 3H), 1.15 (t, 1H), 1.25 (s, 6H), 1 98 (t, 2H), 2.04 (s, 3H), 2.27 (m, 1H), 3.96 (t, 2H), 4 72 (sextet, 1H), 5 52 (br, 2H), 5.58 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6.86 (t, 1H), 7.08-7 35 (m, 6H), 7.38 (d, 2H).

MS m/z: 548 (M+1)

[001047] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-pyridin-3-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-26)

[001048] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF (5 mL) at room temperature. K_2CO_3 was added followed by 3-(3-bromo-propyl)-pyridine and the reaction was allowed to stir at 90°C over night. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and

water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by HPLC to afford the product

^{1}H-NMR ($CDCl_3$) δ 1 12 (m, 4H), 1.83 (m, 2H), 2.01 (s, 3H), 2 24 (m, 1H), 2.76 (t, 2H), 3 89 (t, 2H), 4 73 (m, 1H), 5.60 (brs, 1H), 6 52 (d, 1H), 6.64 (d, 2H), 6.93 (t, 1H), 7 12-7.29 (m, 7H), 7 37 (d, 2H), 7.48 (d, 1H), 8.45 (m, 2H)

MS m/z. 554 36 (M+1).

[001049] (2*S*,4*R*)-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-furan-2-carboxylic acid amide (H-27)

[001050] (2*S*,4*R*)-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-furan-2-carboxylic acid (0.065g, 0 12mmol) was converted to the amide by dissolving in THF (1 mL) at room temperature. HOBt (0.024 g), EDCI (0.033 g), and ammonium chloride (0.013g, 0 232 mmol) was added along with 2 drops of DMF and stirred at room temperature for 11 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (10 ethyl acetate· 1 methanol) to afford the product as a white solid in 61% yield

^{1}H-NMR ($CDCl_3$) δ: 1.13-1 20 (m, 4H), 2 01 (s, 3H), 2.23-2.29 (m, 1H), 4 72-4.74 (m, 1H), 4.99 (s, 2H), 5.59 (bs, 1H) 6.47-6.51 (m, 2H), 6.71 (d, 2H), 6 91 (t, 1H), 7.09-7.38 (m, 9H)

MS m/z· 558 (M+1)

[001051] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-piperazin-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-28)

[001052] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-piperazin-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was prepared from (2*S*,4*R*)-4-[3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-piperazine-1-carboxylic acid tert-butyl ester. (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 40g, 0.92 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0 127g, 0.921 mmol) was added 4-(3-Chloro-propyl)-piperazine-1-carboxylic acid tert-butyl ester (0.242g, 0 921 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography to afford the product as colorless oil in 50% yield

(2*S*,4*R*)-4-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-piperazine-1-carboxylic acid tert-butyl ester (246 mg) was dissolved in

4M HCl in dioxane (2 mL) The mixture was stirred for 2h at room temperature After concentration, the white solid was washed with EtOAc to provide the title compound in 100% yield

^{1}H-NMR (DMSO, 2HCl salt) δ 1 00-1.02 (m, 4H), 1.88-1 94 (m, 3H), 2.10-2.15 (m, 1H), 3.15-3.80 (m, 12H), 4.02 (t, 2H), 4 56-4.59 (m, 1H), 5.49 (bs, 1H), 6.50 (d, 1H), 6 76 (d, 2H), 6.96 (t, 1H), 7.04 (d, 2H), 7.16 (t, 1H), 7.39-7 53 (m, 5H).

MS m/z: 561 (M+1)

[001053] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2,6-difluorophenoxy)-2,2-dimethylbutanoate (H-29)

[001054] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure H, substituting 3,5-difluoro-4-methoxybenzoyl chloride for 6-trifluoromethyl nicotinyl chloride The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was obtained in decent yield.

[001055] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (200 mg, 0.41 mmol) was dissolved in dichloromethane and a solution of BBr_3 (1.0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for until no starting material remained. The reaction was washed with sat $NaHCO_3$ and brine The organic layer were dried over $MgSO_4$, filtered and concentrated down. The residue was purified by flash chromatography using hexanes-ethyl acetate system to give *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (152 mg, 78%)

[001056] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (150 mg, 0.32 mmol) was dissolved in DMF at room temperature and Cs_2CO_3 (259 mg, 0.80 mmol) was added Methyl 4-bromo-2,2-dimethylbutanoate (157 mg, 0.48 mmol) was added and the reaction was stirred at room temperature overnight. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford the product (118 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 1.12-1.14 (d, 3H), 1.21-1.24 (m, 6H), 1.48-1 55 (m, 2H), 2.02 (s, 3H), 2.20-2 32 (m, 1H), 3.64 (s, 3H), 4.11-4.16 (m, 1H), 4.65-4.75 (m, 1H), 5.45-5.55 (m, 1H), 6 51-6 54 (d, 1 H), 6 70-6 73 (m, 1H), 6.76-6.90 (m, 1H), 7.18-7.39 (m, 7H).

MS m/z 599 (M+1).

[001057] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid amide (H-30)

[001058] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid amide was prepared from (2*S*,4*R*)- 1-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid. The acid (0.120 g, 0 22 mmol) was dissolved in DMF (2 5 mL) at room temperature and HOBt (0 044 g, 0.33 mmol), HATU (0.125 g, 0.33 mol), and diisopropylethylamine (0.15 mL, 0 88 mmol) was added followed by ammonium chloride (0.024 g, 0.44 mmol) and stirred at room temperature for 16 h. The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified HPLC purification.

^{1}H-NMR ($CDCl_3$) δ· 1.10 (d, 3H), 1.23 (m, 1H), 1.79(m, 4H), 2 01 (m, 3H), 2.27 (m, 1H), 2.48 (m, 1H), 2 96 (m, 1H), 3.13 (m, 1H), 3 35 (m, 1H), 3 52 (m, 1H), 4.70 (m, 1H), 5.50 (br, 2H), 6.24 (br, 1H), 6 56 (d, 1H), 6 67 (d, 2H), 6.92 (t, 1H), 7 08-7.28 (m, 6H), 7.37 (d, 2H).

MS m/z 545 4 (M+1).

[001059] 2-{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoic acid (H-32)

[001060] Methyl 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoate (90 mg, 0.15 mmol, 1 equ.) was dissolved in methanol/tetrahydrofuran (2/1) (1 ml). A solution of sodium hydroxide (12 mg, 0 30 mmol, 2 eq.) in water (0.5 ml) was added and reaction mixture was stirred at room temperature for 20 h. The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 2-{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoic acid (76 mg, 87 %).

^{1}H-NMR (CDCl3) δ 1 15 (d, 3H), 1.45 (d, 6H), 2.05 (s, 3H), 2.30 (m, 1H), 2.40 (t, 2H), 2.85 (t, 2H), 4 75 (m, 1H), 5.60 (m, 1H), 6.30 (s, 1H), 6.55 (d, 1H), 6.90 (t, 1H), 6 90-7.15 (m, 8H), 7.40 (d, 2H)

MS m/z 576 (M+1).

[001061] Methyl 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoate (H-33) and methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate (H-143)

[001062] Methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate was prepared from (2*S* ,4*R*)- N-(4-chloro-phenyl)-N-[1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide by deprotection of the methoxy and elaboration. (2*S* ,4*R*)- N-(4-chloro-phenyl)-N-[1-(6-methoxy-pyridine-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 062g, 0 13 mmol) was dissolved in methylene chloride and TMSI (0 020mL, 0 13 mmol) was added and stirred at room temperature for 14h. The reaction mixture was concentrated down and methanol was added and stirring was continued for 10h, concentrated down and used directly. *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(6-hydroxypyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (0 060g, 0.13 mmol) was dissolved in 2 mL of dimethylformamide, followed by 0.046g of methyl 4-bromo-2,2-dimethylbutanoate (0.20 mmol) and 0.057g of silver carbonate (0.20 mmol). The flask was covered with aluminum foil and the lights were turned off in the enclosure The reaction was allowed to heat to 80°C for 24 h. Additional methyl 4-bromo-2,2-dimethylbutanoate (0.046g, 0.20 mmol) was added and continued stirring at 80°C for 24h The reaction was concentrated down and partitioned between ethyl acetate and water. The organics were collected together and dried over $MgSO_4$, filtered and concentrated. The residue was purified with 2% methanol/98%methylene chloride to 5% methanol/95% methylene chloride to 10% methanol/90%methylene chloride Two products were obtained the O- and N- alkylated product, methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate (0.025g, 32%) and methyl 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoate (0 025g, 32%).

O-alkylated ^{1}H-NMR ($CDCl_3$) δ: 1.13 (m, 1H), 1.14 (d, 3H), 1.22 (s, 6H), 1 99 (t, 2H), 2.01 (s, 3H), 2.29 (m, 1H), 3 62 (s, 3H), 4.27 (t, 2H), 4.74 (sextet, 1H), 5 58 (bs, 1H), 6 37 (d, 1H), 6 56 (d, 1H), 7.00 (t, 1H), 7.28-7.16 (m, 5H), 7.37 (d, 2H), 8.14 (bs, 1H).

MS m/z = 564 (M+1).

N-alkylated ^{1}H-NMR ($CDCl_3$) δ: 1.11 (m, 1H), 1.12(d, 3H), 1.22 (s, 6H), 1.72-1.90 (m, 2H), 2.01 (s, 3H), 2 25 (m, 1H), 3.67(s, 3H), 3 71-3 88 (m, 2H), 4.64 (, sextet, 1H), 5.51 (bs, 1H), 6.15 (d, 1H), 6.74 (d, 2H), 7.09 (t, 1H), 7 15 -7.33 (m, 4H), 7.37 (d, 2H), 7.57 (s, 1H)

MS m/z . 564 (M+1).

[001063] ***N*-{(2*S*,4*R*)-1-[4-(aminomethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide (H-34)**

[001064] *N*-{(2*S*,4*R*)-1-[4-(aminomethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide was made following general procedure H, substituting 4-cyanobenzoyl chloride for 6-trifluoromethyl nicotinyl chloride The rest of the procedure is followed as indicated in

general procedure H to yield the corresponding nitrile, *N*-(4-chloro-phenyl)-*N*-[(2S,4R)-1-(4-cyano-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide. *N*-(4-Chloro-phenyl)-*N*-[(2S,4R)-1-(4-cyano-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (225 mg, 0 51 mmol) was dissolved in ethanol (7 mL) and cobalt dichloride (0.079 g, 0 61 mmol) and $NaBH_4$ (0.059 g, 1.57 mmol) were added and the mixture was stirred at room temperature for 2h. The slurry was filtered, concentrated, and subjected to flash chromatography (1% NH_4OH, 15%MeOH, EtOAc) to yield the title compound (188 mg, 83%) as a white solid.^{1}H-NMR ($CDCl_3$) δ: 1.00-1 20 (m, 1H), 1.14 (s, 3H), 1.48 (bs, 2H), 2.02 (s, 3H), 2 20-2 36 (m, 1H), 3.79 (s, 2H), 4.73-4 83 (m, 1H), 5.35-5.70 (m, 1H), 6.49 (d, 1H), 6.89 (t, 1H), 7 11-7 29 (m, 8H), 7.37 (d, 2H).
MS m/z 448 (M +1)

[001065] (2*S*,4*R*)-N-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-2,2-dimethyl-propionamide (H-35)

[001066] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (60 mg, 0 122 mmol) was dissolved in methylene chloride (2 mL) and triethylamine (0 034 mL, 0.243 mmol) and cooled to -40 °C. Pivaloyl chloride (10 drops via pipet) was added and the mixture was warmed to 0 °C for 30 minutes. The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (1/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.
^{1}H-NMR ($CDCl_3$) δ 1 1 (s, 3H), 1.1 (s, 9H), 1.2 (m, 1H), 2.0 (m, 2H), 2.0 (s, 3H), 2.3 (m, 1H), 3 4 (q, 2H), 4 0 (t, 2H), 4.7 (m, 1H), 5 6 (bs, 1H), 6.0 (s, 1H), 6.5 (d, 1H), 6 6 (d, 2H), 6.9 (t, 1H), 7.2 (m, 6H), 7.4 (d, 2H).
MS m/z. 576 (M+1).

[001067] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate (H-36)

[001068] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-fluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure H, substituting 3-fluoro-4-methoxybenzoyl chloride for 6-trifluoromethyl nicotinyl chloride The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-fluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.

[001069] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-fluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was dissolved in dichloromethane and a solution of BBr_3 (1.0 M in dichloromethane, 10 mL) was added; the reaction was allowed to stir at room temperature for until no starting material remained. The reaction was washed with sat. $NaHCO_3$ and brine. The organic layer

were dried over $MgSO_4$, filtered and concentrated down. The residue was purified by flash chromatography using hexanes-ethyl acetate system to give *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-fluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide in decent yield

[001070] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-fluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (317 mg, 0 70 mmol) was dissolved in DMF at room temperature and Cs_2CO_3 (567 mg, 1.75 mmol) was added. Methyl 4-bromo-2,2-dimethylbutanoate (465 mg, 1.05 mmol) was added and the reaction was stirred at room temperature overnight The reaction mixture was concentrated under reduced pressure The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (hexanes/ethyl acetate system) to afford the product (176 mg, 43%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ. 1.11-1.13 (d, 3H), 1.22-1.29 (m, 6H), 1.51-1.64 (m, 2H), 2 07-2.09 (m, 5H), 2.25-2.29 (m, 2H), 3.65 (s, 3H), 3 95-3 99 (m, 2H), 4.70-4 75 (q, 1H), 5.27 (b, 1H), 6 51-6.75 (m, 3H), 6 92-7 03 (m, 2H), 7.14-7 38 (m, 6 H).

MS m/z· 581 (M+1).

[001071] (2*S*,4*R*)-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(2-oxo-imidazolidin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-37)

[001072] N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (156 mg, 0 373 mmol) was dissolved in methylene chloride (3 mL) and was added triethylamine (0.078 mL, 0 559 mmol) and 1-chloro-2-isocyanato-ethane 0 038 mL, 0.448 mmol) The reaction was stirred at room temperature over night, and the reaction was quenched with sat. aq $NaHCO_3$ The residue was partitioned between methylene chloride and water, then extracted three times with methylene chloride, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (ethyl acetate) to afford the product

^{1}H-NMR ($CDCl_3$) δ: 1.2 (d, 3H), 1.2 (m, 1H), 2.0 (s, 3H), 2.3 (m, 1H), 4 0 (t, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 5.6 (m, 1H), 6 5 (d, 1H), 6 9 (t, 1H), 7.2 (m, 9H), 7 4 (d, 2H).

MS m/z. 503 (M+1).

[001073] (2*S*,4*R*)- 4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyric acid (H-38)

[001074] (2*S*,4*R*)- 4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyric acid was prepared from (2*S*,4*R*)- 4-[(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyric acid methyl ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and lithium hydroxide (1N) was added and heated 50°C for 2h The mixture was cooled to room

temperature, acidified to form a white precipitate. The solid was filtered to give to afford the product after HPLC purification

^{1}H-NMR ($CDCl_3$) δ· 1.10 (d, 3H), 1.18 (m, 1H), 1.81 (t, 2H), 2.02 (s, 3H), 2.28 (m, 3H), 2.86 (s, 3H), 3.28 (t, 2H), 4 70 (m, 1H), 5.58 (brs, 1H), 6.39 (d, 2H), 6.61 (d, 1H), 6 94 (t, 1H), 7 06-7.27 (m, 6H), 7.36 (d, 2H), 8 90 (br, 1H).

MS m/z 534 (M+1).

[001075] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(4-hydroxy-4-methyl-pentyloxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-39)

[001076] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 1g, 0 23 mmol) was dissolved in DMF (5 mL) at room temperature K_2CO_3 (0 317g, 2.3 mmol) was added. 5-Bromo-2-methyl-pentan-2-ol (0.092g, 0 51 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (70% EtOAc/ 30% Hexane) to afford the product (0.097g, 79%)

^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 3H), 1.15 (t, 1H), 1.26 (s, 6H), 1 52-1.90 (m, 5H), 2.04 (s, 3H), 2 27 (m, 1H), 3.91 (t, 2H), 4.72 (sextet, 1H), 5.48 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6.86 (t, 1H), 7 08-7 35 (m, 6H), 7 38 (d, 2H).

MS m/z: 535 (M+1)

[001077] (2*S*,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid amide (H-40)

(2*S*,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid amide was prepared from (2*S*,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid ethyl ester. The ester (0.100g, 0.16 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature 4 hours. The mixture was cooled to rt, acidified to form a white precipitate The solid was filtered to give (2*S*,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid in 65% yield The acid (0.066g, 0.09mmol) was converted to the amide by dissolving in DMF (2 mL) at room temperature. HATU (0 061 g, 0.16mmol), HOBt (0.021g, 0 15 mmol), and diisopropylethylamine (0.074 mL, 0 43 mmol) were added and stirred for 5 min. followed by ammonium chloride (0.011g, 0 20mmol) The reaction was stirred at room temperature for 12h and concentrated down the residue was diluted with ethyl acetate and washed with 1N HCl and dried over

$MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (5% MeOH/ 95% CH_2Cl_2/NH_4OH to 10% MeOH/ 90% CH_2Cl_2/NH_4OH to 15% MeOH/ 85% CH_2Cl_2/NH_4OH) to afford the product (0 050 mg, 81%).

^{1}H-NMR ($CDCl_3$) δ: 1.11 (d, 3H), 1.37 (m, 1H), 2 00 (s, 3H), 2.22 (m, 3H), 3 82 (t, 2H), 4.57 (t, 2H), 4.72 (sextet, 1H), 5.56 (bs, 1H), 6 49 (d, 1H), 6.60 (d, 2H), 6 90 (t, 1H), 6.89 (t, 1H), 6.93 (d, 2H), 7 11 (d, 2H), 7.15-7.27 (m, 5H), 7.34 (d, 1H).

MS m/z. 586 (M+1)

[001078] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-oxo-oxazolidin-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-41)

[001079] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 5 g, 1.14 mmol) was dissolved in DMF at room temperature and K_2CO_3 (1 26 g, 9.13 mmol) was added. 2-Chloromethyl-oxirane (0 42g, 4.57 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[2-methyl-1-(4-oxiranylmethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.55g, 77%), which was further elaborated to the product following ref. (*Tetrahedron Lett* **2002**, 43(46), 8327)

^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 3H), 1.15 (t, 1H), 2.03 (s, 3H), 2.27 (m, 1H), 3 57 (m, 1H), 3.68 (m, 1H), 4.05 (m, 2H), 4.73 (m, 1H), 4 86 (m, 1H), 5.58 (bs, 1H), 6 52 (d, 1H), 6.67 (d, 2H), 6.86 (t, 1H), 7.08-7 35 (m, 6H), 7.38 (d, 2H).

MS m/z: 535 (M+1)

[001080] 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid (H-42)

[001081] 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid methyl ester (500 mg, 0 89 mmol, 1 eq.) was dissolved in methanol/tetrahydrofuran (2/1) (4 ml). A solution of sodium hydroxide (71 mg, 1.8 mmol, 2 eq) in water (1 ml) was added and reaction mixture heated to 60°C for 20 h. The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude acid. Purification by silica gel chromatography gave pure 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid (292 mg, 60 %).

^{1}H-NMR (MeOD) δ 1.10 (d, 3H), 1.13 (s, 6H), 1 50 (m, 4H), 2.05 (s, 3H), 2 45 (m, 1H), 2 55 (t, 2H), 4.75 (m, 1H), 5.55 (m, 1H), 6.55 (d, 1H), 6.95 (t, 1H), 7.05-7.20 (dd, 4H), 7.25 (t, 1H), 7.40-7.55 (m, 5H)

MS m/z 547 (M+1).

[001082] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoate (H-43)

[001083] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoate was prepared according to general procedure B, substituting methyl 4-[4-(chlorocarbonyl)phenyl]-2,2-dimethylbutanoate for 6-trifluoromethyl nicotinyl chloride. (Methyl 4-[4-(chlorocarbonyl)phenyl]-2,2-dimethylbutanoate was prepared in 5 steps from 4-(4-iodophenyl)butanoic acid 4-(4-iodophenyl)butanoic acid was converted to methyl 4-(4-iodophenyl)butanoate by treatment with trimethylsilyl diazomethane (1.5 equivalents) in benzene/methanol (4/1) at room temperature Lithium enolate formation with lithium diisopropyl amide (1.1 equivalents) in THF at -78 °C followed by quenching with methyl iodide (2 0 equivalents) and aqueous work up then repeating the same protocol afforded, after standard chromatography (10% ethyl acetate/hexanes) methyl 4-(4-iodophenyl)-2,2-dimethylbutanoate. Subsequent treatment of this material with catalytic palladium(II) acetate (0 05 equivalents) and 1,3-bis(diphenylphosphino)propane (0.05 equivalents) in the presence of water (5.0 equivalents) and triethylamine (2.0 equivalents) in DMF at 80 °C under a carbon monoxide atmosphere afforded, after aqueous work up, 4-(4-methoxy-3,3-dimethyl-4-oxobutyl)benzoic acid This material was directly converted to methyl 4-[4-(chlorocarbonyl)phenyl]-2,2-dimethylbutanoate by treatment with excess thionyl chloride in dichloromethane at room temperature for 2 hours then removal of the volatiles in vaccuo) The rest of the procedures were followed as indicated in general procedure B to afford methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoate.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1.21 (m, 1H), 1.13 (d, 3H), 1.18 (s, 6H), 1.73 (ddd, 2H), 2.01 (s, 3H), 2.23-2 30 (m, 1H), 2.43 (ddd, 2H), 3 64 (s, 3H), 4 71-4.79 (m, 1H), 5.60 (br s, 1H), 6 49 (d, 1H), 6.89 (t, 1H), 6.95 (d, 2H), 7.08-7.29 (m, 6H), 7.37 (d, 2H).

MS m/z· 547 (M+1).

[001084] 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid (H-44)

[001085] 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid was synthesized from (2*S*,4*R*)-N-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-

dimethyl-propionic acid (0 030g, 0.057 mmol) by addition of 1 mL of dimethylformamide and TCCA (0.0044g, 0.018 mmol, 0.33 equ) and stirred at room temperature for 40 min. The reaction mixture was diluted with water and acidified with 1N HCl to form a white precipitate. The solid was dried on the lyopholizer and purified with 5% methanol/dichloromethane to 10 % methanol/90% dichloromethane to yield 0.400g, 87% of 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

^{1}H-NMR ($CDCl_3$) δ· 1 10 (d, 3H), 1.13 (m , 1H), 1.29 (s, 6H), 2.03 (s, 3H), 2.27 (m, 1H), 3.92-3 85 (m, 2H), 4 72 (sextet, 1H), 5 51 (bs, 1H), 6.43 (d, 1H), 6 67 (d, 2H), 6.90 (d, 1H), 7.11 (s, 1H), 7.13 (d, 2H), 7.19 (d, 2H), 7 38 (d, 2H)

MS m/z 569 (M+1).

[001086] *N*-(4-aminophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-45)

[001087] Benzyl (4-{acetyl[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]amino}phenyl)carbamate was dissolved in MeOH and was added a catalytic amount of Palladium on Carbon (10 %). The system was purged by Hydrogen gas, the subjected to 1 atm of H_2 for 2h. The reaction was quenched with air and filtered to give the title compound as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.10-1.60 (m, 1H), 1.10 (d, 3H), 2.01 (s, 3H), 2 22-2.38 (m, 1H), 3.70-3.95 (bs, 2H), 3 72 (s, 3H), 4 64-4 80 (m, 1H), 5.45-5.72 (m, 1H), 6.49 (d, 1H), 6.54-6.70 (m, 2H), 6.64 (d, 2H), 6 89 (t, 1H), 6.99 (d, 2H), 7.08-7.20 (m, 3H), 7.30 (d, 1H).

MS m/z: 430 (M +1)

[001088] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(4-methanesulfonylamino-3,3-dimethyl-4-oxo-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-46)

[001089] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (200 mg, 0 37 mmol) was dissolved in methylene chloride (5 mL) and oxalyl chloride (2 mL). A single drop of DMF was added, and the mixture was stirred at room temperature until gas evolution ceased. All volatiles were removed. The slurry was dissolved in methylene chloride (10 mL) and triethylamine (2 mL). Methanesulfonamide (200 mg, 2.10 mmol) was added and the reaction mixture was stirred for 3 hours. The mixture was partitioned between methylene chloride and water; the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by preparatory HPLC.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (m, 1H), 1.2 (s, 3H), 1.3 (s, 3H), 2.0 (s, 3H), 2 1 (t, 1H), 2.3 (m, 1H), 3 4 (m, 4H), 3 9 (m, 2H), 4.7 (m, 1H), 5.6 (bs, 1H), 5 9 (d, 1H), 6.5 (d, 1H), 6.4 (d, 2H), 6 9 (t, 1H), 7 2 (m, 6H), 7.4 (d, 2H).

MS m/z. 626 (M+1).

[001090] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid (H-47)

[001091] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid was prepared from (2*S*,4*R*)- 1-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid ethyl ester (0 300g, 0.522 mol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and lithium hydroxide (1N) was added and heated 50°C for 2h The mixture was cooled to room temperature, acidified to form a white precipitate The solid was filtered to give to afford the product after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.11 (d, 3H), 1 23 (m, 1H), 1.77 (m, 2H), 1 94 (m, 2H), 2.02 (s, 3H), 2.27 (m, 1H), 2.43 (m, 1H), 2.78 (t, 2H), 3 60 (m, 2H), 4.71 (m, 1H), 5 58 (brs, 1H), 6 57 (d, 1H), 6 63 (d, 2H), 6.93 (t, 1H), 7.07-7.28 (m, 6H), 7.37 (d, 2H), 9.30 (br, 1H).

MS m/z 546.3 (M+1).

[001092] *N*-{(2*S*,4*R*)-6-Chloro-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide (H-48)

[001093] *N*-{(2*S*,4*R*)-6-Chloro-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide was prepared following the procedure described for *N*-{(2*S*,4*R*)-1-[3,5-bis(trifluoromethyl)benzoyl]-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide substituting 6-ethyl nicotinyl chloride for 3,5-bistrifluoromethyl benzoyl chloride. (6-Ethyl nicotinyl chloride was prepared in two steps from methyl 6-chloronicotinate as described in the procedure for *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide).

^{1}H-NMR ($CDCl_3$) δ: 1 26 (d, 3H); 1.28 (t, 3H), 1.28-1.31 (m, 1H), 2.02 (s, 3H), 2 22-2.36 (m, 1H), 2 81(q, 2H), 4.70-4.80 (m, 1H), 5.42-5.56 (br, 1H), 6.50 (d, 1H), 6 90-7.00 (m, 2H), 7.20-7.40 (m, 7H), 8 50 (br s, 1H)

MS m/z. 482 (M + 1).

[001094] 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-49)

[001095] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (100 mg, 0.17 mmol, 1 equ.) was dissolved in methanol/tetrahydrofuran (2/1) (1 ml) A solution of sodium hydroxide (21 mg, 0.51 mmol, 3 eq.) in water (0.5 ml) was added and reaction mixture heated to 40°C for 2 h. The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with

ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude acid. Purification by silica gel chromatography (methylene chloride/methanol 98/2) gave pure 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (85 mg, 87 %).
^{1}H-NMR (CDCl3) δ: 0.75 (m, 2H), 1 10 (m, 2H), 1.20 (d, 3H), 1.25 (s, 6H), 1 45 (m, 1H), 2 05 (t, 2H), 2 30 (m, 1H), 3.95 (t, 2H), 4.75 (m, 1H), 5 60 (m, 1H), 6.50 (d, 1H), 6 60 (d, 2H), 6 90 (t, 1H), 7 10-7.45 (m, 8H).
MS m/z 575 (M+1).

[001096] *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-50)

[001097] *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure B, substituting 4-fluoro-3-ethylbenzoyl chloride for 6-trifluoromethyl nicotinyl chloride

[001098] (4-fluoro-3-ethylbenzoyl chloride was prepared in 5 steps from 3-bromo-4-fluorobenzoic acid 3-bromo-4-fluorobenzoic acid was converted to methyl 3-bromo-4-fluorobenzoate by treatment with trimethylsilyl diazomethane (1.5 equivalents) in benzene/methanol (4/1) at room temperature Subsequent reaction with tributyl(vinyl) tin (1.2 equivalents) in DMF in the presence of catalytic dichlororbis(triphenylphosphine) palladium(II) (0.1 equivalents) at 80 °C under an argon atmosphere, followed by aqueous work up and standard chromatography (10% ethyl acetate/hexanes), yielded methyl 4-fluoro-3-vinylbenzoate Hydrogenation of the vinyl group by treatment of this material with palladium on carbon (10% palladium on carbon, 10 % by mass) in methanol under an hydrogen atmosphere then afforded methyl 3-ethyl-4-fluorobenzoate This material was dissolved in methanol/tetrahydrofuran/water (2/1/1) then lithium hydroxide (5.0 equivalents) was added and reaction mixture stirred at room temperature for 2 hours The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-fluoro-3-ethylbenzoic acid. This material was directly converted to 4-fluoro-3-ethylbenzoyl chloride by treatment with thionyl chloride (2 2 equivalents) in dichloromethane at room temperature for 2 hours followed by removal of the volatiles in vaccuo) The rest of the procedures were followed as indicated in general procedure B to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.
^{1}H-NMR ($CDCl_3$) δ 1.03 (t, 3H), 1.15 (d, 3H), 1.22-1.26 (m, 1H), 2.03 (s, 3H), 2 24-2.32 (m, 1H), 2.42-2.58 (m, 2H), 4.70-4.82 (m, 1H), 5.61 (br s, 1H), 6.48 (d, 1H), 6 78 (t, 1H), 6 92 (t, 1H), 6 97-7 02 (m, 1H), 7 07 (d, 1H), 7 13-7.30 (m, 4H), 7.38 (d, 2H).
MS m/z· 465 (M+1).

[001099] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(3-imidazol-1-yl-3-methyl-butoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-51)

[001100] 3-Imidazol-1-yl-3-methyl-butan-1-ol was dissolved in benzene at room temperature with PPh_3 (0.088g, 0.33 mmol) added (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.133g, 0 30 mmol) and stirred for 5 min. DEAD (0.058g, 0.33 mmol) was added and the reaction was stirred for 18 h at room temperature. The reaction was concentrated and purified by silica gel chromatography (4 % MeOH/96 % CH_2Cl_2 to 5 % MeOH/95 % CH_2Cl_2 to 6 % MeOH/94 % CH_2Cl_2) to afford the product in 46% yield

[001101] Preparation of 3-Imidazol-1-yl-3-methyl-butan-1-ol

[001102] 3-Imidazol-1-yl-3-methyl-butan-1-ol was prepared from ethyl-2,2-dimethylacrylate. Ethyl-2,2-dimethylacrylate (2.04 mL, 14.7mmol) and imidazole (0 500g, 7 34 mmol) were mixed and heated to 90°C for 48 h and cooled to room temperature The reaction mixture was diluted with CH_2Cl_2 and water The aqueous layer was extracted 3x CH_2Cl_2 and dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (10% MeOH/ 90% CH_2Cl_2) to give 35% yield of 3-imidazol-1-yl-3-methyl-butyric acid ethyl ester. The ester was reduced to the alcohol (US Patent application WO03047586). 3-imidazol-1-yl-3-methyl-butyric acid ethyl ester (0.500g, 2.5 mmol) was dissolved in THF (40 mL) and cooled to 0°C and 2.55 mL of $LiAlH_4$ (1 0 M in ether) was added dropwise over 15 min. The reaction was allowed to warm up to room temperature over 1 h and quenched with dropwise addition of a sat'd Na_2SO_4 solution The resulting slurry was dried over solid Na_2SO_4 and diluted with ethyl acetate, filtered through a plug of Celite and concentrated down.

^{1}H-NMR ($CDCl_3$) δ: 1 09 (d, 3H), 1.11 (m, 1H), 1.56 (s, 6H), 1.97 (s, 3H), 2.08 (m, 1H), 2.16 (t, 2H), 3.67 (m, 2H), 4.67 (sextet, 1H), 5.51 (bs, 1H), 6 49 (m, 3H), 6.87 (t, 1H), 6.96-7.61 (m, 10 H), 7 64 (m, 1H)

MS m/z· 568 (M+1).

[001103] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(1-ethyl-piperidin-4-ylmethoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-52)

[001104] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-piperidine-1-carboxylic acid benzyl ester (0 25 g) was converted to the piperdine by hydrogenation with Pd/C (0 075 g) under hydrogen in ethanol (17 ml) The reaction mixture was filtered through cellite and concentrated down to give (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(piperidin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (0.17 g, 85%).

[001105] The piperdine was reacted with acetaldehyde, $Na(OAc)_3BH$ in dichloromethane at room temperature overnight. Then washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product (55%)

^{1}H-NMR ($CDCl_3$) δ: 0.98-1.18 (m, 7H), 1 37 (m, 2H), 1 72-1.93 (m, 5H), 2.04 (s, 3H), 2 27 (m, 1H), 2.37 (q, 2H), 2 95 (m, 2H), 3.73 (d, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6.86 (t, 1H), 7.08-7.35 (m, 6H), 7.38 (d, 2H).

MS m/z 560 (M+1)

[001106] (2*S*,4*R*)- 4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyramide (H-53)

[001107] (2*S*,4*R*)- 4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyramide was made from (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid The acid (0.050g, 0.096mmol) was dissolved in DMF (1 mL) at room temperature and HOBt (0 020 g, 0.144 mmol), HATU (0.055 g, 0 144 mol), and diisopropylethylamine (0 067 mL, 0.384 mmol) was added followed by ammonium chloride (0.011g, 0.192 mmol) and stirred at room temperature for 16 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified HPLC purification.

^{1}H-NMR ($CDCl_3$) δ· 1.10 (d, 3H), 1.18 (m, 1H), 1.80 (t, 2H), 2.00 (s, 3H), 2.13 (t, 2H), 2 27 (m, 1H), 2 85 (s, 3H), 3 27 (t, 2H), 4.70 (m, 1H), 5.65 (br, 2H), 5.85 (brs, 1H), 6.39 (d, 2H), 6 59 (d, 1H), 6.93 (t, 1H), 7.03-7.34 (m, 6H), 7.36 (d, 2H).

MS m/z· 533 (M+1).

[001108] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-3-(*S*)-hydroxy-butyric acid (H-54)

[001109] (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (200 mg, 0.46 mmol) was dissolved in DMF (5 mL) at room temperature Cs_2CO_3 (374 mg, 1.15 mmol) was added followed by 4-bromo-3-(*S*)-(*tert*-butyl-dimethyl-silanyloxy)-butyric acid methyl ester (214 mg, 0.69 mmol) and the reaction was stirred at room temperature for 18 hours The mixture was concentrated under reduced pressure and dissolved in ethyl acetate (15 mL) The reaction mixture was washed with sat aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL) The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (5/95 ethyl acetate/hexane – 50/50 ethyl acetate/hexane gradient) to afford slightly yellow solid product (74 mg, 37%)

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[001110] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-3-(*S*)-(tert-butyl-dimethyl-silanyloxy)-butyric acid methyl ester (99 mg, 0.148 mmol) was dissolved in THF (4 mL) To this solution was added tetrabutyl ammonium fluoride (1.0 M in THF, 1 mL). The reaction mixture was stirred at room temperature for 3 hours. The mixture was concentrated under reduced pressure and dissolved in DCM (15 mL). The reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (2/98 methanol / dichloromethane – 10/90 methanol/dichloromethane gradient) to afford white solid product (41 mg, 51%)

[001111] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-3-(*S*)-hydroxy-butyric acid methyl ester (41.2 mg, 0 075 mmol) was dissolved in MeOH/THF (2:1, 3 mL). To this solution was added 2N LiOH (2 mL). The reaction was stirred at room temperature for 18 hours The reaction mixture was concentrated *in vacuo* to remove MeOH and THF. Then 6N HCl aqueous solution was added to acidify the reaction mixture to pH 2-3. The reaction mixture was extracted with DCM (5 mL × 3). The extract was washed with brine (15 mL) and dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by preparatory HPLC to afford the product (35 mg, 87%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 1.05-1.14 (m, 4H), 2.0 (s, 3H), 2.25-2.27 (m, 1H), 2 60-2.62 (m, 2H), 3.87-3.88 (m, 2H), 4.28-4.34 (m, 1H), 4.70-4.77 (m, 1H), 5.58-5.62 (broad, 1H), 6.49-6.93 (m, 4H), 7.12-7 39 (m, 8H).

MS m/z: 538 (M+1).

[001112] (2*S*,4*R*)-N-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionamide (H-55)

[001113] (2*S*,4*R*)-N-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionamide was prepared from (2*S*,4*R*)-N-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down. The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product in a 88% yield.

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.15 (t, 1H), 1 31 (s, 6H), 1.71 (bs, 1H), 2 03 (s, 3H), 2 27 (m, 1H), 3.83 (q, 2H), 4.72 (sextet, 1H), 5.58 (bs, 1H), 6.17(br, 1H), 6 52 (d, 1H), 6 69 (d, 2H), 6.83 (t, 2H), 7 08-7 35 (m, 6H), 7 38 (d, 2H).

MS m/z. 534 (M+1)

[001114] (2*S*,4*R*)-N-(1-{4-[2-(1-Acetyl-piperidin-4-yl)-ethoxy]-benzoyl}-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-(4-chloro-phenyl)-acetamide (H-56)

[001115] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-piperidin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (0 085g, 0.15 mmol) was dissolved in dichloromethane at room temperature and DIEA (0.1 g, 0 56 mmol) was added Acetyl chloride (0 2 mL, 2.8 mmol) was added and the reaction was stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo* The crude residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product (0.068 g, 75%)

^{1}H-NMR ($CDCl_3$) δ: 1.15 (d, 3H), 1.15 (t, 1H), 1.21 (m, 2H), 1.58-1 77 (m, 5H), 1.98 (s, 3H), 2.04 (s, 3H), 2.27 (m, 1H), 2 51 (t, 1H), 2.98 (t, 1H), 3 72 (m, 1H), 3.93 (t, 2H), 4.51 (m, 1H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6.52 (d, 1H), 6.69 (d, 2H), 6 83 (t, 2H), 7.08-7.35 (m, 6H), 7.38 (d, 2H)

MS m/z 588 (M+1)

[001116] 4-(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoic acid (H-57)

[001117] To the solution of Methyl 4-(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate in MeOH/THF (1 mL/1mL) was added excessive LiOH (1N aqueous solution). The reaction mixture was stirred at r.t. for overnight. The reaction was quenched by adding 6N HCl to PH 2. The mixture was concentrated under reduced pressure to remove MeOH and THF. DCM was added. The reaction mixture was washed with brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by preparative HPLC to afford pure product

^{1}H-NMR ($CDCl_3$, 300MHz) δ· 0 90-0.94 (m, 2H), 1.12-1.14 (d, 3H), 1 21-1 24 (m, 3H), 1.60-1.72 (m, 2H), 1.95-2.03 (m, 1H), 2.09 (s, 3H), 2.20-2.27 (m, 1H), 3.45-3.59 (m, 1H), 3.60-3.75 (m, 1H), 4 65-4 75 (m, 1 H), 5.72-5.80 (m, 1H), 6.31-6 34 (m, 1H), 6 45-6 47 (m, 1H), 6.90-6.96 (m, 1H), 7.04-7 08 (m, 1H), 7.15-7 20 (m, 3H), 7.24-7 36 (m, 6H).

MS m/z 567 (M+1).

[001118] *N*-(4-chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[(methylsulfonyl)amino]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (H-58)

[001119] To a solution of *N*-[(2*S*,4*R*)-1-(4-aminobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (208 mg, 0.48 mmol) in methylene chloride (4.0 mL) at 0 °C was added methanesulphonic anhydride (175 mg, 1 01 mmol) and *N,N*-diisopropylethylamine (0.460 mL, 2.63 mmol). The reaction was warmed to room temperature and stirred for 4 days (Analysis by

LCMS indicated a mixture of starting aniline, mono-sulfonamide, and bis-sulfonamide) Additional methanesulphonic anhydride (170 mg, 0.98 mmol) was added and the reaction was stirred an additional 2 days at room temperature The resulting reaction was diluted with dichloromethane (25 mL) and poured into a 1·1 mixture of water and brine (25 mL) The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford crude *N*-((2*S*,4*R*)-1-{4-[bis(methylsulfonyl)amino]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide (273 mg) as a yellow foam. The crude material was used directly in subsequent reactions.

[001120] To a solution of *N*-((2*S*,4*R*)-1-{4-[bis(methylsulfonyl)amino]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide (259 mg, 0 44 mmol) in tetrahydrofuran (5.0 mL) at room temperature was added 1.0 M sodium hydroxide (0.880 mL, 0 88 mmol). The reaction was stirred at room temperature for 2 days. The resulting reaction mixture was poured into a 1·1 mixture of water and saturated sodium bicarbonate (25 mL) and extracted with ethyl acetate (1 x 25 mL). The aqueous layer was neutralized via addition of 1N HCl to pH ~8 and extracted with ethyl acetate (2 x 25 mL). The combined organic layers were washed once with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to afford *N*-(4-chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[(methylsulfonyl)amino]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (190 mg, 76%) as a light-yellow, foamy solid.

^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 3H), 2 04 (s, 3H), 2.05-2 12 (m, 1H), 2.20-2 35 (m, 1H), 2.95 (s, 3H), 4.65-4.80 (m, 1H), 5.44-5.66 (m, 1H), 6.50 (d, 1H), 6 88-7.01 (m, 3H), 7.07-7.32 (m, 6H), 7.35-7.46 (m, 3H).

MS m/z 512 (M+1)

[001121] (2*S*,4*R*)-1-Methyl-pyrrolidine-2-carboxylic acid [3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-amide (H-59)

[001122] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (100 mg, 0 204 mmol) was dissolved in methylene chloride (2 mL) and pyridine (2 mL). N-methyl proline (33 mg, 0.255 mmol) and EDC (63 mg, 0 255 mmol) were added and the reaction was stirred for 1 hour. The mixture was partitioned between methylene chloride and water, the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate) to afford the product

^{1}H-NMR ($CDCl_3$) δ: 1 1 (s, 3H), 1.2 (m, 1H), 1.8 (m, 2H), 2 0 (m, 2H), 2.0 (s, 3H), 2.2 (m, 2H), 2.3 (m, 1H), 2.4 (s, 3H), 2.6 (m, 1H), 3 2 (m, 2H), 3.4 (q, 2H), 4.0 (t, 2H), 4.1 (m, 1H), 4.8 (m 1H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6 9 (t, 1H), 7.2 (m, 6H), 7.4 (d, 2H).

MS m/z 603 (M+1).

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[001123] 4-(4-{[(2*R*,4*S*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-60)

[001124] 4-(4-{[(2*R*,4*S*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid was prepared following the procedure to prepare 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid, substituting *N*-(4-chlorophenyl)-*N*-[(2*R*,4*S*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide for *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

^{1}H-NMR ($CDCl_3$) δ. 1.14 (d, 3H), 1.15 (t, 1H), 1.25 (s, 6H), 2.02 (t, 2H), 2.05 (m, 2H), 2 27 (m, 1H), 3 96 (t, 2H), 4.72 (sextet, 1H), 5 52 (br, 2H), 5.58 (bs, 1H), 6 52 (d, 1H), 6 67 (d, 2H), 6 86 (t, 1H), 7 08-7.35 (m, 6H), 7 38 (d, 2H)

MS m/z 549 (M+1)

[001125] (2*S*,4*R*)-N-(1-{4-[3-(Acetyl-ethyl-amino)-propoxy]-benzoyl}-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-(4-chloro-phenyl)-acetamide (H-61)

[001126] (2*S*,4*R*)-N-{1-[4-(3-Acetylamino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (30 mg, 0.056 mmol) was dissolved in DMF (1 mL) Sodium hydride (20 mg, 0.833 mmol) and iodoethane (10 drops via pipet) were added and the reaction was stirred at room temperature over night The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by preparatory HPLC.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (m, 7H), 2.0 (m, 8H), 2.3 (m, 1H), 3.3 (q, 1H), 3.4 (q, 1H), 3.4 (t, 2H), 3.9 (t, 2H), 4 7 (m, 1H), 5.6 (bs, 1H), 6 5 (d, 1H), 6.7 (d, 2H), 6 9 (t, 1H), 7 2 (m, 6H), 7 4 (d, 2H)

MS m/z 562 (M+1)

[001127] N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(4-hydroxy-4-methylpentyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-62)

[001128] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(4-oxopentyl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure H, substituting 4-(4-oxopentyl)benzoyl chloride for 6-trifluoromethyl nicotinyl chloride to afford *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(4-oxopentyl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide ^{1}H-NMR ($CDCl_3$) 1 14 (d, 4H), 1.87 (q, 2H), 2.01 (s, 3H), 2.04 (m, 1H), 2.06 (s, 3H), 2.32 (t, 2H),2.52 (t, 2H), 4.74 (q, 1H), 5.60 (br, 1H), 6.47 (d, 1H), 6.96 (m, 3H), 7.20 (m, 8H) MS m/z: 503 (M+1). (4-(4-oxopentyl)benzoyl chloride was prepared in six steps from pent-4-en-2-ol. (as follows: Pent-4-en-2-ol (4.0g, 46.44 mmol) was dissolved in CH_2Cl_2 (30 mL). TBDMSCl (13 93 g, 92.88 mmol) and imidazole (6.31g, 92.88 mmol) were added at 0^{0}C. The reaction mixture was stirred at RT for

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overnight The organic phase was washed with sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (hexane) to give 5 14g of desired product as a colorless oil (55%yield). ^{1}H-NMR ($CDCl_3$) δ: 0.02 (s, 6H), 0 89 (s,9H), 1.11 (d,3H), 2.14(q,2H), 3 80 (q, 1H), 5.03 (m, 2H), 5 80 (m,1H). MS m/z: 200 (M+1)

[001129] To a solution of ethyl 4-iodobenzoate (4.15g, 15.03 mmol) in DMF (20 mL), was added *tert*-butyl(dimethyl)[(1-methylbut-3-en-1-yl)oxy]silane (3.0g, 15 03 mmol) and $Pd(OAc)_2$ (342 mg, 1.50mmol), triethyl amine (2 mL, 30.06 mmol) and DPPP (1 05g, 2.55 mmol) under Argon. The mixture was stirred at 80°C for overnight. After concentrating, the residue was dissolved in EtOAc (20 mL). The organic phase was washed with Sat. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (Hexane: EtOAc, 20:1) to give 3.15g of desired product as a yellow oil (60% yield). ^{1}H-NMR ($CDCl_3$) δ. 0.02 (s, 6H), 0.86 (s,9H), 1 16 (d,3H), 1.36 (t, 3H), 2.34(q, 2H), 3.89 (q, 1H), 4 34 (q, 2H), 6.38 (m, 2H), 7 36 (d, 2H), 7.95 (d, 2H). MS m/z: 348 (M+1).

[001130] To a solution of ethyl ethyl 4-(*E*-4-{[*tert*-butyl(dimethyl)silyl]oxy}pent-1-en-1-yl)benzoate (3 15 g, 9.07 mmol) in THF (10 mL), was added TBAF (18.15 mL, 18 15 mmol, 1M solution in THF) at RT. The reaction mixture was stirred at RT for 2h The organic phase was washed with Sat $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated The residue was purified by column chromatography (hexane· EtOAc, 4:1) to give 1 25g of desired product as a yellow oil (58% yield) ^{1}H-NMR ($CDCl_3$) δ: 1.19 (d,3H), 1 25 (t, 3H), 2.34(m, 2H), 3 91 (m, 1H), 4 34 (q, 2H), 6.38 (m, 2H), 7.36 (d, 2H), 7 93 (d, 2H). MS m/z: 237 (M+1).

[001131] A solution of ethyl 4-[(1*E*)-4-hydroxypent-1-en-1-yl]benzoate (1 25 g, 5.29 mmol) and Pd/C (10% weight, 0 125g) in EtOH (20 mL) was degassed and bubbled through H_2 The mixture was stirred at RT for overnight. After filtering through celite, the organic solution was concentrated to give a colorless oil which was used in the next step without purification (1.1g, 88% yield). ^{1}H-NMR ($CDCl_3$) δ: 1.15 (d,3H), 1.35 (t, 3H), 2.70(m, 2H), 2.66 (t, 2H), 3 80 (quan., 1H), 4 33 (q, 2H), 7.23 (d, 2H), 7.94 (d, 2H) MS m/z. 239 (M+1).

[001132] To a solution of ethyl 4-(4-hydroxypentyl)benzoate (1 1g, 4.62 mmol) and triethyl amine (1 9 mL, 13.86mmol) in CH_2Cl_2 (20 mL), was added sulfur trioxide pyridine complex (2.2g, 13 86 mmol) in DMSO (2 mL) at 0°C The mixture was stirred at 0°C for 2h The reaction mixture was washed with 1N HCl solution, dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (Hexane EtOAc, 3:1) to give 0 5 g of desired product as a colorless oil (50% yield) ^{1}H-NMR ($CDCl_3$) δ:1 36 (t, 3H), 1 86 (q, 2H), 2.09 (s, 3H), 2.40 (t, 2H), 2 67 (t, 2H), 4.32 (q, 2H), 7 23 (d, 2H), 7.95 (d, 2H) MS m/z: 237 (M+1)

[001133] To a solution of ethyl 4-(4-oxopentyl)benzoate (500mg, 2.11mmol) in THF/EtOH/H_2O (5 mL, 10:1:1), was added NaOH (254 mg, 6.33mmol). The mixture was reflux for overnight. After

acidification, the mixture was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated The residue was purified by column chromatography (EtOAc) to give 0.31 g of desired product as a white solid (70% yield) ^{1}H-NMR ($CDCl_3$) 1.87 (q, 2H), 2 10 (s, 3H), 2.50 (t, 2H), 2.70 (t, 2H), 7.24 (d, 2H), 8 01 (d, 2H). MS m/z: 207 (M-1, ES$^-$).

[001134] To a solution of N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-(4-(4-oxopentyl)benzoyl)-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (40 mg, 0 079mmol) in THF (2mL), was added MeMgBr (68 uL, 0.095 mmol, 1 4 M solution in THF) at 0^{0}C. The mixture was stirred at 0^{0}C for 2h. After quenching with sat. NH_4Cl solution, the mixture was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$ and concentrated. The residue was purified by column chromatography (EtOAc) to give 16 mg of desired product as a white solid (40% yield).

^{1}H-NMR ($CDCl_3$): 1.14 (m, 10H), 1.37 (m, 2H), 1.61 (m, 2H), 2 01 (s, 3H), 2.22 (m, 1H), 2 49 (t, 2H), 4.74 (q, 1H), 5.60 (br, 1H), 6 49 (d, 1H), 6.97 (m, 3H), 7 20 (m, 8H)

MS m/z: 519 (M+1).

[001135] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-63)

[001136] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (200 mg, 0 41 mmol) was dissolved in dichloromethane and a solution of BBr_3 (1.0 M in dichloromethane, 3.0 mL) was added; the reaction mixture was stirred at room temperature for until no starting material remained The reaction mixture was washed with sat. $NaHCO_3$ and brine carefully. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography using Hexanes-EtOAc system to give *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (152 mg, 78%)

^{1}H-NMR ($CDCl_3$) δ 1.12 (d, 3H), 1 24 (m, 2H), 2.07 (s, 3H), 2.25 (b, 1H), 4 70 (m, 1H), 6 52 (d, 1H), 6.78 (d, 2H), 7.18 (t, 1H), 7 20-7.40 (m, 6H).

MS m/z. 471 (M+1)

[001137] (2*S*,4*R*)-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-carbamic acid methyl ester (H-64)

[001138] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (150 mg, 0 30 mmol) was dissolved in DCM (1 mL). To this solution was added TEA (36 4 mg, 0 36 mmol) followed by methyl chloroformate (34 mg, 0.36 mmol). The reaction mixture was stirred at room temerature for 18 hours The mixture was concentrated under reduced pressure and dissolved in DCM (15 mL). The reaction mixture was washed with sat. aq $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). The organic phase was

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5/95 ethyl acetate/hexane – 50/50 ethyl acetate/hexane gradient) to afford white solid product (71 mg, 52%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.68-0 88 (m, 2H), 1.00-1.05 (m, 4H), 1.23 (s, 3H), 1.61-1.64 (broad, 1H) 2.02 (s, 3H), 2 22-2 33 (m, 1H), 3.31-3.37 (m, 1H), 3 62 (s, 3H), 3.93-3.97 (m, 1H), 4.73-4.75 (m, 1H) 5 28-5 31 (broad, 1H), 6.50-6.93 (m, 4H), 7 12-7 39 (m, 8H).

MS m/z. 551 (M+1).

[001139] Methyl 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylate (H-65)

[001140] Methyl 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylate was prepared following general procedure H, substituting methyl 5-(chlorocarbonyl)thiophene-2-carboxylate for 6-trifluoromethyl nicotinyl chloride (methyl 5-(chlorocarbonyl)thiophene-2-carboxylate was prepared in one step from thiophene-2,5-dicarboxylic acid monomethyl ester. Treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded methyl 5-(chlorocarbonyl)thiophene-2-carboxylate in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford methyl 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylate

^{1}H-NMR (CDCl3) δ: 1.10 (d, 3H), 2.05 (s, 3H), 2 20 (m, 1H), 3.80 (s, 3H), 4 65 (m, 1H), 5.50 (m, 1H), 6 45 (d, 1H), 6.80 (d, 1H), 7.00 (t, 1H), 7.15 (d, 2H), 7.20-7.40 (m, 5H).

MS m/z 483 (M+1).

[001141] (2*S*,4*R*)-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-furan-2-carboxylic acid (H-66)

[001142] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.28g, 0.64 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0 125g, 0.89 mmol) was added. 5-chloromethyl-furan-2-carboxylic acid methyl ester (0 130g, 0 64 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography to afford the product as colorless oil in 53% yield.

[001143] (2*S*,4*R*)-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-furan-2-carboxylic acid methyl ester (0.145g, 0 25 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added. The mixture was stirred at room temperature 4 hours The mixture was cooled to rt, acidified to form a

white precipitate The solid was filtered to give (2*S*,4*R*)-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-furan-2-carboxylic acid as a white solid.

^{1}H-NMR ($CDCl_3$) δ: 1.12-1 19 (m, 4H), 2.03 (s, 3H), 2 23-2.29 (m, 1H), 4 73-4.75 (m, 1H), 4 95 (s, 2H), 5 59 (bs, 1H) 6.48-6.51 (*m*, 2H), 6.69 (d, 2H), 6 91 (t, 1H), 7 12-7 37 (*m*, 9H)

MS m/z 559 (M+1)

[001144] (2*S*,4*R*)-N-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-pentanoic acid amide (H-67)

[001145] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.146 g, 0.34 mmol) was dissolved in 5 ml DMF at room temperature and K_2CO_3 (0.186 g, 1 35 mmol) was added. 5-Bromo-pentanoic acid ethyl ester (0.14 g, 0 67 mmol) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford the (2*S*,4*R*)-N-5-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-pentanoic acid ethyl ester (0 148 g, 78%)

[001146] The ester was hydrolyzed to the acid by dissolving in 10 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0 182 g in 5 ml water) was added. The mixture was heated to 40 °C for 3 hours. The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give (2*S*,4*R*)-N-5-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-pentanoic acid (0.128 g, 91%).

[001147] (2*S*,4*R*)-N-5-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-pentanoic acid amide was prepared from the acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid amide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford pure product in 69% yield.

^{1}H-NMR ($CDCl_3$) δ: 1 13 (d, 3H), 1.15 (t, 1H), 1.68 (m, 4H), 1.95 (s, 3H), 2.16-2 37 (m, 3H), 3 86 (t, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 5.79 (bs, 1H), 6 52 (d, 1H), 6 67 (d, 2H), 6 86 (t, 1H), 7.08-7 35 (m, 6H), 7 38 (d, 2H).

MS m/z· 534 (M+1)

[001148] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(2-methylpyrimidin-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-68)

[001149] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(2-methylpyrimidin-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure H, substituting 2-methylpyrimidine-5-carbonyl chloride for 6-trifluoromethyl nicotinyl chloride (2-methylpyrimidine-5-carbonyl chloride was prepared in four steps. To a solution of 3,3-dimethoxypropionate in ethylene glycol dimethyl ether was added sodium hydride at 0°C, then methyl formate The reaction mixture was warmed up to 50°C for 30 m. and then stirred at room temperature for 20h Anhydrous diethyl ether was added and the precipitate was filtered to give sodium 2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate. To a solution of acetamide hydrochloride in dimethylformamide was added preformed sodium 2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate. Reaction mixture was heated to 100°C for 1h. to give methyl 2-methylpyrimidine-5-carboxylate. Hydrolysis of the ester with sodium hydroxide gave 2-methylpyrimidine-5-carboxylic acid. Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded 2-methylpyrimidine-5-carbonyl chloride in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(2-methylpyrimidin-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide.

^{1}H-NMR (CDCl3) δ: 1 15 (d, 3H), 2 05 (s, 3H), 2 30 (m, 1H), 2.70 (s, 3H), 4.75 (m, 1H), 5 55 (m, 1H), 6 50 (d, 1H), 7.00 (t, 1H), 7.20-7 45 (m, 6H), 8.40 (s, 2H)

MS m/z. 435 (M+1).

[001150] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-dioxidoisothiazolidin-2-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-69)

[001151] To a solution of *N*-[(2*S*,4*R*)-1-(4-aminobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (321 mg, 0 74 mmol) in methylene chloride (7.0 mL) at 0 °C was added triethylamine (0 654 mL, 4.70 mmol) and 3-chloropropane-1-sulfonyl chloride (0.610 mL, 4.90 mmol). The reaction was warmed to room temperature and stirred for 2 days To the resulting reaction was added potassium carbonate (496 mg, 3.59 mmol) and *N,N*-dimethylformamide (2 0 mL). The reaction was stirred overnight (14 h) at room temperature. Next, 1N sodium hydroxide (1.5 mL) was added and the reaction stirred an additional 3 days at room temperature The resulting reaction was diluted with methylene chloride (15 mL) and poured into water (25 mL). The aqueous layer was extracted with methylene chloride (2 x 25 mL) and the combined organic layers were washed once with brine. The organics were then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (0-5% methanol / methylene chloride gradient) to afford 85% pure product (220 mg). A portion of this material (100 mg) was further purified via HPLC to afford pure *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-

1-[4-(1,1-dioxidoisothiazolidin-2-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (73 mg, 18%)

^{1}H-NMR ($CDCl_3$) δ 1.10-1.14 (m, 1H), 1.14 (d, 3H), 2 02 (s, 3H), 2.22-2 34 (m, 1H), 2 45-2.56 (m, 2H), 3.30-3 40 (m, 2H), 3.66-3 76 (m, 2H), 4.67-4 82 (m, 1H), 5.54-5 64 (m, 1H), 6.52 (d, 1H), 6.93 (t, 1H), 6.98-7 05 (m, 2H), 7.12-7 31 (m, 5H), 7 34-7 42 (m, 3H).

MS m/z 538 (M+1)

[001152] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-dichloro-4-ethylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-70)

[001153] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-dichloro-4-ethylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure H, substituting 4-ethyl-3,5-dichlorobenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (4-ethyl-3,5-dichlorobenzoyl chloride was prepared in two steps from 3,5-dichlorobenzoic acid. To a solution of 3,5-dichlorobenzoic acid in tetrahydrofuran was added lithium diisopropyl amide at -78°C After the reaction mixture was stirred at -78°C for 1 h ethyl iodide was added and reaction mixture stirred at room temperature for 2h. to give 4-ethyl-3,5-dichlorobenzoic acid. Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded 4-ethyl-3,5-dichlorobenzoyl chloride in decent yield). The rest of the procedures were followed as indicated in general procedure B to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-dichloro-4-ethylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide.

^{1}H-NMR ($CDCl_3$) δ 1.00 (t, 3H), 1 10 (d, 3H), 2.05 (s, 3H), 2.20 (m, 1H), 2 80 (q, 2H), 4 65 (m, 1H), 5.50 (m, 1H), 6 50 (d, 1H), 6.95 (d, 1H), 7.00 (s, 2H), 7.2 (m, 3H), 7.25-7 40 (m, 3H)

MS m/z 517 (M+1).

[001154] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester (H-71)

[001155] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF at room temperature and K_2CO_3 was added. Ethyl-4-bromobutyrate was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford the product.

^{1}H-NMR ($CDCl_3$) δ. 1.10 (d, 3H), 1 11 (m, 1H), 1 20 (t, 3H), 2.43 (t, 2H), 1.99 (s, 3H), 2 24(m, 1H), 3.90 (t, 2H), 4.09 (q, 2H), 4.72 (sextet, 1H), 5.55 (bs, 1H), 6.49 (d, 1H)< 6 62 (d, 2H), 6.90(t, 1H), 7 11 (d, 2H), 7 16 (m, 1H), 7.18 (d, 2H), 7 26 (d, 1H), 7.34 (d, 2H).

MS m/z: 549 (M+1)

[001156] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-benzoic acid methyl ester (H-72)

[001157] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (150 mg, 0 35 mmol) was dissolved in DMF (5 mL) at room temperature. Cs_2CO_3 (283 mg, 0 87 mmol) was added followed by methyl 3-(bromomethyl)benzoate (119 mg, 0 52 mmol) and the reaction was stirred at room temperature for 18 hours The mixture was concentrated under reduced pressure and dissolved in ethyl acetate (15 mL). The reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5/95 ethyl acetate/hexane – 50/50 ethyl acetate/hexane gradient) to afford slightly yellow solid product (111 mg, 54%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ 1.02-1 08 (d, 3H), 1.55 (s, 1H), 2 02 (s, 3H), 2.24-2.32 (m, 1H,), 3.88-3 91 (s, 3H), 4.70-4.78 (m, 1H), 5 02-5.05 (s, 2H), 5 58-5.61 (b, 1H), 6 51-6.53 (m, 3H), 6.89-7.29 (m, 8H), 7 36-7.46 (m, 2H), 7 56-7 58 (m, 1H), 7 97-8.04 (m, 2H).

MS m/z 584 (M+1).

[001158] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester (H-73)

[001159] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester was prepared from (2*S*,4*R*)-trifluoro-methanesulfonic acid 4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl ester by adding piperidine-4-carboxylic acid ethyl ester (4 eq.), Cs_2CO_3 (3 eq.), 10 % $Pd_2(dba)_3$, BINAP (0.20 equ), and 10 % 18-Crown-6 (0 10 eq.) in toluene at 110 ^{0}C over night. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by HPLC to afford the product

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1 24 (m, 4H), 1 54-1.74 (mm, 4H), 2 00 (s, 3H), 2.27 (m, 1H), 2.57 (m, 1H), 2,80 (m, 1H), 3 01 (m, 1H), 3.48 (m, 1H), 3.71 (m, 1H), 4.10 (q, 2H), 4 70 (m, 1H), 5.56 (brs, 1H), 6.56 (d, 1H), 6.64 (d, 2H), 6.92 (t, 1H), 7.07-7.28 (m, 6H), 7.35 (d, 2H)

MS m/z: 574 31 (M+1)

[001160] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-74)

[001161] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure H, substituting 6-ethyl nicotinyl chloride for 6-trifluoromethyl nicotinyl chloride. (6-Ethyl nicotinyl chloride was prepared in two steps from methyl 6-chloronicotinate To a solution of methyl 6-chloronicotinate (2.50 g, 14 6 mmol) in tetrahydrofuran (80 mL) and *N*-methyl pyrrolidone (3 mL) was added iron (III) acetyl acetonate (500 mg), followed by dropwise addition of a solution of ethyl magnesium bromide in ether (9 80 mL, 17.5 mmol). The reaction was stirred at room temperature for 2 hours (*JACS* **2002**, *124*, 13856-13863) The resulting reaction was quenched using (saturated) aqueous ammonium chloride The mixture was extracted with ethyl acetate, and the organics were separated and washed with brine, then dried over anhydrous sodium sulfate, filtered and concentrated in vacuo The crude product was purified on silica gel by flash chromatography using hexanes/ethyl acetate (10-30%) to afford methyl 6-ethylnicotinate in 66% yield. The methyl ester was then hydrolysed in the presence of aqueous lithium hydroxide in methanol at room temperature overnight to give 6-ethylnicotinic acid. Further treatment of 6-ethyl nicotinic acid with oxalyl chloride and catalytic DMF in dichloromethane gave the desired 6-ethyl nicotinyl chloride).

^{1}H-NMR ($CDCl_3$) δ: 1.16 (d, 3H), 1.24 (t, 3H), 1.24-1.26 (m, 1H), 2.02 (s, 3H), 2.24-2.38 (m, 1H), 2 70-2.85 (q, 2H), 4.70-4.80 (m, 1H), 5.44-5 64 (m, 1H), 6.50 (d, 1H), 6.92-6.98 (t, 2H), 7.20-7.40 (m, 8H), 8 50 (br s, 1H).

MS m/z: 448 (M + 1).

[001162] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-trifluoromethanesulfonylamino-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-75)

[001163] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (34 mg, 0 069 mmol) was dissolved in methylene chloride (0.5 mL) and triethylamine (0.019 mL, 0.138 mmol) and cooled to -40 °C. Trifluoromethanesulfonic anhydride (0 015 mL, 0 086 mmol) was added and the mixture was warmed to 0 °C for 30 minutes The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (1/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1 1 (s, 3H), 1 2 (m, 1H), 1.9 (m, 2H), 2.0 (s, 3H), 2.3 (m, 1H), 3.6 (m, 2H), 4.0 (t, 2H), 4.7 (m, 1H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (t, 1H), 6.7 (d, 1H), 6.9 (t, 1H), 7 2 (m, 7H), 7 4 (d, 2H).

MS m/z· 624 (M+1).

[001164] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(2-oxo-oxazolidin-3-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-76)

[001165] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (50 mg, 0 102 mmol) was dissolved in methylene chloride (3 mL) and triethylamine (0.150 mL, 1.08 mmol) and cooled to -40 °C. 2-Bromoethylchloroformate (0 016 mL, 0 153 mmol) was added and the reaction was allowed to warm to room temperature After 1 hour at room temperature, DMF (2 mL) and Cs_2CO_3 (100 mg, 0.307 mmol) were added and the mixture was stirred over night The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (1/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (s, 3H), 1.2 (m, 1H), 1.9 (m, 2H), 2 0 (s, 3H), 2.3 (m, 1H), 3 4 (t, 2H), 3.5 (t, 2H), 3.9 (t, 2H), 4.3 (t, 2H), 4.7 (m, 1H), 5 6 (bs, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6.9 (t, 1H), 7.2 (m, 6H), 7.4 (d, 2H)

MS m/z. 562 (M+1).

[001166] (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionic acid (H-77)

[001167] (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionic acid was prepared following the procedure for (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester, substituting 3-amino-propionic acid methyl ester for piperidine-4-carboxylic acid ethyl ester to yield the (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenylamino)-propionic acid methyl ester. The ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and lithium hydroxide (1N) was added and heated 50°C for 2h The mixture was cooled to room temperature, acidified to form a white precipitate The solid was filtered to give to afford the product after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1.23 (m, 1H), 2.03 (s, 3H), 2.27 (m, 1H), 2.51 (s, 2H), 3.30 (t, 2H), 4.71 (m, 1H), 5.61 (brs, 1H), 6.27 (d, 2H), 6.59 (d, 1H), 6.93 (t, 1H), 7 01 (d, 2H), 7.02-7.27 (m, 4H), 7.37 (d, 2H), 8 90 (br, 1H).

MS m/z: 506.3 (M+1).

[001168] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-78)

[001169] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure H, substituting 3,5-difluoro-4-methoxybenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (3,5-Difluoro-4-methoxybenzoyl chloride was prepared in one step from 3,5-difluoro-4-methoxybenzoic acid. 3,5-difluoro-4-methoxybenzoic acid was treated with oxalyl chloride and catalytic amount of DMF to afford 3,5-difluoro-4-methoxybenzoyl chloride in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide in decent yield
^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 3H), 1.24 (m, 2H), 2.02 (s, 3H), 2.28 (b, 1H), 3.94 (s, 3H), 4 70 (m, 1H), 6 52 (d, 1H), 6.72 (d, 2H), 6.90 (t, 1H), 7.17-7 23 (m, 3H), 7 28-7 38 (m, 3H)
MS m/z· 484 (M+1).

[001170] (2*S*,4*R*)-4-{4-[4-(Acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-2,2-dimethyl-butyric acid (H-79)

[001171] 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (300 mg, 0.545 mmol) was dissolved in ethanol. Pd/C (10% Palladium) was added, followed by H_2 gas (1 atm--balloon). After 3 hours, the reaction mixture was filtered and concentrated. The crude residue was purified by silica gel chromatography (100% ethyl acetate to 5% methanol/ethyl acetate gradient) to afford the product.
^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (m, 1H), 1 2 (s, 3H), 1 3 (s, 3H), 2.0 (s, 3H), 2.1 (t, 1H), 2 3 (m, 1H), 3 9 (m, 2H), 4.7 (m, 1H), 5.6 (bs, 1H), 5.9 (d, 1H), 6.5 (d, 1H), 6 4 (d, 2H), 6 9 (t, 1H), 7.2 (m, 7H), 7 4 (d, 2H), 10.8 (bs, 1H).
MS m/z· 515 (M+1).

[001172] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-fluoro-acetic acid (H-80)

[001173] (2*S*,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-fluoro-acetic acid ethyl ester (100 mg) was dissolved in methanol/THF (1.1, 5 mL), and potassium hydroxide (1.0N, 1 mL) was added. After 1 hour, the reaction was acidified and extracted with methylene chloride. The organic layer was dried, filtered, and concentrated The crude residue was purified by silica gel chromatography 100% ethyl acetate to 5% methanol/ethyl acetate gradient to afford the product.
^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (m, 1H), 2.0 (s, 3H), 2.3 (m, 1H), 4.8 (m, 1H), 5.6 (bs, 1H), 5.9 (d, 1H), 6.5 (d, 1H), 6 9 (m, 3H), 7 2 (m, 6H), 7 4 (d, 2H), 11 1 (bs, 1H).
MS m/z· 511 (M+1)

[001174] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid ethyl ester (H-81)

[001175] To a solution of diethyl azodicarboxylate (120 mg) in 5 ml THF at 0°C, was added PPh_3 (181 mg). The mixture was stirred for 10 min at 0°C. Then (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (200 mg) was added The mixture was stirred for 20 min at 0°C. 4-Hydroxy-cyclohexanecarboxylic acid ethyl ester (80 mg) was added The final reaction mixture was stirred for overnight at RT. The mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The residue was purified by silica gel chromatography (30/70 hexanes/ethyl acetate gradient) to afford pure (2*S*,4*R*)-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-cyclohexanecarboxylic acid ethyl ester (100mg, 37%).

^{1}H-NMR ($CDCl_3$) δ 1 13 (d, 4H), 1 22 (t, 3H), 1.26-1.60 (m, 5H), 2 00-2.18 (m, 5H), 2 20-2.39 (m, 3H), 4.11 (q, 2H), 4.72 (sextet, 1H), 5 60 (bs, 1H), 6.53 (d, 1H), 6 64 (d, 2H), 6.91 (t, 1H) 7.11-7.38 (m, 8H)

MS m/z 589 (M+1)

[001176] (1R,2R)-2-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylic acid (H-82)

[001177] *Trans*-2-Hydroxymethyl-cyclopentanecarboxylic acid methyl ester (0 127 g, 0.81 mmol) was dissolved in 10 ml toluene at room temperature with PPh_3 (0.211g, 0.81 mmol), then added N-(4-chlorophenyl)-N-[(2S,4R)-1-(4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (0 1g, 0.23 mmol) and stirred for 5 min DEAD (0.141g, 0 81 mmol) was added and the reaction was stirred for 18 h at room temperature. The reaction was concentrated and purified by silica gel chromatography (45 % dichloromethane /55% ethyl acetate) to afford methyl 2-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylate (0.12 g, 90%)

[001178] 2-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylate was hydrolyzed to the acid by dissolving in 5 ml methanol and potassium carbonate (0.100 g in 4 ml water) was added. The mixture was stirred for 2 days. The mixture was cooled to room temperature and methanol was removed *in vacuo*. The mixture was acidified to form a white precipitate The solid was filtered to give (1*R*,2*R*)-2-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylic acid (0.012 g, 10%)

^{1}H-NMR ($CDCl_3$) δ 1 12 (m, 1H), 1.18 (d, 3H), 1 51 (m, 1H), 1.74 (m, 2H), 1.96 (m, 3H), 2 02 (s, 3H), 2 28 (m, 1H), 2.65 (m, 2H), 3.89 (m, 2H), 4 77 (m, 1H), 5.60 (m, 1H), 6 48 (d, 1H), 6.61 (m, 2H), 6.88 (t, 1H), 7 19 (m, 6H), 7.37 (d, 2H)
MS m/z: 562 (M+1)

[001179] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-ureido-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-84)

[001180] To a solution of (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (50 mg, 0.10 mmol) in DCM (1 mL) was added trimethylsilyl isocyanate (23 mg, 0 20 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction was quenched by adding 0.2 mL of water and concentrated under reduced pressure. The crude residue was purified by preparatory HPLC to afford the product (9 mg, 17%).
MS m/z 536 (M+1).

[001181] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(2-imidazol-1-yl-ethoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-85)

[001182] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 065g, 0.15 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0 12 g, 0 87 mmol) was added. 1-(2-Bromo-ethyl)-1H-imidazole (0.08g, 0.45 mmol) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product (0.06g, 76%).
^{1}H-NMR ($CDCl_3$) δ· 1 13 (d, 3H), 1.15 (t, 1H), 1.98 (s, 3H), 2 27 (m, 1H), 4.13 (t, 2H), 4.28 (t, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.48 (d, 1H), 6.64 (d, 2H), 6.91 (t, 1H), 6.98 (s, 1H), 7.03 (s, 1H), 7.08-7.35 (m, 6H), 7.38 (d, 2H), 7 55 (s, 1H)
MS m/z 529 (M+1)

[001183] (2*S*,4*R*)-1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid ethyl ester (H-86

[001184] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF at room temperature and K_2CO_3 was added. 1-(3-Bromo-propyl)-1H-imidazole-2-carboxylic acid ethyl ester (prepared from the dibromide and the corresponding imidazole with NaH in THF) was added and the reaction was allowed to heat to 80°C

overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (5% MeOH/ 95% CH_2Cl_2/NH_4OH to 10% MeOH/ 90% CH_2Cl_2/NH_4OH) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1 11 (m, 1H), 1.38 (t, 3H), 2.01 (s, 3H), 2 22 (m, 2H), 3 83 (m, 2H), 4.35 (q, 2H), 4.55 (m, 2H), 4 71 (sextet, 1H), 5.58 (bs, 1H), 6.49 (d, 1H), 6.63 (d, 2H), 6.90 (t, 1H), 7.08-7 28 (m, 9H), 7.36 (d, 1H)

[001185] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (H-87)

[001186] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.126 g, 0 242 mmol) was dissolved in 3 ml DMF at room temperature and K_2CO_3 (0 267 g, 1 94 mmol) was added. 4-Bromo-2,2-dimethyl-butyric acid methyl ester (0.202 g, 0 969 mmol, prepared according to the procedure from *Tetrahedron* 1994, 50(32), 9825-30) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford the (2*S*,4*R*)-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid methyl ester (0.105 g, 77%).

[001187] The ester was hydrolyzed to the acid by dissolving in 6 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.042 g in 2 ml water) was added. The mixture was heated to 40 °C for 3 hours The mixture was cooled to rt, acidified to form a white precipitate The solid was filtered to give (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-butyric acid (0 085 g, 83%).

^{1}H-NMR ($CDCl_3$) δ 1.14 (d, 3H), 1 15 (t, 1H), 1.25 (s, 6H), 2.02 (t, 2H), 2 05 (m, 2H), 2 27 (m, 1H), 3 96 (t, 2H), 4.72 (sextet, 1H), 5.52 (br, 2H), 5 58 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6.86 (t, 1H), 7.08-7 35 (m, 6H), 7.38 (d, 2H).

MS m/z. 549 (M+1).

[001188] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-difluoroethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-88)

[001189] *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-difluoroethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure H, substituting 4-(1,1-difluoroethyl)benzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (4-(1,1-difluoroethyl)benzoyl chloride was prepared in 3 steps from 1-(4-iodophenyl)ethanone. Treatment of 1-(4-

iodophenyl)ethanone with neat [Bis(2-methoxyethyl)amino]sulfur trifluoride (1.7 equivalents) at 85 °C under argon in the presence of ethanol (0.1 equivalents), then quenching with saturated aqueous sodium bicarbonate followed by standard aqueous work up and chromatography (hexanes) afforded 1-(1,1-difluoroethyl)-4-iodobenzene Subsequent lithium-halogen exchange with n-butyl lithium (1.2 equivalents) in THF at -78 °C under argon and quenching of the resultant organolithium species by bubbling carbon dioxide through the reaction mixture afforded 4-(1,1-difluoroethyl)benzoic acid which was converted to 4-(1,1-difluoroethyl)benzoyl chloride by treatment with thionyl chloride (2.2 equivalents) in dichloromethane at room temperature for 2 hours followed by removal of the volatiles in vaccuo) The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-difluoroethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide.

^{1}H-NMR ($CDCl_3$) δ 1.16 (d, 3H), 1.22-1.26 (m, 1H), 1.82 (t, 3H), 2 03 (s, 3H), 2.24-2.35 (m, 1H), 4.72-4.83 (m, 1H), 5.63 (br s, 1H), 6.47 (d, 1H), 6.90 (t, 1H), 7.16-7 46 (m, 10H).

MS m/z. 483 (M+1)

[001190] *N*-[(2*S*,4*R*)-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide (H-89)

[001191] *N*-[(2*S*,4*R*)-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide was prepared following general procedure H, substituting 3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl chloride was prepared in one step from 3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoic acid. 3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoic acid was treated with oxalyl chloride and catalytic amount of DMF to afford 3,5-difluoro-4-methoxybenzoyl chloride in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford *N*-[(2*S*,4*R*)-1-(3-{[*tert*-butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide

^{1}H-NMR ($CDCl_3$) δ: 0 1(s, 9H), 0.9 (s, 6H), 1.15 (d, 3H), 2 07 (s, 4H), 2.30 (b, 1H), 4.75 (m, 1H), 6.55 (d, 1H), 6.68 (d, 1H), 6.62-6.70 (m, 3H) 7 15-7 25 (m, 4H), 7.35-7 42 (m, 2H).

MS m/z: 568 (M+1)

[001192] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid amide (H-90)

[001193] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid amide was prepared from (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-

carboxylic acid. The acid (0.2 g, 0.366 mmol) was dissolved in DMF (3 mL) at room temperature and HOBt (0 74 g, 0.55 mmol), HATU (0 209 g, 0 55 mol), and diisopropylethylamine (0 25 mL,) was added followed by ammonium chloride (0 040 g, 0.74 mmol) and stirred at room temperature for 16 h The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine The organics were dried over $MgSO_4$, filtered and concentrated down The crude residue was purified HPLC purification

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1 20 (m, 1H), 1.73 (m, 2H), 1 84(m, 2H), 2.01 (s, 3H), 2.24 (m, 2H), 2 65 (m, 2H), 3.66 (m, 2H), 4 70 (m, 1H), 5 62 (br, 2H), 6.93 (br, 1H), 6 56 (d, 1H), 6.60 (d, 2H), 6 92 (t, 1H), 7.05-7.27 (m, 6H), 7 37 (d, 2H).

MS m/z: 545.3 (M+1).

[001194] (2*S*,4*R*)- N-{1-[4-(1-Acetyl-piperidin-4-ylmethoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (H-91)

[001195] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(piperidin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (0 075 g, 0 14 mmol) was dissolved in dichloromethane at room temperature. DIEA (0.1 mL, 0.56 mmol) and acetyl chloride (0 2 mL, 2.8 mmol) was added The reaction was stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* The crude residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product (0.049g, 49%)

^{1}H-NMR ($CDCl_3$) δ 1 13 (d, 3H), 1.15 (t, 1H), 1 24 (m, 2H), 1.81 (m, 2H), 1.93 (m, 1H), 2.04 (s, 3H), 2 09 (s, 3H), 2.27 (m, 1H), 2.55 (t, 1H), 3 09 (t, 1H), 3.73 (m, 2H), 3.85 (m, 1H), 4.63 (m, 1H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6 52 (d, 1H), 6.67 (d, 2H), 6.86 (t, 1H), 7.08-7 35 (m, 6H), 7.38 (d, 2H)

MS m/z 574 (M+1)

[001196] (2*S*,4*R*)-N-5-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-pentanoic acid (H-92)

[001197] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.12 g, 0.28 mmol) was dissolved in 5 ml DMF at room temperature and K_2CO_3 (0 155 g, 1.12 mmol) was added. 5-Bromo-2,2-dimethyl-pentanoic acid methyl ester (0.123 g, 0 56 mmol, prepared according to the procedure from *Tetrahedron* 1994, 50(32), 9825-30) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford (2*S*,4*R*)-N-5-(4-{4-[acetyl-(4-

chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-pentanoic acid methyl ester (0.076 g, 48%)

[001198] The ester was hydrolyzed to the acid by dissolving in 8 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.03 g in 2 ml water) was added. The mixture was heated to 40 °C for 3 hours. The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give the product (0.057 g, 79%)

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.15 (t, 1H), 1 27 (s, 6H), 1.70 (m, 4H), 1.1.98 (s, 3H), 2.28 (m, 1H), 3.89 (t, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6 86 (t, 1H), 7.08-7 35 (m, 6H), 7.38 (d, 2H).

MS m/z· 535 (M+1)

[001199] (2*S*,4*R*)-4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyric acid methyl ester (H-93)

[001200] (2*S*,4*R*)- 4-[(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-amino]-butyric acid methyl ester was prepared from (2*S*,4*R*)- (4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-carbamic acid ethyl ester. (2*S*,4*R*)- (4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-methyl-carbamic acid ethyl ester was dissolved in acetonitrile (2 mL). Iodotrimetylsilane was added and the reaction was allowed to stir at room temperature over night. Excess reagent was quenched by the addition of methanol (1 mL) and the mixture was concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The extracts were washed with 1 M sodium hydroxide, saturated aqueous sodium thiosulfate and brine, dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography to yield N-(4-chloro-phenyl)-N-[2-methyl-1-(4-methylamino-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide .

[001201] (2*S*,4*R*)- (N-(4-chloro-phenyl)-N-[2-methyl-1-(4-methylamino-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.015g, 0.033 mmol) was dissolved in CH_2Cl_2 (0.5 mL) at room temperature. Sodium borohydride (0.007g, 1.5 eq.) was added followed by 4-oxo-butyric acid methyl ester (0 020 g, 4 eq.) and the reaction was allowed to stir over night The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (33% Hexane / EA gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.09-1.24 (m, 4H), 1.84 (m, 2H), 2.00 (s, 3H), 2.27 (m, 3H), 2.86 (s, 3H), 3.29 (t, 2H), 3 62 (s, 3H), 4.70 (m, 1H), 5.58 (brs, 1H), 6.39 (d, 2H), 6.59 (d, 1H), 6.96 (t, 1H), 7.05-7.21 (m, 5H), 7.25 (d, 1H), 7.36 (d, 2H)

MS m/z: 548 (M+1)

[001202] **(2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-difluoro-butyric acid (H-94)**

[001203] 2,2-Difluoro-4-hydroxy-butyric acid methyl ester (0.27 g, 3.21 mmol, prepared according to US Patent 4421690 procedure) was dissolved in toluene at room temperature with PPh_3 (0.421g, 3 21 mmol), then added (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.20g, 0.46 mmol) and stirred for 5 min DEAD (0.028g, 3.21 mmol) was added and the reaction was stirred for 18 h at room temperature. The reaction was concentrated and purified by silica gel chromatography (45 % CH_2Cl_2 /55%EtOAc) to afford (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-difluoro-butyric acid methyl ester (0.23 g, 87%)

[001204] The ester was hydrolyzed to the acid by dissolving in 8 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.1 g in 4 ml water) was added The mixture was heated to 40 °C overnight The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give the product (0.038 g, 97%)

^{1}H-NMR ($CDCl_3$) δ· 1.13 (d, 3H), 1 15 (t, 1H), 2.04 (s, 3H), 2.18-2.44 (bs, 4H), 3 95 (t, 2H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6 86 (t, 1H), 7.08-7.35 (m, 6H), 7.38 (d, 2H)
MS m/z· 557 (M+1).

[001205] **{[3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propyl]amino}acetic acid (H-95)**

[001206] {[3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propyl]amino}acetic acid was prepared from (2*S*,4*R*)-N-{1-[4-(3-amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide. (2*S*,4*R*)-N-{1-[4-(3-amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (0 036g, 0.07 mmol) was dissolved in dimethylformamide, ethyl bromoacetate (0.008mL, 0.07 mmol) and potassium carbonate (0.021g, 0.14 mmol) were added The reaction was heated to 50°C for 17h The reaction was concentrated down and purified using 50% ethyl acetate/ 50% hexane to 100% ethyl acetate

[001207] ^{1}H-NMR ($CDCl_3$) δ: 0.91 (t, 1H), 1 12 (d, 3H), 1.24 (t, 3H), 2.02 (s, 3H), 2 04 (m, 2H), 2 28 (m, 1H), 3.47-3.53 (m, 2H), 3.94-4.02 (m, 3H), 4.06 (m, 1H), 4 10-4.22 (q, 2H), 4.54 (d, 2H), 4 72 (sextet, 1H), 5 61 (bs, 1H), 6 51 (d, 1H), 6.64 (d, 2H), 6.92 (t, 1H), 7 12 (d, 2H), 7 16-7.21 (m, 3H), 7 27 (d, 1H), 7.36 (d, 2H). MS m/z = 577 (M+1).

[001208] {[3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propyl]amino}acetic ethyl ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added. The mixture was stirred at room

temperature overnight. The mixture was cooled to rt, acidified to form a white precipitate The solid was filtered to give {[3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propyl]amino}acetic acid (0.003g, 60% yield).
MS m/z : 564 (M+1)

[001209] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-ethyl-butyramide (H-96)

[001210] (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-1-ethylidene-pentG-2,4-dienyloxy)-butyric acid (0 064g, 0.123mmol) was converted to the amide by dissolving in THF (2 mL) at room temperature HOBt (0.025 g), EDCI (0 028 g), and ethylamine (0.36 mmol) was added along with 2 drops of DMF and stirred at room temperature for 11 h. The reaction was diluted with ethyl acetate, washed with 1N NaOH, 1N HCl and brine. The organics were dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (50% ethyl acetate/50% hexane to 100% ethyl acetate) to afford the product (0 050 g, 74%).
^{1}H-NMR ($CDCl_3$) δ: 1.06 (t, 3H), 1.13 (d, 3H), 1.15 (t, 1H), 1 81 (s, 1H), 2.04 (s, 3H), 2 06 (m, 2H), 2 27 (m, 1H), 2.32 (t, 2H), 3 28 (q, 2H), 3.91 (t, 2H), 4 72 (sextet, 1H), 5.66 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6.88 (t, 1H), 7 08-7 35 (m, 6H), 7.38 (d, 2H)
MS m/z: 548 (M+1)

[001211] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-pyrazol-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-97)

[001212] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (75 mg, 0.17 mmol) was dissolved in DMF (1 mL) at room temperature. K_2CO_3 (47 mg, 0 34 mmol) was added followed by 1-(3-bromopropyl)-pyrazole (64 mg, 0.34 mmol) (prepared from the reaction of 1,3-dibromopropane and pyrazole with sodium hydride in tetrahydrofuran). The reaction was allowed to stir at 70^{0}C for 3hrs. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate. Organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (1/99 methanol / dichloromethane – 3/97 methanol / dichloromethane gradient) to afford the product.
^{1}H-NMR ($CDCl_3$) δ 1.1 (d, 3H), 1.2 (m, 1H), 2 0 (s, 3H), 2.3 (m, 1H), 2.3 (m, 2H), 3 8 (t, 2H), 4.3 (t, 2H), 4.7 (m, 1H), 5.6 (m, 1H), 6 2 (t, 1H), 6.5 (d, 1H), 6 65 (d, 2H), 6 9 (t, 1H), 7.1-7.4 (m, 9H), 7.5 (s, 1H)
MS m/z· 443/445 (M+1).

[001213] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(2-ethylpyrimidin-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-98)

[001214] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(2-ethylpyrimidin-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was prepared following general procedure H, substituting 2-ethylpyrimidine-5-carbonyl chloride for 6-trifluoromethyl nicotinyl chloride (2-ethylpyrimidine-5-carbonyl chloride was prepared in four steps To a solution of 3,3-dimethoxypropionate in ethylene glycol dimethyl ether was added sodium hydride at 0°C, then methyl formate. The reaction mixture was warmed up to 50°C for 30 m. and then stirred at room temperature for 20h Anhydrous diethyl ether was added and the precipitate was filtered to give sodium 2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate. To a solution of propionamide hydrochloride in dimethylformamide was added preformed sodium 2-(dimethoxymethyl)-3-methoxy-3-oxoprop-1-en-1-olate. Reaction mixture was heated to 100°C for 1h. to give methyl 2-ethylpyrimidine-5-carboxylate Hydrolysis of the ester with sodium hydroxide gave 2-ethylpyrimidine-5-carboxylic acid. Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded 2-ethylpyrimidine-5-carbonyl chloride in decent yield). The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(2-ethylpyrimidin-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide.

^{1}H-NMR (CDCl3) δ 1.15 (d, 3H), 1 25 (t, 3H), 2.05 (s, 3H), 2 30 (m, 1H), 2.90 (q, 2H), 4 75 (m, 1H), 5.55 (m, 1H), 6.50 (d, 1H), 7.00 (t, 1H), 7.20-7.45 (m, 6H), 8 40 (s, 2H).

MS m/z: 449 (M+1)

[001215] (2*S*,4*R*)- 3-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-5-methyl-3H-imidazole-4-carboxylic acid (H-99)

[001216] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF at room temperature and K_2CO_3 was added. 3-(3-Bromo-propyl)-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester (prepared from the dibromide and the corresponding imidazole with NaH in THF) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (2% MeOH/ 95% CH_2Cl_2 to 10% MeOH/ 90% CH_2Cl_2) to afford (2*S*,4*R*)-3-[3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-5-methyl-3H-imidazole-4-carboxylic acid ethyl ester. The ester (0.080g, 0.12 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added. The mixture was stirred at room temperature 16 hours The mixture was cooled to room temperature, acidified to form a white precipitate. The solid was filtered to give (2*S*,4*R*)- 3-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-

amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-5-methyl-3H-imidazole-4-carboxylic acid in 61% yield. 290

^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H), 1 29 (m, 1H), 2 05 (s, 3H), 2 34 (m, 2H), 2.45 (m, 1H), 2 61 (s, 3H), 4.08 (m, 2H), 4.43 (m, 2H), 4.73 (sextet, 1H), 5 53 (bs, 1H), 6 55 (d, 1H), 6 73 (d, 2H), 6.96 (t, 1H), 7 18 (m, 3H), 7 41 (m, 5H), 9.08 (s, 1H).

MS m/z 601 (M+1)

[001217] 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylic acid (H-100)

[001218] Methyl 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylate (80 mg, 0 17 mmol, 1 eq.) was dissolved in methanol (6 ml). A solution of potassium carbonate (200 mg, 1 4 mmol, 8 eq.) in water (2 ml) was added and reaction mixture was stirred at room temperature for 20 h The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylic acid (76 mg, 99 %).

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 2.05 (s, 3H), 2.25 (m, 1H), 4.70 (m, 1H), 5.55 (m, 1H), 6.55 (d, 1H), 6 85 (d, 1H), 7 05 (t, 1H), 7.15-7 45 (m, 7H).

MS m/z. 469 (M+1).

[001219] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid amide (H-101)

[001220] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid amide was prepared from (2*S*,4*R*)-N-1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid amide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down. The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford pure product (63%).

^{1}H-NMR ($CDCl_3$) δ 1.16 (d, 3H), 1 15 (t, 1H), 1.77-1.96 (m, 4H), 2.04 (s, 3H), 2 16-2 48 (m, 5H), 3.96 (t, 2H), 4.72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6 86 (t, 1H), 7.08-7 35 (m, 6H), 7 38 (d, 2H)

MS m/z 560 (M+1)

[001221] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-oxo-oxazolidin-3-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-102)

[001222] N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (61 mg, 0 142 mmol) was dissolved in methylene chloride (2 mL) and was added triethylamine (0.100 mL, 0 700 mmol) 2-Bromoethylchloroformate (0.023 mL, 0 213 mmol) was added and the reaction was allowed to warm to room temperature After 1 hour at room temperature, DMF (2 mL) and Cs_2CO_3 (100 mg, 0 307 mmol) were added and the mixture was stirred over night The mixture was partitioned between methylene chloride and water, the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by silica gel chromatography (1/1 hexanes/ethyl acetate to 100% ethyl acetate gradient) to afford the product.
^{1}H-NMR ($CDCl_3$) δ· 1.2 (d, 3H), 1 2 (m, 1H), 2.0 (s, 3H), 2 3 (m, 1H), 3 8 (t, 2H), 4.4 (t, 2H), 4.8 (m, 1H), 5.6 (m, 1H), 6 5 (d, 1H), 6.9 (t, 1H), 7.2 (m, 8H), 7.4 (d, 2H).
MS m/z. 504 (M+1).

[001223] 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-(diethylamino)butanoic acid (H-103)

[001224] 2-tert-Butoxycarbonylamino-4-hydroxy-butyric acid (0 79 g, 3.6 mmol) was dissolved in 15 ml methanol at room temperature and (trimethylsilyl)diazomethane (2M solution in hexane) was added till solution become yellow. The mixture was concentrated down to afford crude 2-tert-butoxycarbonylamino-4-hydroxy-butyric acid methyl ester.

[001225] The ester was dissolved in 20 ml toluene at room temperature with PPh_3 (0.94g, 3.6 mmol), then added N-(4-chlorophenyl)-N-[(2*S*,4*R*)-1-(4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (0 31g, 0 71 mmol) and stirred for 5 min. DEAD (0.626g, 3 6 mmol) was added and the reaction was stirred for 18 h at room temperature The reaction was concentrated and purified by silica gel chromatography (45 % CH_2Cl_2 /55%EtOAc) to afford crude methyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-[(tert-butoxycarbonyl)amino]butanoate (0.47 g).

[001226] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-[(tert-butoxycarbonyl)amino]butanoate was dissolved in 20 ml dichloromethane and 4 ml HCl in dioxane (4M) was added. The mixture was stirred 2 hours and concentrated down The residue was washed with ether, then partition between 1M NaOH and dichloromethane. The dichloromethane layer was removed and dried with $MgSO_4$. Sodium triacetoxyborohydride (0 61 g, 2.9 mmol) and acetaldehyde (0.33 ml, 5.8 mmol) was added. The mixture was stirred 2 days and washed with 1M NaOH. The mixture was then concentrated and

purified by silica gel chromatography (40 % CH_2Cl_2 /60%EtOAc) to afford methyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-(diethylamino)butanoate (0 075 g, 17%).

[001227] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-(diethylamino)butanoate was hydrolyzed to the acid by dissolving in 6 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.04 g in 2 ml water) was added. The mixture was heated to 50 °C for 18 hours. The mixture was cooled to room temperature and concentrated Then neutralized with 1M HCl and extracted with dichloromethane. The dichloromethane solution was dried and concentrated. The residue was purified by silica gel chromatography (87 % CH_2Cl_2 /13%methanol) to afford 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-(diethylamino)butanoic acid (0.04 g, 55%).

^{1}H-NMR ($CDCl_3$) δ 1.14 (m, 1H), 1.19 (d, 3H), 1 38 (m, 7H), 2.01 (m, 1H), 2.03 (s, 3H), 2.31 (m, 2H), 2 92 (m, 2H), 3.26 (m, 2H), 3 ~~79~~ (m, 1H), 4.23 (m, 2H), 4.70 (m, 1H), 5.58 (br, 2H), 6 48 (d, 1H), 6 61 (d, 2H), 6 88 (t, 1H), 7 19 (m, 6H), 7.37 (d, 2H).

MS m/z. 593 (M+1)

[001228] 3-(4-{(2*S*,4*R*)-4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-benzylamino)-propionic acid *tert*-butyl ester (H-104)

[001229] *N*-{(2*S*,4*R*)-1-[4-(aminomethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide (145 mg, 0.32mmol) was dissolved in methylene chloride (2.5 mL) and *tert*-butyl acrolate (0.052 mL, 0.36 mmol) and stirred at room temperature overnight. The mixture was concentrated then subjected to flash chromatography (50% hexanes / 50% ethyl acetate) to afford the title compound (159 mg, 85%) as a white solid

^{1}H-NMR ($CDCl_3$) δ: 1.13 (s, 3H), 1 15-1.20 (m, 1H), 1 41 (s, 9H), 1.73-2.05 (m, 1H), 2 02 (s, 3H), 2.20-2.37 (m, 1H), 2.40 (t, 2H), 2.77 (t, 2H), 3.72 (s, 2H), 4 69-4.82 (m, 1H), 5 42-5.76 (m, 1H), 6.48 (d, 1H), 6 87 (t, 1H), 7.08-7 31 (m, 8H), 7.37 (d, 2H).

MS m/z· 576 (M +1)

[001230] *N*-{(2*S*,4*R*)-1-[3,5-Bis(trifluoromethyl)benzoyl]-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide (H-105)

[001231] *N*-{(2*S*,4*R*)-1-[3,5-Bis(trifluoromethyl)benzoyl]-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide was prepared following general procedure H up to intermediate 4, substituting benzyl [(2*S*,4*R*)-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate for benzyl [(2S,4R)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]carbamate.

^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t), 1 20 (1H, m), 2 02 (s, 3H), 2.25-2 37 (m, 1H), 4.70-4 80 (m, 1H), 5.42-5 56 (m, 1H), 6.40 (d, 1H), 6.90(dd, 1H), 7.20-7.40 (m, 5H), 7.60 (s, 2H), 7 80 (s, 1H)
MS m/z· 589 (M + 1).

[001232] N-(4-Chloro-phenyl)-N-[(2*S*,4*R*)-2-methyl-1-(4-pyrrolidin-2-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (H-106)

[001233] Benzyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pyrrolidine-1-carboxylate (237mg, 0 381 mmol) was dissolved in HBr/Acetic acid (5 mL) and stirred for 2h. The reddish slurry was partitioned between Et_2O and 1N HCl. The HCl/water layer was washed 3X with Et_2O to rid the benzyl bromide. The water layer was neutralized with 1N NaOH, and washed 3X with methylene chloride. The organic layer was dried over $MgSO_4$, filtered and concentrated to afford the title compound (170 mg, 91%) as a white solid.^{1}H-NMR ($CDCl_3$) δ: 1.05-1 20 (m, 1H), 1 13 (s, 3H), 1.50-1.62 (m, 1H), 1.76-1 90 (m, 2H), 2.02 (s, 3H), 2 05-2 20 (m, 2H), 2.20-2.38 (m, 1H), 2 93-3.03 (m, 1H), 3.09-3.18 (m, 1H), 4.05 (t, 1H), 4 72-4.82 (m, 1H), 5.45-5.75 (m, 1H), 6.49 (d, 1H), 6 88 (t, 1H), 7 11-7 29 (m, 8H), 7 37 (d, 2H).
MS m/z· 488 (M +1)

[001234] (2*S*,4*R*)-N-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-N-methyl-succinamic acid methyl ester (H-107)

[001235] (2*S*, 4*R*)-N-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-N-methyl-succinamic acid methyl ester was prepared from (2*S*, 4*R*)-N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide To a solution of (2*S*, 4*R*)-N-[1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (115 mg, 0.265 mmoles) in dichloromethane (5.0 mL) was added diisopropylethylamine (50 uL, 0.265 mmoles) followed by the addition of methyl succinyl chloride (44 mg, 0 291 mmoles) and was stirred at room temperature overnight. Reaction mixture was diluted with dichloromethane and extracted with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Product was purified on silica gel by flash chromatography using hexane/ethyl acetate (1·1), ethyl acetate (100%) and ethyl acetate/methanol (10%) to afford (2*S*, 4*R*)-N-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-succinamic acid methyl ester (55 mg, 35%).^{1}H-NMR (CDCl3) *δ*: 1.11 (3H, s, overlapping 1H, t), 2.00 (3H, s), 2.30 (1H, m), 2.60-2.80 (2x2H, m), 3 70 (3H, s), 4.70 (1H, m), 5.55 (1H, m), 6.55 (1H, d), 6.90(1H, dd), 7 10-7.40 (9H, complex), 7 80 (1H, br,s). ESI-MS m/z: 548 (M + 1)

[001236] To a solution of (2*S*, 4*R*)-N-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-succinamic acid methyl ester (55 mg, 0 100 mmoles) in

DMF was added sodium hydride (60% dispersion in oil). After 30 minutes, iodomethane (16 uL, 0 11 mmoles) was added to the reaction mixture and stirred at room temperature overnight Reaction was quenched with water and extracted with ethyl acetate. Combined organics were washed with saturated aqueous sodium bicarbonate, brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. Product was purified on silica gel by flash chromatography using 100% ethyl acetate and 90% ethyl acetate/ 10% methanol to afford (2*S*,4*R*)-N-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-N-methyl-succinamic acid methyl ester (16 mg, 26%).

^{1}H-NMR (CDCl3) δ: 1.11 (3H, s; overlapping 1H, t), 2 00 (3H, s), 2.30 (1H, m, 2H, m), 2.60 (2H, m), 3.18 (3H, s), 3 65 (3H, s), 4 80 (1H, m), 5.60 (1H, m), 6 55 (1H, d), 6.90(1H, dd), 7.00-7 40 (10H, complex)

ESI-MS m/z· 562 (M + 1)

[001237] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-pyrrol-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-108)

[001238] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (75 mg, 0.17 mmol) was dissolved in DMF (1 mL) at room temperature. K_2CO_3 (47 mg, 0.34 mmol) was added followed by 1-(3-bromopropyl)-pyrrole and the reaction was allowed to stir at 70°C for 3hrs. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate Organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (1/1 ethyl acetate/hexanes) to afford the product

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1 2 (m, 1H), 2 0 (s, 3H), 2.1 (m, 2H), 2 3 (m, 1H), 3 8 (t, 2H), 4.1 (t, 2H), 4.8 (m, 1H), 5.6 (m, 1H), 6.1 (d, 2H), 6 5 (d, 1H), 6.6 (d, 2H), 6 65 (d, 2H), 6.9 (t, 1H), 7 1-7.3 (m, 6H), 7.4 (d, 2H)

MS m/z 442/444 (M+1).

[001239] (2*S*,4*R*)-2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-isopropyl-acetamide (H-109)

[001240] (2*S*,4*R*)- 2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-isopropyl-acetamide was made from (4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid ethyl este (0.050g, 0 096 mmol) by addition of isopropylamine (0.680 mL, 8 mmol) with trace sodium cyanide in ethanol (1 mL) to give 43 % Yield of (2*S*,4*R*)- 2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-isopropyl-acetamide after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ. 1.12-1 19 (m, 10H), 2 02 (s, 3H), 2.28 (m, 1H), 4 11 (m, 1H), 4.37 (s, 2H), 4 73 (m, 1H), 5 59 (brs, 1H), 6.24 (br, 1H), 6.48 (d, 1H), 6.70 (d, 2H), 6.90 (t, 1H), 7 12-7.30 (m, 6H), 7 37 (d, 2H)
MS m/z· 534 (M+1).

[001241] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester (H-110)

[001242] (2*S*,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid tert-butyl ester was prepared following the procedure for (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester, substituting piperazine-1-carboxylic acid tert-butyl ester for piperidine-4-carboxylic acid ethyl ester to yield the product.
^{1}H-NMR ($CDCl_3$) δ: 1 10 (d, 3H), 1.24 (m, 1H), 1.45 (s, 9H), 2.00 (s, 3H), 2.27 (m, 1H), 3.12 (t, 4H), 3.52 (t, 4H), 4.71 (m, 1H), 5 56 (brs, 1H), 6 54 (d, 1H), 6.62 (d, 2H), 6 92 (t, 1H), 7 09-7 28 (m, 6H), 7 36 (d, 2H).
MS m/z. 603 4 (M+1).

[001243] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(1-{4-[2-(1-methanesulfonyl-piperidin-4-yl)-ethoxy]-benzoyl}-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-111)

[001244] 4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester (0.119 g, 0.52 mmol) was dissolved in toluene at room temperature with PPh_3 (0.136g, 0 52 mmol), then added (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.150g, 0 35 mmol) and stirred for 5 min DEAD (0.090g, 0.52 mmol) was added and the reaction was stirred for 18 h at room temperature The reaction was concentrated and purified by silica gel chromatography (45 % CH_2Cl_2 /55%EtOAc) to afford (2*S*,4*R*)-4-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester (0.2 g, 90%)

[001245] The ester was convert to (2*S*,4*R*)-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(2-piperidin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide by reacting with HCl (4M in dioxane) in dichloromethane at room temperature for 3 hours The piperidine was dissolved in dichloromethane at room temperature and DIEA was added. Methanesulfonyl chloride was added and the reaction was stirred at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford the product in a 76% yield

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.15 (t, 1H), 1 22-1.38 (m, 2H), 1 68-1.87 (m, 5H), 2.04 (s, 3H), 2.27 (m, 1H), 2 67 (t, 2H), 2.76 (s, 3H), 3.77 (m, 2H), 3.94 (t, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6 69 (d, 2H), 6.83 (t, 2H), 7.08-7.35 (m, 6H), 7 38 (d, 2H)
MS m/z: 624 (M+1)

[001246] 4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-112)

[001247] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture stirred at 40 °C overnight The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid.
^{1}H-NMR ($CDCl_3$) δ: 1 12-1.16 (m, 6H), 1.22-1.32 (m, 1H), 1.25 (s, 6H), 2.02 (t, 2H), 2.13-2.31 (m, 3H), 3.95 (t, 2H), 4 70-4.77 (m, 1H), 5.60 (br s, 1H), 6 52 (d, 1H), 6 62 (d, 2H), 6.91 (t, 1H), 7 11-7 24 (m, 6H), 7.37 (d, 2H).
MS m/z: 563 (M+1)

[001248] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-benzoic acid (H-113)

[001249] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-benzoic acid methyl ester (93 mg, 0 16 mmol) was dissolved in MeOH/THF (2:1, 3 mL). To this solution was added LiOH (2M in H_2O, 2 mL) The reaction was stirred at room temperature for 18 hours The reaction mixture was concentrated *in vacuo* to remove MeOH and THF. Then 6N HCl aqueous solution was added to acidify the reaction mixture to pH 2-3. The reaction mixture was extracted with DCM (5 mL x 3) The extract was washed with water (15 mL), brine (15 mL) and dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by preparatory HPLC to afford the product (90 mg, 100%).
^{1}H-NMR ($CDCl_3$, 300MHz) δ: 1.08-1.09 (d, 3H), 1.21-1 26 (s, 1H), 2.03 (s, 3H), 2.24-2 32 (m, 1H), 4 70-4.78 (m, 1H), 5.02-5.05 (s, 2H), 5.58-5 61 (b, 1H), 6 51-6.53 (m, 3H), 6 89-7.29 (m, 8H), 7 36-7.46 (m, 2H), 7 56-7 58 (m, 1H), 7.97-8.04 (m, 2H)
MS m/z: 570 (M+1).

[001250] 3-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzyl)amino]propanoic acid (H-114)

[001251] 3-(4-{(2*S*,4*R*)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-benzylamino)-propionic acid *tert*-butyl ester (10 mg, 0.017 mmol, 1 equ) was stirred in a 1/1 mixture of methylene chloride/trifluoroacetic acid (0 8 mL) at room temperature for 2 h. Reaction mixture was concentrated to give 3-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzyl)amino]propanoic acid as the trifluoroacetic acid salt (12 mg, quant.).

^{1}H-NMR (MeOD) δ. 1 05 (d, 3H), 2.00 (s, 3H), 2.35 (m, 1H), 2 65 (t, 2H), 3 15 (t, 2H), 4.10 (s, 2H), 4 70 (m, 1H), 5.50 (m, 1H), 6.45 (d, 1H), 6 80 (t, 1H), 7.10 (t, 1H), 7.20-7.45 (m, 9H).

MS m/z: 575 (M+1)

[001252] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(3-methanesulfonylamino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-115)

[001253] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (29 mg, 0 059 mmol) was dissolved in methylene chloride (0 5 mL) and triethylamine (10 drops via pipet) and cooled to -40 °C. Methanesulfonyl chloride (5 drops via pipet) was added and the mixture was warmed to 0 °C for 30 minutes. The mixture was partitioned between methylene chloride and water; the methylene chloride layer was dried over $MgSO_4$, filtered and concentrated The crude residue was purified by silica gel chromatography (50% hexanes/ 50% ethyl acetate – 100% ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ. 1 1 (d, 3H), 1.2 (m, 1H), 1.9 (m, 2H), 2.0 (s, 3H), 2.3 (m, 1H), 2.9 (s, 3H), 3 3 (q, 2H), 3.9 (t, 2H), 4.6 (t, 1H), 4.7 (m, 1H), 5.6 (bs, 1H), 6 5 (d, 1H), 6.7 (d, 2H), 6.9 (t, 1H), 7.2 (m, 6H), 7 4 (d, 2H).

MS m/z. 570 (M+1).

[001254] 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoic acid (H-116)

[001255] 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoic acid was prepared from methyl 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoate. methyl 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoate (0.010g, 0.017 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and methanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature overnight. The mixture was cooled to rt, acidified to pH = 5 with 1N HCl to form a white precipitate

(0 006g, 63%). The solid was filtered to give 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoic acid
MS m/z 550 (M+1)

[001256] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid (H-117)

[001257] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 17 g, 0.39 mmol) was dissolved in 5 ml DMF at room temperature and K_2CO_3 (0 323 g, 2.34 mmol) was added. 1-(2-Bromo-ethyl)-cyclobutanecarboxylic acid ethyl ester (0.184 g, 0.78 mmol) prepared according to the procedure from *Tetrahedron* **1994**, 50(32), 9825-30 was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford the 1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-cyclobutanecarboxylic acid ethyl ester (0.155 g, 67%)

[001258] The ester was hydrolyzed to the acid by dissolving in 8 ml tetrahydrofuran/methanol (1/1) and potassium hydroxide (0.08 g in 3 ml water) was added. The mixture was heated to 40 °C for 3 hours. The mixture was cooled to rt, acidified to form a white precipitate. The solid was filtered to give the product (0.145 g, 98%).

^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H), 1.15 (t, 1H), 1.96 (m, 4H), 2 04 (s, 3H), 2 27 (m, 1H), 2.29 (t, 2H), 2.49 (m, 2H), 3.96 (t, 2H), 4 72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6 86 (t, 1H), 7.08-7 35 (m, 6H), 7 38 (d, 2H).
MS m/z: 561 (M+1)

[001259] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(2-oxo-imidazolidin-1-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-118)

[001260] (2*S*,4*R*)-N-{1-[4-(3-Amino-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide (120 mg, 0 24 mmol) was dissolved in DCM (3 mL) at room temperature. TEA (48 mg, 0.48 mmol) was added followed by 2-chloroethyl isocyanate (51 mg, 0.48 mmol) and the reaction was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and dissolved in ethyl acetate (15 mL). The reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL) The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (5/95 ethyl acetate/hexane – 50/50 ethyl acetate/hexane gradient) to afford to afford slight yellow solid product (163 mg, 100%)

[001261] (2*S*,4*R*)-N-[1-(4-{3-[3-(2-Chloro-ethyl)-ureido]-propoxy}-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-(4-chloro-phenyl)-acetamide (151 mg, 0.25 mmol) was dissolved in DMF (3 mL) at room temperature. Cs_2CO_3 (98 mg, 0.30 mmol) was added. The reaction was stirred at room temperature for 18 hours. The mixture was concentrated under reduced pressure and dissolved in ethyl acetate (15 mL). The reaction mixture was washed with sat aq $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL) The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by preparatory HPLC to afford the product (0.009 g, 6.4%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ· 1.11-1.14 (d, 3H), 1 88-1 93 (m, 1H), 1.98-2 01 (m, 5H), 2.26-2.27 (m, 1H), 3 27-3 29 (m, 1H), 3 43-3 47 (1, 2H), 3.77-3.83 (m, 1H) 3.93-3 96 (m, 1H), 4 17-4.20 (m, 1H), 4 51-4 57 (m, 1H), 4.72-4.74 (m, 1H), 4.97-4.10 (broad,1H), 5 52-5.65 (b, 1H), 6.50-6 93 (m, 4H), 7 12-7.39 (m, 8H).

MS m/z 562 (M+1).

[001262] (2S,4R)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-119)

[001263] (2S,4R)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was made from (4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid ethyl ester (0.050g, 0 096 mmol) by addition of morpoline (0 400mL, 4.0 mmol) with trace sodium cyanide in ethanol (1 mL) to give 63% yield of (2S,4R)- N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-2-oxo-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.13 (m, 4H), 2 01 (s, 3H), 2.27 (m, 1H), 3 52-3.63 (m, 8H), 4.67 (s, 2H), 4.76 (m, 1H), 5 57 (brs, 1H), 6 49 (d, 1H), 6.70 (d, 2H), 6.90 (t, 1H), 7.13-7 28 (m, 6H), 7.36 (d, 2H).

MS m/z· 562 (M+1).

[001264] ***N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-vinylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-120)**

[001265] *N*-(4-Chlorophenyl)-*N*-[(2*S*, 4*R*)-1-(4-fluoro-3-vinylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure H, substituting 4-fluoro-3-vinylbenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (4-fluoro-3-vinylbenzoyl chloride was prepared in 4 steps from 3-bromo-4-fluorobenzoic acid. 3-bromo-4-fluorobenzoic acid was converted to methyl 3-bromo-4-fluorobenzoate by treatment with trimethylsilyl diazomethane (1 5 equivalents) in benzene/methanol (4/1) at room temperature Subsequent reaction with tributyl(vinyl) tin (1.2 equivalents) in DMF in the presence of catalytic dichlororbis(triphenylphosphine) palladium(II) (0.1 equivalents) at 80 °C under an argon atmosphere, followed by aqueous work up and

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standard chromatography (10% ethyl acetate/hexanes), yielded methyl 4-fluoro-3-vinylbenzoate. This material was dissolved in methanol/tetrahydrofuran/water (2/1/1) then lithium hydroxide (5.0 equivalents) was added and reaction mixture stirred at room temperature overnight The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-fluoro-3-vinylbenzoic acid. This material was directly converted to 4-fluoro-3-vinylbenzoyl chloride by treatment with thionyl chloride (2 5 equivalents) in dichloromethane at room temperature for 2 hours followed by removal of the volatiles in vaccuo). The rest of the procedures were followed as indicated in general procedure H to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-vinylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

^{1}H-NMR ($CDCl_3$) δ. 1.16 (d, 3H), 1.22-1 26 (m, 1H), 2.03 (s, 3H), 2 24-2.31 (m, 1H), 4.72-4 82 (m, 1H), 5.31 (d, 1H) 5 61 (br s, 1H), 5 65 (d, 1H), 6.51 (d, 1H), 6 71 (dd, 1H), 6.80 (dd, 1H), 6.91-7.01 (m, 2H), 7.15-7 31 (m, 4H), 7 37-7 45 (m, 3H)

MS m/z: 463 (M+1).

[001266] ***N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-121)**

[001267] N-(4-chlorophenyl)-N-[(2S,4R)-1-(4-ethoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was made following general procedure I, substituting bromo-ethane for ethyl 4-bromoacetate

^{1}H-NMR ($CDCl_3$) δ: 1.14 (d, 3H), 1.17 (m, 1H), 1.33 (t, 3H), 2.02 (s, 3H), 2 25 (m, 1H), 3 93 (q, 2H), 4.69 (m, 1H), 5.58 (br, 1H), 6.52 (d, 1H), 6 64 (d, 2H), 6.93 (t, 1H), 7.18 (m, 6H), 7 36 (d, 2H)

MS m/z: 463 (M+1)

[001268] **(2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid (H-122)**

[001269] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid was made from (2*S*,4*R*)- 1-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and lithium hydroxide (1N) was added and heated 50°C for 2h The mixture was cooled to room temperature, acidified to form a white precipitate. The solid was filtered to give to afford the product after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1.23 (m, 1H), 1.64 (m, 2H), 2.00 (m, 5H), 2 34 (m, 1H), 2 59 (m, 1H), 2.84 (m, 1H), 3.08 (m, 1H), 3.40 (m, 1H), 3.67 (m, 1H), 4.71 (m, 1H), 5.58 (brs, 1H), 6.57 (d, 1H), 6.66 (d, 2H), 6 93 (t, 1H), 7.07-7.28 (m, 6H), 7.37 (d, 2H), 9.30 (br, 1H).

MS m/z: 546.3 (M+1).

[001270] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-sulfamoyl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-123)

[001271] (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propane-1-sulfonic acid (175 mg, 0 315 mmol) was dissolved in methylene chloride (3 mL) and cooled to 0 °C PCl_5 (78 mg, 0.378 mmol) was added and the reaction was stirred at room temperature over night The mixture was partitioned between methylene chloride and water, the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude sulfonyl chloride was dissolved in acetone (5 mL); concentrated ammonium hydroxide (3 5 mL) was added After 15 minutes, the mixture was partitioned between methylene chloride and water, the organic layer was dried over Na_2SO_4, filtered and concentrated The crude residue was purified by preparatory HPLC to afford the product.

^{1}H-NMR ($CDCl_3$) δ· 1.1 (d, 3H), 1 1 (m, 1H), 2.0 (s, 3H), 2 2 (m, 3H), 3.2 (t, 2H), 3 9 (t, 2H), 4.8 (d, 1H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6 9 (t, 1H), 7 2 (m, 8H), 7.4 (d, 2H)

MS m/z. 556 (M+1).

[001272] 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid (H-124)

[001273] 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid was prepared following general procedure H, substituting methyl 3-(chlorocarbonyl)benzoate for 6-trifluoromethyl nicotinyl chloride (Methyl 3-(chlorocarbonyl)benzoate was prepared in one step from 3-(methoxycarbonyl)benzoic acid Treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded methyl 3-(chlorocarbonyl)benzoate in decent yield) Hydrolysis of methyl 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoate with lithium hydroxide, water, methanol and tetrahydrofuran yielded 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid

^{1}H-NMR ($CDCl_3$) δ: 1.18 (d, 3 H), 1.18 – 1 26 (m, 1H), 2 05 (s, 3 H), 2.27 – 2.39 (m, 1 H), 4.74 – 4 86 (m, 1 H), 5.53 – 5.70 (m, 1 H), 6.48 (d, 1 H), 6.88 (t, 1 H), 7 13 – 7.24 (m, 5 H), 7 32 (d, 1 H), 7.40 (d, 2 H), 7.97 – 8.02 (m, 1 H), 8 12 (bs, 1 H).

MS m/z 463 (M+1)

[001274] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{1-[4-(3-cyano-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-125)

[001275] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF at room temperature and K_2CO_3 was added 4-Bromobutylnitrile was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1 15 (m, 1H), 1.90 (m, 1H), 2.02 (s, 3H), 2.09 (m, 1H), 2.30 (m, 1H), 2 54 (t, 2H), 3.99 (t, 2H), 4 72 (sextet, 1H), 5 6 (bs, 1H), 6.52 (d, 1H), 6 65 (d, 2H), 6.93 (t, 1H), 7 15 (m, 5H), 7 27 (t, 1H), 7.37 (d, 2H)

MS m/z. 502 (M+1).

[001276] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(3-methyl-[1,2,4]oxadiazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-126)

[001277] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(3-methyl-[1,2,4]oxadiazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide was prepared from (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid methyl ester. Acetamide oxime (0.043 g, 0.58 mmol) was supended in THF under N_2 and NaH (60% dispersion in oil) (0.025g, 1.0 mmol) was added followed by 4A° molecular sieves and heated to 60 °C for 1h (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid methyl ester was added and heated to reflux for 4.5 h The reaction was filtered and concentrated down and partitioned between CH_2Cl_2 and water The aqueous layer was extracted 3x CH_2Cl_2 and dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography (100% EtOAc) to afford (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(3-methyl-[1,2,4]oxadiazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide in 44% yield.

^{1}H-NMR ($CDCl_3$) δ: 1.12 (d, 3H), 1.13 (m, 1H), 2 00 (s, 3H), 2.23 (m, 2H), 2.38 (s, 3H), 3.00 (m, 2H), 3 96 (m, 2H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6.49 (d, 1H), 6 62 (d, 2H), 6.91 (t, 1H), 7.31-7 25 (m, 7 H), 7 34 (d, 1H).

MS m/z: 559 (M+1).

[001278] *N*-(4-chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(difluoromethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide (H-127)

[001279] N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(difluoromethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide was made following general procedure I, substituting methyl chlorodifluoroacetate for ethyl 4-bromoacetate.

^{1}H-NMR ($CDCl_3$) δ 1 16 (d, 3H), 1.17 (m, 1H), 2.02 (s, 3H), 2 29 (m, 1H), 4 75 (m, 1H), 5.58 (br, 1H), 6 52 (d, 1H), 6.93 (m, 3H), 7 19 (m, 6H), 7.38 (m, 3H).

MS m/z 485 (M+1)

[001280] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid amide (H-128)

[001281] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid amide was prepared from (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid amide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down. The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford pure product in a 67% yield

^{1}H-NMR ($CDCl_3$) δ. 1.15 (d, 3H), 1.17 (t, 1H), 2.03 (s, 3H), 2.27 (m, 1H), 4 26 (bs, 2H), 4.72 (sextet, 1H), 4.78 (bs, 2H), 5 58 (bs, 1H), 6.48 (d, 1H), 6 64 (d, 2H), 6 91 (t, 1H), 6.98 (s, 1H), 7 03 (s, 1H), 7.08-7.40 (m, 10H).

MS m/z. 572 (M+1).

[001282] (2*S*,4*R*)-N-(1-{4-[3-(4-Acetyl-piperazin-1-yl)-propoxy]-benzoyl}-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-(4-chloro-phenyl)-acetamide (H-129)

[001283] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-piperazin-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (168 mg) was dissolved in CH_2Cl_2 (2mL). Acetic chloride (47 mg) and DIEA (52 uL) were added. The reaction mixture was stirred at room temperature overnight. The organic phase was washed with sat. $NaHCO_3$ (2 x 5 mL), dried over Na_2SO_4 and concentrated The residue was purified by silica gel chromatography (EtOAc) to afford pure (2*S*,4*R*)-N-(1-{4-[3-(4-acetyl-piperazin-1-yl)-propoxy]-benzoyl}-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-N-(4-chloro-phenyl)-acetamide (100mg, 57%).

^{1}H-NMR ($CDCl_3$) δ. 1.13 (d, 4H), 1.88-1.94 (m, 2H), 2.02 (s, 3H), 2.06 (s, 3H), 2.20-2 48 (m, 7H), 3.43 (bs, 2H), 3.59 (bs, 2H), 3.94 (t, 2H), 4.74 (sextet, 1H), 5.60 (bs, 1H), 6 53 (d, 1H), 6 66 (d, 2H), 6.91 (t, 1H) 7 11-7.38 (m, 8H)

MS m/z: 603 (M+1).

[001284] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid ethyl ester (H-130)

[001285] (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-3-carboxylic acid ethyl ester was prepared following the procedure for (2*S*,4*R*)- 1-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester, substituting piperidine-3-carboxylic acid ethyl ester for piperidine-4-carboxylic acid ethyl ester to yield the product.

^{1}H-NMR ($CDCl_3$) δ. 1.10 (d, 3H), 1.23 (t, 3H), 1 23 (m, 1H), 1.77 (m, 2H), 1.94 (m, 2H), 2.01 (s, 3H), 2.28 (m, 1H), 2.40 (m, 1H), 2 77 (t, 2H), 3 62 (m, 2H), 4.11 (q, 2H), 4 70 (m, 1H), 5.58 (brs, 1H), 6 56 (d, 1H), 6.64 (d, 2H), 6.92 (t, 1H), 7 07-7 28 (m, 6H), 7.35 (d, 2H).

MS m/z. 574 4 (M+1).

[001286] 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoic acid (H-131)

[001287] Methyl 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoate (70 mg, 0 12 mmol, 1 eq.) was dissolved in methanol/tetrahydrofuran (2/1) (3 ml). A solution of sodium hydroxide (8 mg, 0.20 mmol, 1 7 eq) in water (1 ml) was added and reaction mixture heated to 40^{0}C for 8 h. The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude acid Purification by silica gel chromatography (methylene chloride/methanol: 99/1 to 98/2 gradient) gave pure 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoic acid (56 mg, 84 %)

^{1}H-NMR ($CDCl_3$) δ. 1 15 (d, 3H), 1.50 (m, 4H), 2 05 (s, 3H), 2 30 (m, 1H), 2.55 (m, 2H), 4 80 (m, 1H), 5.60 (m, 1H), 6.55 (d, 1H), 6.75 (d, 1H), 6.90 (m, 3H), 7.20-7.40 (m, 6H).

MS m/z: 565 (M+1).

[001288] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(2-oxo-pyrrolidin-1-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (H-132)

[001289] N-(3-hydroxypropyl)-2-pyrrolidone was dissolved in benzene at room temperature with PPh_3 (0.044g, 0 16 mmol) added (2*S*,4*R*)-N-(4-chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 100g, 0.22 mmol) and stirred for 5 min DEAD (0 029g, 0.16mmol) was added and the reaction was stirred for 18 h at room temperature The

reaction was concentrated and purified by silica gel chromatography (4 % MeOH/96 % CH_2Cl_2 to 5 % MeOH/95 % CH_2Cl_2 to 6 % MeOH/94 % CH_2Cl_2) to afford the product in 45% yield.

^{1}H-NMR ($CDCl_3$) δ 1.13 (d, 3H), 1 14 (m, 1H), 1 96 (m, 4H), 2.02 (s, 3H), 2.34 (t, 3H), 3 39 (q, 4H), 3 90 (m, 2H), 4.72 (sextet, 1H), 5 59 (bs, 1H), 6.52 (d, 1H), 6.63 (d, 2H), 7.18 (m, 6H), 7 37 (d, 2H)

MS m/z 560 (M+1).

[001290] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(3-ethyl-2-oxo-oxazolidin-5-ylmethoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-133)

[001291] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(3-ethyl-2-oxo-oxazolidin-5-ylmethoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide was prepared from (2*S*,4*R*)-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(2-oxo-oxazolidin-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide following ref (*Tetrahedron Lett* **2002**, 43(46), 8327)

^{1}H-NMR ($CDCl_3$) δ 1.15 (m, 7H), 2.03 (s, 3H), 2.27 (m, 1H), 3.28 (q, 2H), 3 47 (m, 1H), 3.63 (t, 1H), 4.05 (d, 2H), 4 73 (m, 2H), 5 58 (bs, 1H), 6.47 (d, 1H), 6 67 (d, 2H), 6.86 (t, 1H), 7 08-7.35 (m, 6H), 7 38 (d, 2H).

MS m/z 563 (M+1)

[001292] 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-134)

[001293] *N*-[(2*S*,4*R*)-6-chloro-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide was elaborated to 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid following procedures described for 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid.

^{1}H-NMR ($CDCl_3$) δ 1 10 (d, 3H), 1.13 (t, 1H), 1 24 (s, 6H), 2.01 (s, 3H), 2.03 (t, 2H), 2.27 (m, 1H), 3 96 (t, 2H), 4.71 (sextet, 1H), 5.54 (bs, 1H), 6 43 (d, 1H), 6.65 (d, 2H), 6.89 (d, 1H), 7.10-7 20 (m, 5H), 7.38 (d, 2H).

MS m/z: 583 (M+1).

[001294] (2*S*,4*R*)- 4-[4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-2,2-dimethyl-butyric acid methyl ester (H-135)

[001295] (2*S*,4*R*)- 4-[4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-2,2-dimethyl-butyric acid methyl ester was prepared from (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid ethyl ester by removal of the carbamate. (2*S*,4*R*)- 4-

(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazine-1-carboxylic acid ethyl ester was dissolved in acetonitrile (2 mL). Iodotrimetylsilane was added and the reaction was allowed to stir at room temperature over night. Excess reagent was quenched by the addition of methanol (1 mL) and the mixture was concentrated under reduced pressure. The crude residue was partitioned between ethyl acetate and saturated aqueous sodium bicarbonate. The extracts were washed with 1 M sodium hydroxide, saturated aqueous sodium thiosulfate and brine, dried over sodium sulfate, filtered, concentrated and purified by silica gel chromatography to yield N-(4-chloro-phenyl)-N-[2-methyl-1-(4-piperazin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide.

[001296] (2*S*,4*R*)- N-(4-chloro-phenyl)-N-[2-methyl-1-(4-piperazin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was dissolved in DMF at room temperature K_2CO_3 was added followed by 4-Bromo-2,2-dimethyl-butyric acid methyl ester and the reaction was allowed to stir at 90 ^{0}C over night. The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by HPLC to afford the product

^{1}H-NMR ($CDCl_3$) δ 1 12 (d, 3H), 1.18 (s+m,7H), 1.75 (m, 2H), 2.01 (s, 3H), 2.32 (m, 3H), 2.52 (m, 4H), 3 16 (m, 4H), 3.64 (s, 3H), 4.71 (m, 1H), 5.60 (brs, 1H), 6.56 (d, 1H), 6.62 (d, 2H), 6.93 (t, 1H), 7.08-7.29 (m, 6H), 7.36 (d, 2H)

MS m/z· 631 (M+1).

[001297] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2-methyl-butyric acid methyl ester (H-136)

[001298] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (230 mg, 0.531 mmol) was dissolved in DMF (5 mL) at room temperature. Cs_2CO_3 (433 mg, 1.33 mmol) was added followed by 4-chloro-2-methyl-butyric acid methyl ester (120 mg, 0.796 mmol) and the reaction was allowed to stir overnight. The mixture was partitioned between methylene chloride and water; the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel chromatography (1/1 hexanes/ ethyl acetate – ethyl acetate gradient) to afford the product.

^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1.2 (d, 3H), 1.2 (m, 1H), 1.8 (m, 1H), 2.0 (s, 3H), 2 1 (m, 1H), 2.2 (m, 1H), 2.7 (m, 1H), 3.7 (s, 3H), 3.9 (t, 2H), 4.7 (m, 1H), 5.6 (bs, 1H), 6.5 (d, 1H), 6.6 (d, 2H), 6.9 (t, 1H), 7.2 (m, 6H), 7 4 (d, 2H).

MS m/z 549 (M+1).

[001299] (2*S*,4*R*)-N-1-[2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid (H-137)

[001300] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.165 g, 0.38 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0.315g, 2.28 mmol) was added 1-(2-Bromo-ethyl)-1H-imidazole-2-carboxylic acid methyl ester (0.304 g, 1.14 mmol) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (50% EtOAc/ 50% Hexane) to afford (2*S*,4*R*)-N-1-[2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-ethyl]-1H-imidazole-2-carboxylic acid methyl ester (0.176g, 83%)

[001301] The ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature 4 hours. The mixture was cooled to room temperature, acidified to form a white precipitate The solid was filtered to give the product in a 74% yield

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.15 (t, 1H), 1 98 (s, 3H), 2.27 (m, 1H), 4 29 (bs, 2H), 4 72 (sextet, 1H), 5.09 (bs, 2H), 5.58 (bs, 1H), 6.48 (d, 1H), 6 64 (d, 2H), 6.91 (t, 1H), 6 98 (s, 1H), 7.03 (s, 1H), 7.08-7.40 (m, 10H), 8.65 (bs, 1H).

MS m/z· 573 (M+1)

[001302] 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoic acid (H-138)

[001303] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoate was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture stirred at 40 °C overnight. The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoic acid.

^{1}H-NMR ($CDCl_3$) δ 1.14 (d, 3H), 1 22 (s, 6H), 1.22-1 26 (m, 1H), 1.75 (ddd, 2H), 2 03 (s, 3H), 2.24-2.32 (m, 1H), 2.49 (ddd, 2H), 4 72-4.80 (m, 1H), 5.60 (br s, 1H), 6.49 (d, 1H), 6 89 (t, 1H), 6.97 (d, 2H), 7.08-7.29 (m, 6H), 7.37 (d, 2H).

MS m/z 533 (M+1)

[001304] 5-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(glycoloyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid (H-139)

[001305] Methyl 5-(4-{[(2*S*,4*R*)-4-[[(acetyloxy)acetyl](4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate (100 mg, 0 16 mmol, 1 eq) was

dissolved in methanol/tetrahydrofuran (2/1) (2 ml) A solution of sodium hydroxide (32 mg, 0 81 mmol, 5 eq.) in water (1 ml) was added and reaction mixture heated to 45°C for 8 h and at room temperature for 20h The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give the crude acid Purification by silica gel chromatography gave pure 5-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(glycoloyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid (63 mg, 70 %).

^{1}H-NMR (MeOD) δ· 1.10 (d, 3H), 1 15 (s, 6H), 1.45 (m, 4H), 2.45 (m, 1H), 2.50 (t, 2H), 3.90-4.10 (dd, 2H), 4.75 (m, 1H), 5.55 (m, 1H), 6.55 (d, 1H), 6.95 (t, 1H), 7 00-7 20 (m, 5H), 7.30-7 55 (m, 5H).

MS m/z 563 (M+1).

[001306] (2*S*,4*R*)- [4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetic acid (H-140)

[001307] (2*S*,4*R*)- [4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetic acid was prepared following the procedure for (2*S*,4*R*)- 1-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-4-carboxylic acid ethyl ester, substituting piperazin-1-yl-acetic acid ethyl ester for piperidine-4-carboxylic acid ethyl ester to yield the (2*S*,4*R*)- [4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperazin-1-yl]-acetic acid ethyl ester. The ester was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and lithium hydroxide (1N) was added and heated 50°C for 2h. The mixture was cooled to room temperature, acidified to form a white precipitate. The solid was filtered to give to afford the product after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 3H), 1.20 (m, 1H), 2.00 (s, 3H), 2 24 (m, 1H), 3.04 (t, 4H), 3.50 (m, 6H), 4 70 (m, 1H), 5.56 (brs, 1H), 6 51 (d, 1H), 6.63 (d, 2H), 6.89 (t, 1H), 7.07-7.25 (m, 6H), 7.35 (d, 2H).

MS m/z· 561 (M+1).

[001308] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxymethyl)-piperidine-1-carboxylic acid benzyl ester (H-141)

[001309] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0 31 g, 0 71 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0.392 g, 2.84 mmol) was added. 4-Bromomethyl-piperidine-1-carboxylic acid benzyl ester (0.668 g, 2 14 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The

crude residue was purified by silica gel chromatography (60% EtOAc/ 40% Hexane) to afford the product (0.25g, 53%)

^{1}H-NMR ($CDCl_3$) δ 1 13 (d, 3H), 1.15 (t, 1H), 1 24 (m, 2H), 1.76 (m, 2H), 1 88 (m, 1H), 2 04 (s, 3H), 2 27 (m, 1H), 2 75 (m, 2H), 3.68 (d, 2H), 4 17 (bs, 2H), 4.72 (sextet, 1H), 5.12 (s, 2H), 5.58 (bs, 1H), 6 52 (d, 1H), 6.67 (d, 2H), 6 86 (t, 1H), 7.08-7.38 (m, 13H)

MS m/z: 666 (M+1)

[001310] (2*S*,4*R*)-2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-(2-hydroxy-ethyl)-acetamide (H-142)

[001311] (2S,4R)-2-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-(2-hydroxy-ethyl)-acetamide was made from (4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid ethyl ester (0.050g, 0.096 mmol) by addition of 2-amino-ethanol (0.145 mL, 2.4 mmol) with trace sodium cyanide in ethanol (1 mL) at room temperature to give a 50% yield of (2S,4R)-2-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-N-(2-hydroxy-ethyl)-acetamide after HPLC purification.

^{1}H-NMR ($CDCl_3$) δ: 1.13 (m, 4H), 2.02 (s, 3H), 2 26 (m, 1H), 2.70 (br, 1H), 3.46 (t, 2H), 3 68 (t, 2H), 4 41 (t, 2H), 4.72 (m, 1H), 5.58 (brs, 1H), 6.50 (d, 1H), 6 67 (d, 2H), 6 90 (t, 1H), 7 02 (br, 1H), 7 13-7.28 (m, 6H), 7.36 (d, 2H).

MS m/z. 536 2 (M+1)

[001312] 2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylpropanoic acid (H-144)

[001313] 2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylpropanoic acid was prepared according to general procedure I, substituting ethyl 2-bromo-2-methylpropanoate for ethyl 4-bromoacetate to afford ethyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylpropanoate.

[001314] This material was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture heated to 40°C for 2 h The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylpropanoic acid

^{1}H-NMR ($CDCl_3$) δ· 1 10-1 14 (m, 1H), 1 13 (d, 3H), 1.53 (d, 6H), 2.24 (s, 3H), 2.27-2.31 (m, 1H), 4 72-4 79 (m, 1H), 5.60 (br s, 1H), 6 49 (d, 1H), 6 68 (d, 2H), 6.87 (t, 1H), 7 11 (t, 2H), 7.08-7.18 (m, 4H), 7.37 (d, 2H).
MS m/z: 521 (M+1)

[001315] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2-methyl-butyric acid (H-145)

[001316] (2*S*,4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2-methyl-butyric acid methyl ester (100 mg) was dissolved in methanol/THF, and lithium hydroxide (1.0N, 2 mL) was added After 1 hour, the reaction was acidified and extracted with methylene chloride The organic layer was dried, filtered, and concentrated The crude residue was purified by silica gel chromatography ethyl acetate – 5%MeOH/ethyl acetate gradient) to afford the product.
^{1}H-NMR ($CDCl_3$) δ: 1.1 (d, 3H), 1 2 (d, 3H), 1 2 (m, 1H), 1.8 (m, 1H), 2 0 (s, 3H), 2.1 (m, 1H), 2 2 (m, 1H), 2 7 (m, 1H), 3.9 (t, 2H), 4 7 (m, 1H), 5 6 (bs, 1H), 6 5 (d, 1H), 6.6 (d, 2H), 6 9 (t, 1H), 7 2 (m, 6H), 7.4 (d, 2H), 10 6 (bs, 1H).
MS m/z· 535 (M+1).

[001317] 3-[1-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-1*H*-pyrrol-3-yl]propanoic acid (H-146)

[001318] *N*-[(2S,4R)-1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-*N*-(4-chloro-phenyl)-acetamide was made following general procedure H, substituting 4-nitrocarbonyl chloride for 6-trifluoromethyl nicotinyl chloride, followed by reduction to using excess NH_4CO_2H, catalyic Pt(sulfided), in ethanol at reflux for 30m, filtration and concentration.

[001319] *N*-[(2S,4R)-1-(4-Amino-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-*N*-(4-chloro-phenyl)-acetamide (181 mg, 0 433 mmol) was dissolved in glacial acetic acid (6 mL) and heated to 90 °C. 2,5-dimethoxy-tetrahydrofuran-3-carbaldehyde was dissolved in glacial acetic acid (2 mL) and added drop wise to the aniline mixture. After 15m at 90 °C, the reaction was quenched with water, and extracted 2X with methylene chloride. The organics were combined and concentrated, and the yellowish residue was subjected to flash chromatography (EtOAc) to afford the corresponding aldehyde (150 mg, 70%).

[001320] In a round bottom flask at 0 °C was added the aldehyde (87 mg, 0.175 mmol), triethylphosphonoacetate (40 mL, 0.201 mmol), methylene chloride (1 5 mL), $NaOH/H_2O$ (50% v/v, 1.5 mL), and catalytic ammonium iodide. After 1 hour, the slurry was partitioned between methylene chloride and water. The organic layer was collected and concentrated, and the residue was subject to flash chromatography (EtOAc) to yield (E)-3-[1-(4-{(2S,4R)-4-[Acetyl-(4-chloro-phenyl)-amino]-2-

methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-1H-pyrrol-3-yl]-acrylic acid ethyl ester (97 mg, 96%) as a white solid.

[001321] This product (80 mg, 0.16 mmol) was dissolved in EtOAc (3mL) and acetic acid (1 drop). The mixture was subjected to $ZnBr_2$ (7 mg, 0.032 mmol) and 1 atm H_2 gas for 4h The reaction mixture was filtered, concentrated and used without further purification The crude residue was dissolved in MeOH (2 mL) and 1N NaOH (2 mL) and stirred overnight The mixture was monitored by TLC, neutralized (1N HCl), and partitioned between EtOAc and water. The organic layer was concentrated and the crude residue was purified by preparative HPLC to afford the title compound as a white solid

MS m/z 556 (M +1)

[001322] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{1-[4-(3-dibenzylsulfamoyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-147)

[001323] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (300 mg, 0 693 mmol) was dissolved in DMF (10 mL) at room temperature Cs_2CO_3 (1 12 g, 3 46 mmol) was added followed by 3-chloro-propane-1-sulfonic acid dibenzylamide (350 mg, 1.03 mmol) and the reaction was allowed to stir overnight The mixture was partitioned between methylene chloride and water, the organic layer was dried over Na_2SO_4, filtered and concentrated. The crude residue was purified by silica gel chromatography (2/1 hexanes/ ethyl acetate) to afford the product.

^{1}H-NMR ($CDCl_3$) δ. 1.1 (d, 3H), 1.1 (m, 1H), 2.0 (s, 3H), 2.2 (m, 3H), 3.0 (t, 2H), 3.9 (t, 2H), 4.3 (s, 4H), 4.7 (d, 1H), 5.6 (bs, 1H), 6 5 (d, 1H), 6.6 (d, 2H), 6 9 (t, 1H), 7.2 (m, 18H).

MS m/z 736 (M+1).

[001324] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (H-148)

[001325] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was synthesized according to general procedure C replacing *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide with *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-2-methylpropanamide and substituting 4-bromo-2,2-dimethylbutanoate for ethyl 4-bromoacetate. The rest of general procedure I was followed as indicated to afford Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

^{1}H-NMR ($CDCl_3$) δ: 1.12-1 26 (m, 16H), 2.00 (t, 2H), 2.20-2.27 (m, 1H), 2.61 (sp, 1H), 3.64 (s, 3H), 3.91 (t, 2H), 4.68-4.78 (m, 1H), 5 60 (br s, 1H), 6.51 (d, 1H), 6.61 (d, 2H), 6.92 (t, 1H), 7.07-7.31 (m, 6H), 7.39 (d, 2H).
MS m/z· 592 (M+1).

[001326] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(3-pyrrolidin-1-yl-propoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-149)

[001327] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.1g, 0.23 mmol) was dissolved in DMF (5 mL) at room temperature. K_2CO_3 (0.317g, 2.3 mmol) was added. 1-(3-Bromo-propyl)-pyrrolidine (0 177g, 0.92 mmol) was added and the reaction was allowed to heat to 80°C overnight The reaction mixture was concentrated *in vacuo* The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (10% methanol/ 90% dichloromethane) to afford the product (0.01g, 8%).
^{1}H-NMR ($CDCl_3$) δ: 1 13 (d, 3H), 1 15 (t, 1H), 1.58-1.76 (m, 2H), 2 04 (s, 3H), 2.05-2.18 (m, 2H), 2.27 (m, 1H), 2.38 (m, 2H), 3.28 (t, 2H), 3.33 (m, 4H), 3.96 (t, 2H), 4 72 (sextet, 1H), 5.54 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6.88 (t, 1H), 7 08-7.35 (m, 6H), 7.38 (d, 2H).
MS m/z: 546 (M+1)

[001328] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-pyrrol-1-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-150)

[001329] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.11g, 0 25 mmol) was dissolved in DMF at room temperature and K_2CO_3 (0.207g, 1.5 mmol) was added 1-(2-Bromo-ethyl)-1H-pyrrole (0.088g, 0 5 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by silica gel chromatography (70% EtOAc/ 30% Hexane) to afford the product (0.114g, 85%)
^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1.15 (t, 1H), 1.98 (s, 3H), 2.27 (m, 1H), 4.11 (t, 2H), 4.17 (t, 2H), 4.72 (sextet, 1H), 5.58 (bs, 1H), 6 12 (t, 2H), 6.48 (d, 1H), 6.57 (d, 2H), 6.68 (t, 2H), 6 86 (t, 1H), 7.08-7.35 (m, 6H), 7.38 (d, 2H).
MS m/z 528 (M+1)

[001330] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (H-151)

[001331] Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was synthesized according to general procedure C replacing *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide with *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]propanamide and substituting 4-bromo-2,2-dimethylbutanoate for ethyl 4-bromoacetate (*N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]propanamide was prepared following general procedure A by replacing 4-fluorobenzoyl chloride with 4-methoxybenzoyl chloride and by substituting acetyl chloride with propanoyl chloride; the rest of the procedure was followed as indicated to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]propanamide) The rest of general procedure C was followed as indicated to afford Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate.

^{1}H-NMR ($CDCl_3$) δ 1.12-1.16 (m, 7H), 1.22 (s, 6H), 2 00 (t, 2H), 2.13-2 31 (m, 3H), 3.63 (s, 3H), 3 91 (t, 2H), 4 69-4 77 (m, 1H), 5.60 (br s, 1H), 6.51 (d, 1H), 6.61 (d, 2H), 6 92 (t, 1H), 7 11-7.24 (m, 6H), 7 37 (d, 2H).

MS m/z. 577 (M+1).

[001332] 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzamide (H-152)

[001333] To a solution of 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid (90 2 mg, 0.195 mmol) in dimethylformamide (5 mL) at room temperature was added diisopropylethylamine (136 uL, 0 780 mmol) followed by addition of O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (110 9 mg, 0 292 mmol) and 1-Hydroxybenzotriazole hydrate (HOBT) (39.4 mg, 0 292 mmol) The reaction was allowed to stir overnight at room temperature. The mixture was partitioned between sodium bicarbonate (saturated) (20 ml) and ethyl acetate (20 ml). The aqueous layer was extracted 2 additional times with ethyl acetate (20 ml). The organics were collected together and washed with a brine solution (15 ml). The organics were dried over sodium sulfate, filtered and concentrated down to give a light white solid (40 mg, quant) of 3-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (d, 3 H), 1.22 (m 1H), 1.89 (bs, 2H), 2 03 (s, 3 H), 2.25 – 2.36 (m, 1 H), 4 78 – 4 93 (m, 1 H), 5.56 – 5.67 (m, 1 H), 6 52 (d, 1 H), 6 62 – 6.68 (m, 1 H), 6.93 (m, 1 H), 7.15 – 7.27 (m, 4 H), 7 36 – 7.41 (m, 3 H), 7 63 (d, 1 H), 7 97 (d, 1 H).

MS m/z 462 (M+1)

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[001334] 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpent-3-enoic acid (H-153)

[001335] Purification of crude material in the last step of the synthesis of 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid also allowed to isolate 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpent-3-enoic acid as a by-product in the synthesis (5 mg).

^{1}H-NMR (MeOD) δ: 1.10 (d, 3H), 1 20 (s, 6H), 2.05 (s, 3H), 2 45 (m, 1H), 3.20 (d, 2H), 4 75 (m, 1H), 5 55 (m, 1H), 5.55-5 60 (m, 2H), 6.55 (d, 1H), 6.95 (t, 1H), 6.90-7.05 (dd, 2H), 7.05-7.20 (m, 4H), 7 25-7 45 (m, 4H).

MS m/z: 545 (M+1).

[001336] Methyl 2-{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoate (H-154)

[001337] Methyl 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoate was prepared following general procedure B, substituting methyl 3-[4-(chlorocarbonyl)phenyl]propanoate for 6-trifluoromethyl nicotinyl chloride (methyl 3-[4-(chlorocarbonyl)phenyl]propanoate was prepared in three steps from 4-iodobenzoic acid. To a solution of 4-iodobenzoic acid in dimethylformamide were added methyl acrylate, palladium acetate and triethylamine. Reaction mixture was heated to 100^{0}C for 5 h. to give 4-(3-methoxy-3-oxoprop-1-en-1-yl)benzoic acid. Hydrogenation of this intermediate afforded 4-(3-methoxy-3-oxopropyl)benzoic acid. Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded methyl 3-[4-(chlorocarbonyl)phenyl]propanoate in decent yield)

[001338] Methyl 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoate (200 mg, 0.4mmol, 1equ.) was dissolved in methanol/tetrahydrofuran (2/1) (1.5 ml) A solution of sodium hydroxide (32 mg, 0 8 mmol, 2 eq.) in water (0.5 ml) was added and reaction mixture stirred at room temperature for 20 h. The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoic acid (190 mg, 97 %).

[001339] To a suspension of 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoic acid (50 mg, 0.10 mmol, 1 equ) in methylene chloride (0 5 mL) was added a 2M solution of oxalyl chloride in methylene chloride (82 uL, 0 16 mmol, 1.6 equ.). Reaction mixture was stirred at room temperature for 30m , and then concentrated to give 3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-

yl]carbonyl}phenyl) propanoyl chloride. To a solution of the preformed acid chloride in methylene chloride (0 5 mL) was added methyl-alfG-amino-isobutyrate hydrochloride (31 mg, 0.20 mmol, 2 equ) and diisopropylethylamine (52 uL, 0 30 mmol, 3 equ.). Reaction mixture was stirred at room temperature for 20h.and concentrated. The residue was dissolved in ethyl acetate and washed with water, brine, and then dried over magnesium sulfate, filtered and concentrated The crude residue was purified by silica gel chromatography (ethyl acetate/hexane· 4/1 to 10/0 gradient) to afford methyl 2-{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoate (105 mg, 46 %).

^{1}H-NMR ($CDCl_3$) δ. 1.15 (d, 3H), 1.45 (d, 6H), 2.05 (s, 3H), 2.30 (m, 1H), 2.40 (t, 2H), 2 90 (t, 2H), 3 70 (s, 3H), 4 80 (m, 1H), 5.60 (m, 1H), 5.90 (s, 1H), 6 55 (d, 1H), 6.90 (t, 1H), 6 90-7 15 (m, 8H), 7 40 (d, 2H).

MS m/z. 590 (M+1)

[001340] (2*S*,4*R*)-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-ethyl-carbamic acid methyl ester (H-155)

[001341] (2*S*,4*R*)-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-carbamic acid methyl ester (41 mg, 0.074 mmol) was dissolved in THF/DMF (10:1, 3 mL). To this solution was added Sodium Hydride (2 mg, 0.089 mmol), followed by ethyl iodide (14 mg, 0.089 mmol). The reaction was stirred at room temperature for 7 hours and was quenched by adding 1 mL of water The mixture was concentrated under reduced pressure and dissolved in DCM (15 mL) The reaction mixture was washed with sat. aq. $NaHCO_3$ (15 mL), water (15 mL) and brine (15 mL) The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (5/95 ethyl acetate/hexane – 50/50 ethyl acetate/hexane gradient) to afford slightly yellow solid product (15 mg, 35%)

^{1}H-NMR ($CDCl_3$, 300MHz) δ 0 68-0 83 (m, 2H), 1 00-1.14 (m, 2H), 1.18-1 26 (m, 3H), 1.23 (t, 3H), 1.59-1 67 (broad, 1H), 1 61-1 64 (broad, 1H), 1.96-2 02 (m, 5H) 2 26-2 31 (m, 1H), 3.25-3 37 (m, 4H), 3.62-3 64 (m, 3H), 3.89-3.91 (m, 2H), 4.73-4 77 (m, 1H) 5.5-5.65 (broad, 1H), 6.50-6.93 (m, 4H), 7.12-7.39 (m, 8H).

MS m/z: 579 (M+1)

[001342] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-{1-[4-(3-diethylamino-2-hydroxy-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-156)

[001343] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-oxiranylmethoxy-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide was further elaborated to (2*S*,4*R*)-N-{1-[4-(3-amino-2-hydroxy-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide

following ref (*Tetrahedron Lett* **2002**, 43(46), 8327). The amine was reacted with acetaldehyde, $Na(OAc)_3BH$ in dichloromethane at room temperature overnight. Then washed with 1N NaOH, dried over $MgSO_4$, filtered and concentrated down The crude residue was purified by HPLC to afford the product in 38% yield.

^{1}H-NMR ($CDCl_3$) δ: 1.05-1.23 (m, 10H), 2 03 (s, 3H), 2.27 (m, 1H), 2 69-2.95 (m, 6H), 3 85 (m, 1H), 3 98 (m, 1H), 4.18 (m, 1H), 4 72 (sextet, 1H), 5 58 (bs, 1H), 6.58 (d, 1H), 6 67 (d, 2H), 6 86 (t, 1H), 7.08-7.35 (m, 6H), 7.38 (d, 2H).

MS m/z: 564 (M+1)

[001344] (2*S* ,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid (H-157)

[001345] (2*S* ,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid was prepared from (2*S* ,4*R*)- 1-[3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid ethyl ester. The ester (0.100 g, 0.16 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and ethanol and sodium hydroxide (1N) was added. The mixture was stirred at room temperature 4 hours. The mixture was cooled to room temperature, acidified to form a white precipitate The solid was filtered to give (2*S* ,4*R*)- 1-[3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-propyl]-1H-imidazole-2-carboxylic acid in 65% yield.

MS m/z · 587 (M+1)

[001346] [4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidin-1-yl]acetic acid (H-158)

[001347] [4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidin-1-yl]acetic acid was prepared following general procedure H, substituting *tert*-butyl 4-(4-(chlorocarbonyl)phenyl)piperidine-1-carboxylate for 6-trifluoromethyl nicotinyl chloride (*tert*-butyl 4-(4-(chlorocarbonyl)phenyl)piperidine-1-carboxylate was prepared by treatment of 4-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)benzoic acid with oxalyl chloride and catalytic DMF followed by removal of volatiles). The rest of the procedures were followed as indicated in general procedure B to afford the corresponding BOC-protected amine.

[001348] The *tert*-butyl carboxylate was removed by stirring the compound in 4N HCl/dioxane for 3h, followed by concentration. The resulting hydrochloride salt (40 mg, 0.079 mmol) was heated in acetonitrile (3 mL), ethyl bromoacetate (88 uL, 0.79 mmol), and potassium carbonate (110 mg, 0 79 mmol) at 65 °C for 2h The crude slurry was subjected to flash chromatography (5% MeOH, EtOAc)

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to yield the corresponding ethyl ester The ester was saponified with NaOH in MeOH/THF, then subjected to preparative HPLC to afford the title product as a white solid

^{1}H-NMR ($CDCl_3$) δ· 1.02-1.22 (m, 1H), 1.13 (s, 3H), 1 92 (d, 2H), 2 02 (s, 3H), 2.10-2.38 (m, 3H), 2 57-2.70 (m, 1H), 2.79 (t, 2H), 3.49 (s, 2H), 3.65-3 80 (m, 2H), 4.55 (bs, 1H), 4.70-4.82 (m, 1H), 5 40-5.75 (m, 1H), 6.48 (d, 1H), 6 88 (t, 1H), 7.00-7.30 (m, 8H), 7 37 (d, 2H)

MS m/z: 560 (M +1)

[001349] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide (H-159)

[001350] (2*S*,4*R*)-N-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide was prepared from (2*S*,4*R*)- 4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-1-ethylidene-pentG-2,4-dienyloxy)-butyric acid by coupling NH_4Cl, HATU, DIEA, HOBt in DMF at room temperature to yield (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide. The reaction mixture was concentrated down and partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over magnesium sulfate, filtered and concentrated down. The residue was purified by silica gel chromatography (10% methanol / 90 % dichloromethane) to afford pure (2*S*,4*R*)-N-4-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyramide in 46% yield

^{1}H-NMR ($CDCl_3$) δ: 1.13 (d, 3H), 1 15 (t, 1H), 1.68 (bs, 2H), 2.04 (s, 3H), 2.08 (m, 2H), 2.27 (m, 1H), 2 38 (t, 2H), 3.97 (t, 2H), 4 72 (sextet, 1H), 5.48 (bs, 1H), 6.52 (d, 1H), 6.67 (d, 2H), 6 86 (t, 1H), 7 08-7.35 (m, 6H), 7.38 (d, 2H).

MS m/z. 520 (M+1)

[001351] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (H-160)

[001352] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate was made from *N*-(4-chloro-2-methylphenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide following general procedure C, substituting 4-bromo-2,2-dimethylbutanoate for ethyl 4-bromoacetate to yield methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate.

^{1}H-NMR (CDCl3) δ· 1 10 (d, 3H), 1.25 (s, 6H), 1 95 (s, 3H), 2 05 (t, 2H), 2 20 (m, 1H), 2.30 (s, 3H), 3.70 (s, 3H), 3.95 (t, 2H), 4.75 (m, 1H), 5.60 (m, 1H), 6.50 (d, 1H), 6 60 (d, 2H), 6.95 (t, 1H), 7.15-7 30 (m, 6H), 7 40 (s, 1H).

MS m/z· 577 (M+1)

[001353] 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (H-161)

[001354] Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate (60 mg, 0.10 mmol, 1 equ.) was dissolved in methanol/tetrahydrofuran (2/1) (0.8 ml). A solution of sodium hydroxide (12 mg, 0.30 mmol, 3 eq.) in water (0.3 ml) was added and reaction mixture heated to 40°C for 2 h The mixture was concentrated and the residue was acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid (50 mg, 89 %)

^{1}H-NMR (CDCl3) δ· 1.10 (d, 3H), 1 25 (s, 6H), 1 90 (s, 3H), 2.05 (m, 3H), 2.30 (s, 3H), 3 95 (t, 2H), 4.75 (m, 1H), 5 60 (m, 1H), 6 50 (d, 1H), 6.60 (d, 2H), 6 90 (t, 1H), 7.10-7.35 (m, 6H), 7.40 (s, 1H)

MS m/z 563 (M+1).

[001355] Benzyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pyrrolidine-1-carboxylate (H-162)

[001356] Benzyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pyrrolidine-1-carboxylate was prepared following general procedure H, substituting benzyl 2-(4-(chlorocarbonyl)phenyl)pyrrolidine-1-carboxylate for 6-trifluoromethyl nicotinyl chloride. (Benzyl 2-(4-(chlorocarbonyl)phenyl)pyrrolidine-1-carboxylate was prepared by treatment of 4-(1-(benzyloxycarbonyl)pyrrolidin-2-yl)benzoic acid with oxalyl chloride and catalytic DMF followed by removal of volatiles). The rest of the procedures were followed as indicated in general procedure B to afford benzyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pyrrolidine-1-carboxylate

^{1}H-NMR ($CDCl_3$) δ: 1.00-1.20 (m, 1H), 1.12 (s, 3H), 1.68-1.90 (m, 3H), 2.02 (s, 3H), 2 15-2.40 (m, 2H), 3 48-3.70 (m, 2H), 4.70-5.20 (m, 4H), 5.42-5 75 (m, 1H), 6 40-6.75 (m, 2H), 6.90-7.42 (m, 15H)

MS m/z· 622 (M +1)

[001357] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-163)

[001358] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure B, substituting 4-ethyl-3-fluorobenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (4-ethyl-3-fluorobenzoyl chloride was prepared in five steps from commercially available 4-bromo-3-fluorobenzoic acid 4-Bromo-3-

fluorobenzoic acid (0.828g, 3 8 mmol) was dissolved in 20 mL of benzene/ methanol (5.1) mixture. To the above mixture was added trimethylsilyldiazomethane until the reaction showed a light yellow color. Let stir for 30 minutes and concentrate down to yield methyl 4-bromo-3-fluorobenzoate Methyl 4-bromo-3-fluorobenzoate was dissolved in 2 mL of DMF and vinyl tributyl tin (0.431 mL, 1.5 mmol), and degassed for 5 min with nitrogen gas To the above mixture was added $Pd(PPh_3)_2Cl_2$ (0 086g, 0.12 mmol) and heated at 80°C with a condenser for 16 h. Cool to room temperature and dilute with ethyl acetate and wash with a 10% solution of KF in water. The mixture was allowed to stir for ~30 min at room temperature, then filter and extract the aqueous with ethyl acetate (3x) Dry over $MgSO_4$, filter and concentrate down. The residue was concentrated down and purified with 100% hexane to 10% ethyl acetate/90% hexane to yield 0.140g, 63% of methyl 3-fluoro-4-vinylbenzoate. Methyl 3-fluoro-4-vinylbenzoate (0.750g, 4 1 mmol) was reduced in the presence of Pd on carbon (10%) in ethanol to provide methyl 4-ethyl-3-fluorobenzoate (0.450g, 59%). Methyl 4-ethyl-3-fluorobenzoate was hydrolyzed to the acid by dissolving in tetrahydrofuran and methanol and sodium hydroxide (1N) was added The mixture was stirred at room temperature overnight The mixture was cooled to rt, acidified to pH = 5 with 1N HCl to form a white precipitate (0.270 g, 65%) The solid was filtered to give 4-ethyl-3-fluorobenzoic acid. The acid was converted to the acid chloride as described in general procedure B).

^{1}H-NMR ($CDCl_3$) δ·1 12 (m, 1H), 1.13 (d, 3H), 1.18 (t, 3H), 2 02 (s, 3H), 2 27 (m, 1H), 3 58 (q, 2H), 4 75 (sextet, 1H), 5.59 (bs, 1H), 6.52 (d, 1H), 6.72 (d, 1H), 6.89 -7.00 (m, 3H), 7 14 -7.21 (m, 3H), 7.28 (d, 1H), 7.36 (d, 2H)

MS m/z : 465 (M+1)

[001359] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3,5-difluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (H-164)

[001360] *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3,5-difluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide was prepared following general procedure B, substituting 4-ethyl-3,5-difluorobenzoyl chloride for 6-trifluoromethyl nicotinyl chloride. (4-ethyl-3,5-difluorobenzoyl chloride was prepared in two steps from 3,5-difluorobenzoic acid. To a solution of 3,5-difluorobenzoic acid in tetrahydrofuran was added lithium diisopropyl amide at -78°C After the reaction mixture was stirred at -78°C for 1 h ethyl iodide was added and reaction mixture stirred at room temperature for 2h to give 4-ethyl-3,5-difluorobenzoic acid Subsequent treatment of this carboxylic acid with oxalyl chloride and catalytic DMF afforded 4-ethyl-3,5-difluorobenzoyl chloride in decent yield) The rest of the procedures were followed as indicated in general procedure B to afford *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3,5-difluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

^{1}H-NMR (CDCl3) δ 1 05 (t, 3H), 1.15 (d, 3H), 2 05 (s, 3H), 2.30 (m, 1H), 2 60 (q, 2H), 4 75 (m, 1H), 5.55 (m, 1H), 6.50 (d, 1H), 6.85 (d, 2H), 7.00 (t, 1H), 7.2 (m, 3H), 7.25-7.45 (m, 3H) MS m/z: 483 (M+1). J20

[001361] 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoic acid (H-165)

[001362] 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoic acid was prepared from methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate (0.005g, 0.0086 mmol) was hydrolyzed to the acid by dissolving in tetrahydrofuran and methanol and sodium hydroxide (1N) was added. The mixture was stirred at room temperature overnight The mixture was cooled to rt, acidified to pH = 5 with 1N HCl to form a white precipitate (0.002g, 42%). The solid was filtered to give 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoic acid.

^{1}H-NMR ($CDCl_3$) δ. 0 86 (m, 1H), 1.14 (d, 3H), 1 25 (s, 6H), 2.01(s, 3H), 2 04 (t, 2H), 2.29 (s, 1H), 4 32 (t, 2H), 4.74 (sextet, 1H), 5.53 (bs, 1H), 6.40 (d, 1H), 6 56 (d, 1H), 6 98 (t, 1H), 7.16-7.31 (m, 5H), 7.37 (d, 2H), 8.12 (s, 1H)

MS m/z . 552 (M+1).

[001363] 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid methyl ester (H-166)

[001364] 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid methyl ester was prepared following general procedure B, substituting methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate for 6-trifluoromethyl nicotinyl chloride.(Methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate was prepared in four steps from 2,2-dimethyl-4-pentanoic acid. 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 %) 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 to 96/4 gradient) to provide 4-(4-methoxycarbonyl-4-methyl-pent-1-enyl)-benzoic acid as a light brown solid (915 mg, 50 %). 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 ?ul, 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 %). 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 0^0C. 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 methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate as an oil).

[001365] To the prepared methyl 5-[4-(chlorocarbonyl)phenyl]-2,2-dimethylpentanoate (2.9 mmol, 1.0 eq) was added a solution of N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide (754 mg, 2.4 mmol, 0.83 eq.) in methylene chloride (8 ml) followed by diisopropylethylamine (505 ul, 2.9 mmol, 1.0 eq.) and reaction mixture was stirred at room temperature for 20 h. The mixture was concentrated and the residue dissolved in ethyl acetate and washed with water, brine, and then dried over magnesium sulfate, filtered and concentrated. The crude residue was purified by silica gel chromatography (ethyl acetate/hexane 1/3 to 1/2 gradient) to afford 5-(4-{(2S,4R)-4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2*H*-quinoline-1-carbonyl}-phenyl)-2,2-dimethyl-pentanoic acid methyl ester (675 mg, 50 %).

^{1}H-NMR (CDCl3) δ: 1.10 (s, 6H), 1 15 (d, 3H), 1.45 (m, 4H), 2.05 (s, 3H), 2.45 (m, 1H), 2.55 (t, 2H), 3 58 (s, 3H), 4.75 (m, 1H), 5.55 (m, 1H), 6 45 (d, 1H), 6 85 (t, 1H), 6.95 (d, 2H), 7.05-7.35 (m, 8H).

MS m/z· 561 (M+1).

[001366] (2*S*,4*R*)- N-(4-Chloro-phenyl)-N-{1-[4-(3-imidazol-1-yl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide (H-167)

[001367] (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(4-hydroxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide (0.1g, 0 23 mmol) was dissolved in DMF (5 mL) at room temperature

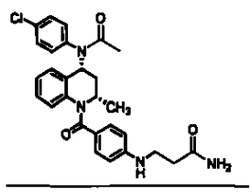
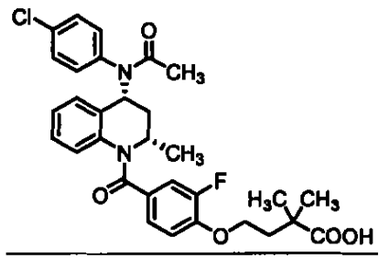
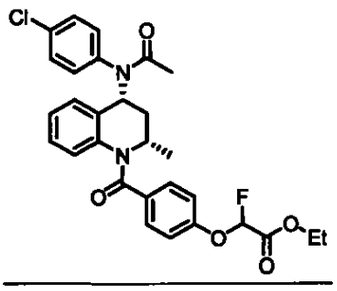
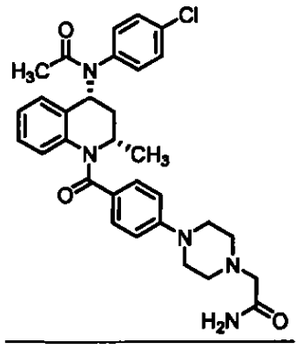
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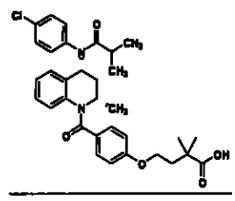
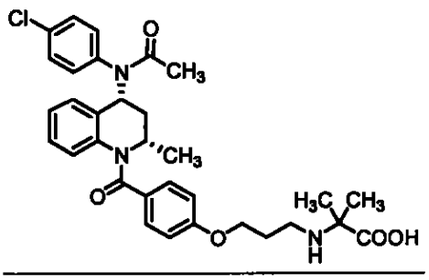
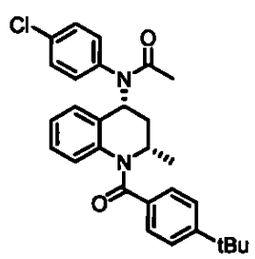
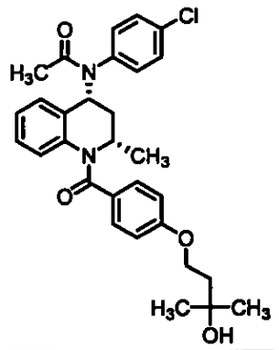
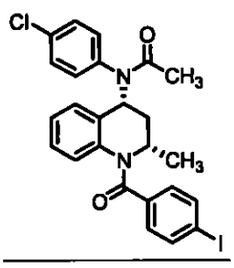
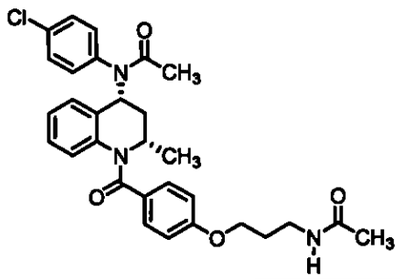
K_2CO_3 (0 317g, 2.3 mmol) was added. 1-(3-Bromo-propyl)-1H-imidazole (0.174g, 0.92 mmol) was added and the reaction was allowed to heat to 80°C overnight. The reaction mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, then extracted three times with ethyl acetate, dried over $MgSO_4$, filtered and concentrated down. The crude residue was purified by silica gel chromatography (60% EtOAc/ 40% Hexane) to afford the product (0.020g, 16%)

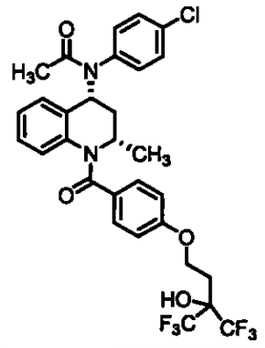
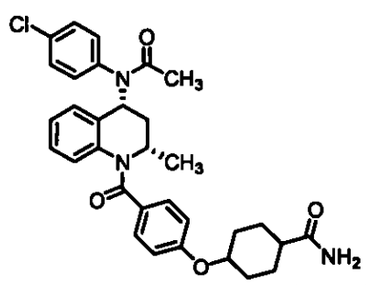
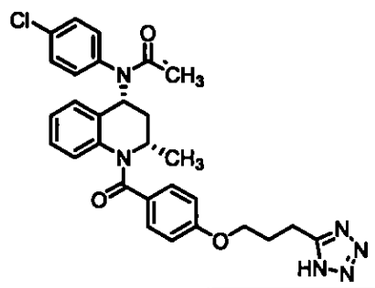
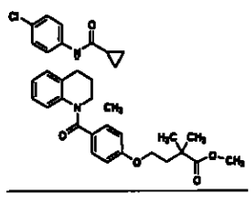
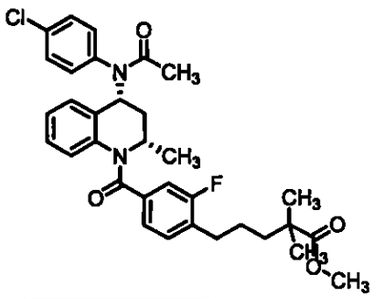
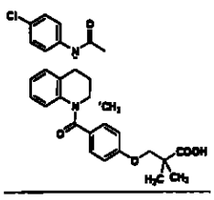
^{1}H-NMR ($CDCl_3$) δ 1.16 (d, 3H), 1 15 (t, 1H), 2.02 (s, 3H), 2.18 (m, 2H), 2.28 (m, 1H), 3 85 (t, 2H), 4 17 (t, 2H), 4.72 (sextet, 1H), 5.58 (bs, 1H), 6.52 (d, 1H), 6 67 (d, 2H), 6 84 (s, 1H), 6.88 (t, 1H), 7 03 (s, 1H), 7 08-7 35 (m, 6H), 7 38 (d, 2H), 7.43 (s, 1H)

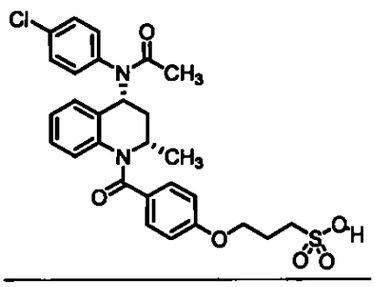
MS m/z. 543 (M+1)

Table 9: Exemplary Compounds:

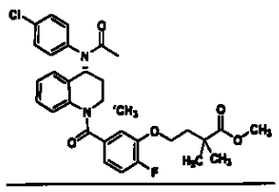
 **H-1**	 **H-2**
 **H-3**	 **H-4**

 H-5	 H-6
 H-7	 H-8
 H-9	 H-10

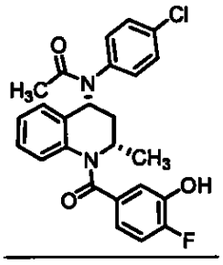
 H-11	 H-12
 H-13	 H-14
 H-15	 H-16



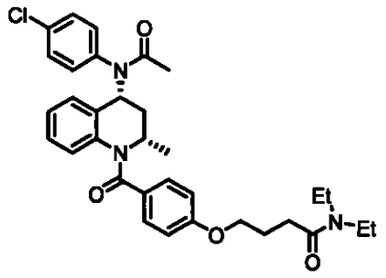
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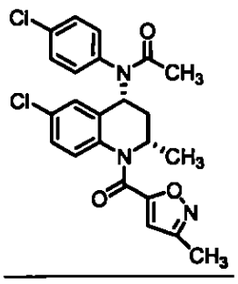
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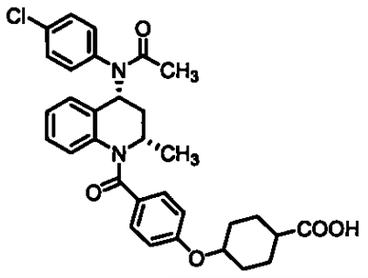
H-19



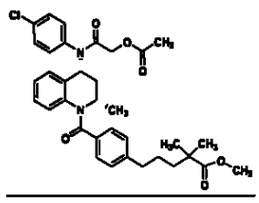
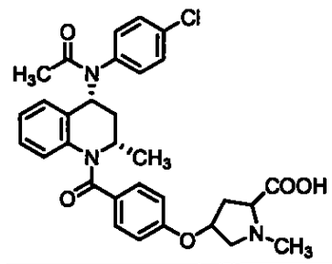
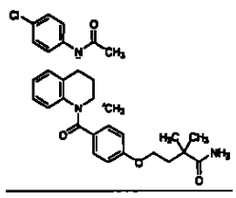
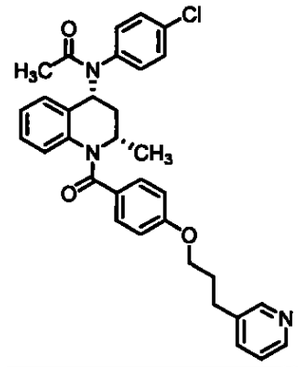
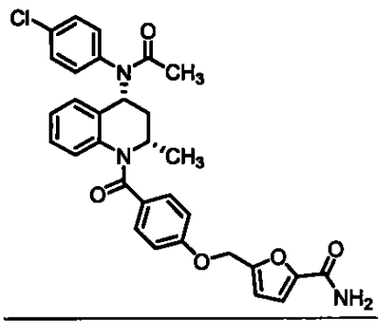
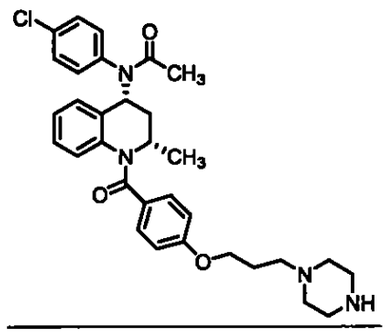
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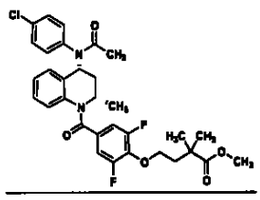
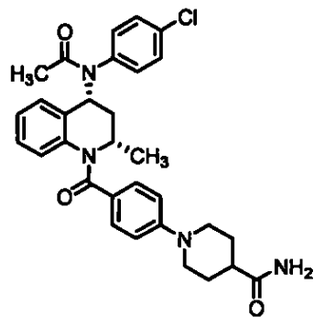
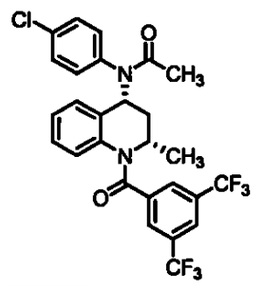
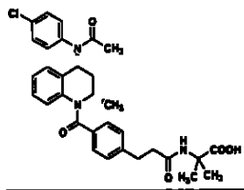
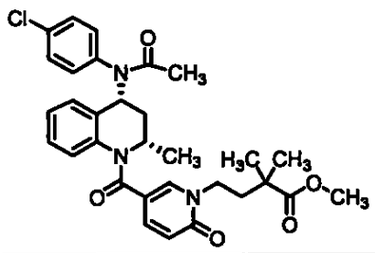
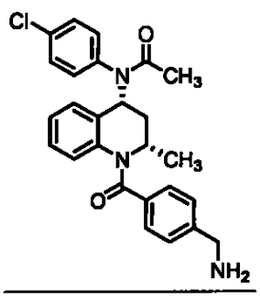


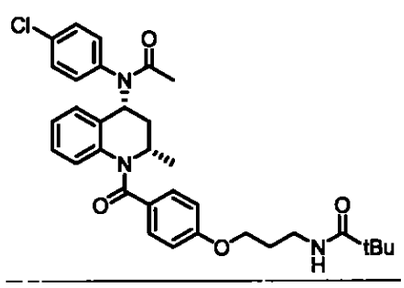
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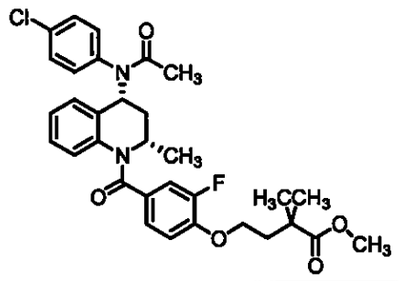
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 H-25	 H-26
 H-27	 H-28

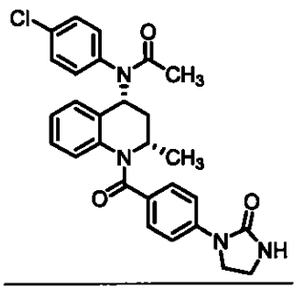
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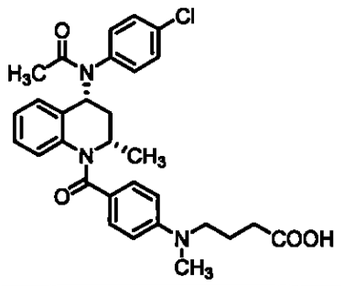
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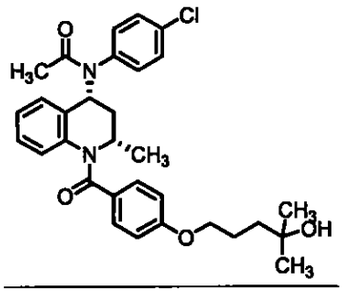
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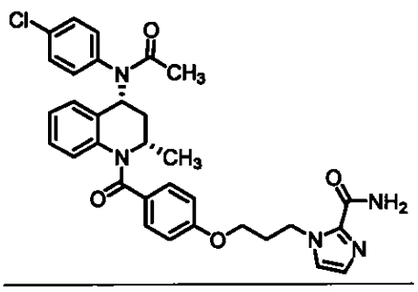
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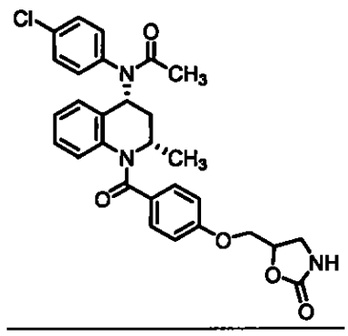
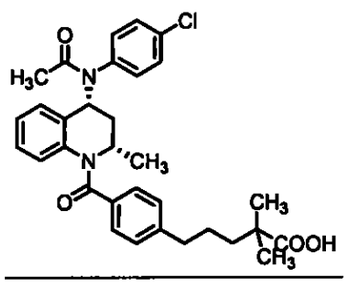
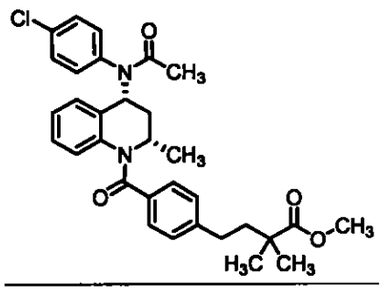
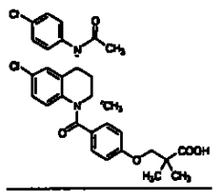
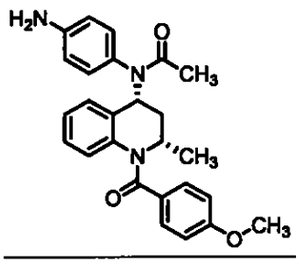
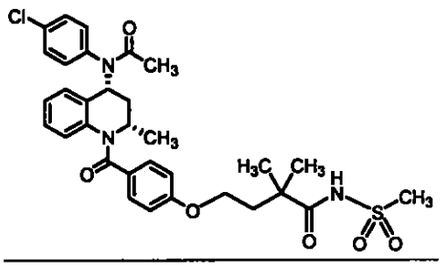
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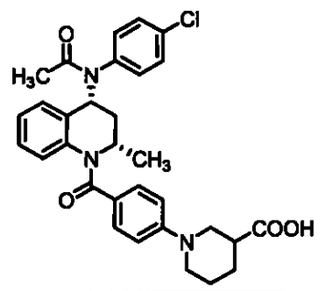
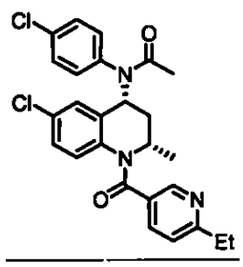
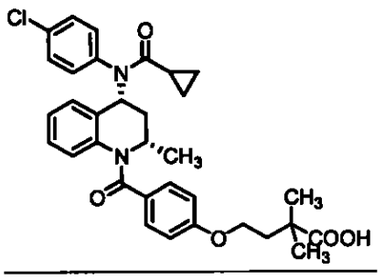
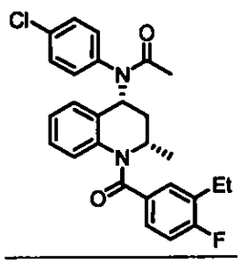
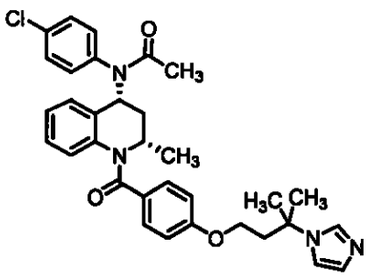
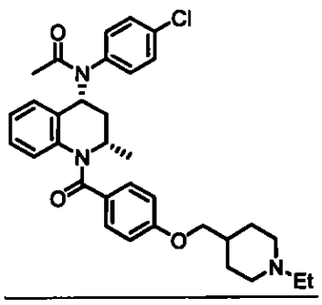


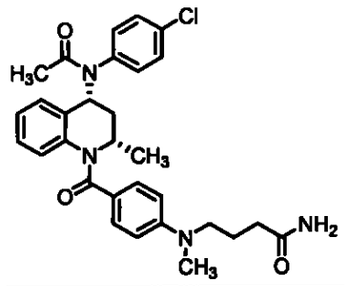
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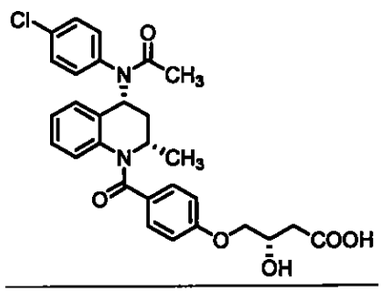
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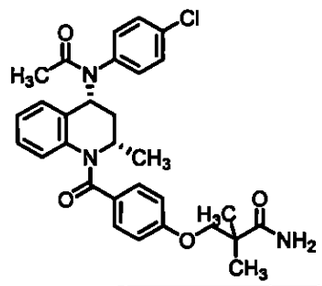
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 H-49	 H-50
 H-51	 H-52



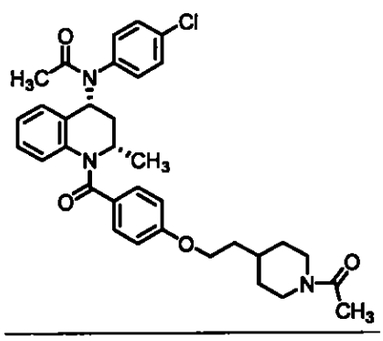
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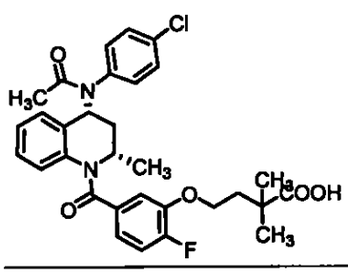
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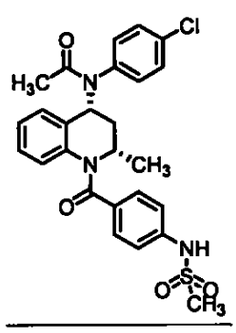
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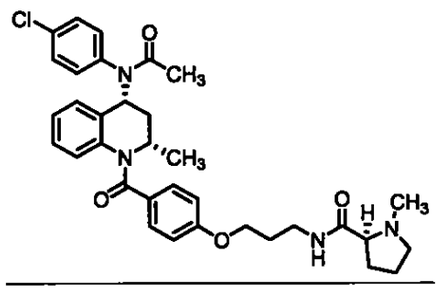
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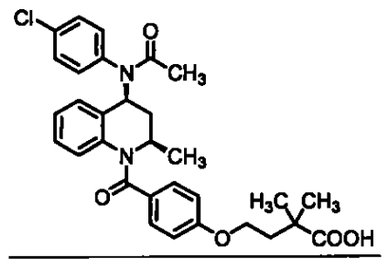
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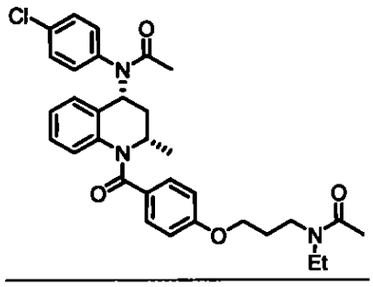
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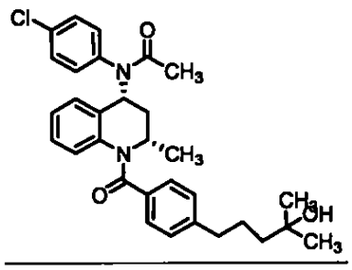
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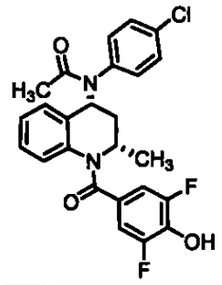
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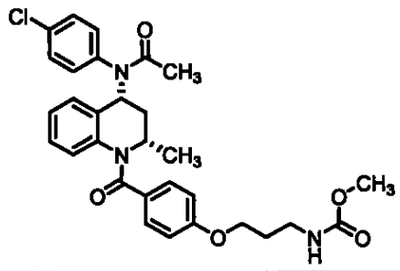
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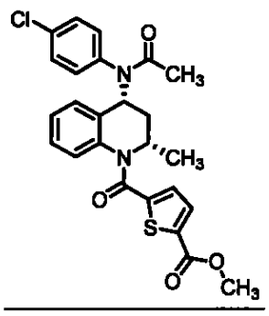
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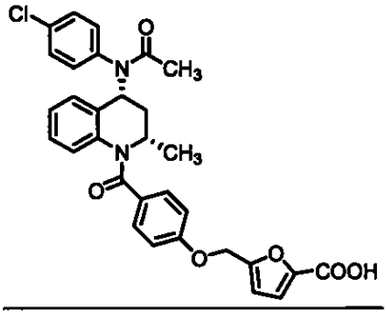
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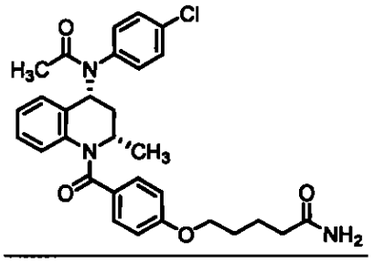
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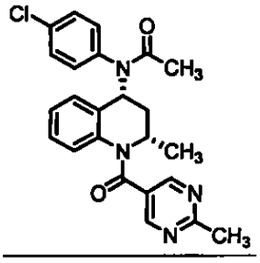
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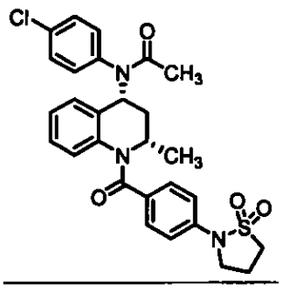
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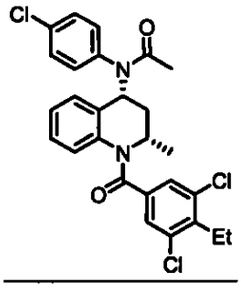
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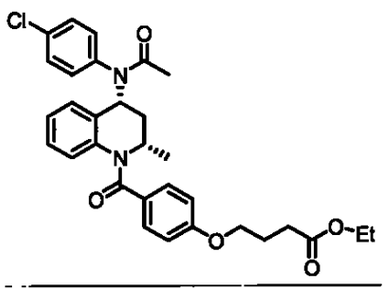
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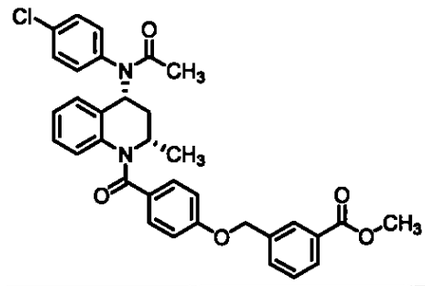
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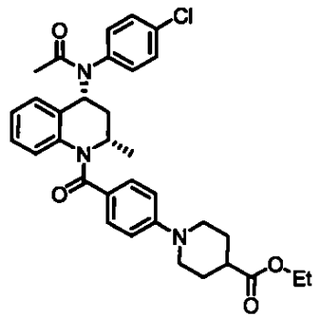
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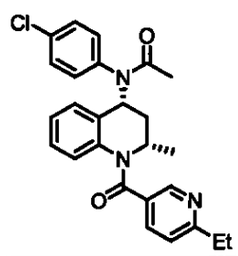
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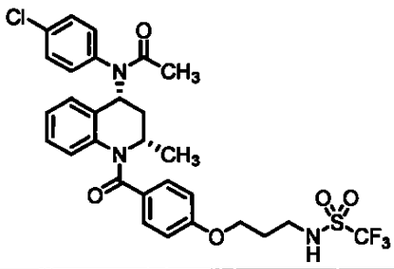
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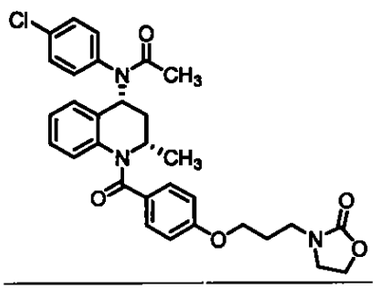
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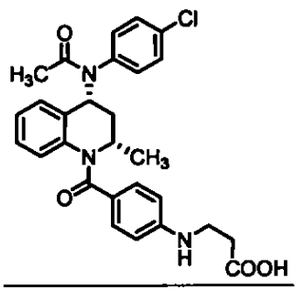
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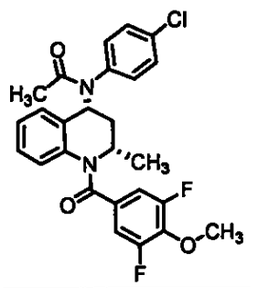
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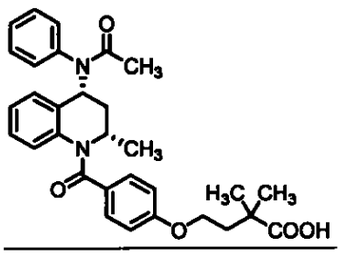
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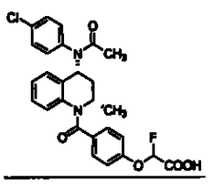
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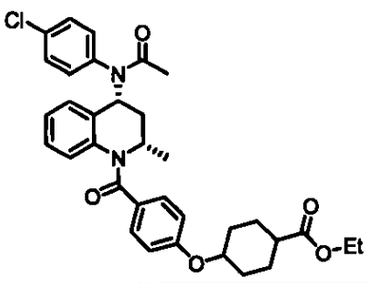
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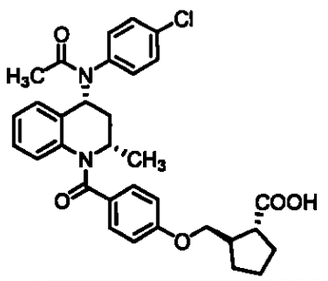
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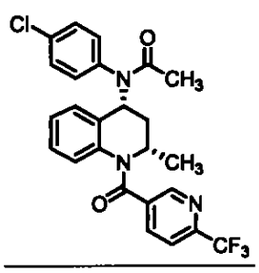
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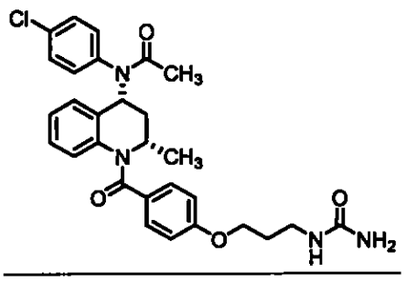
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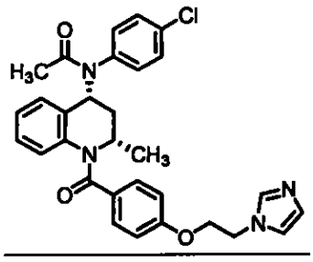
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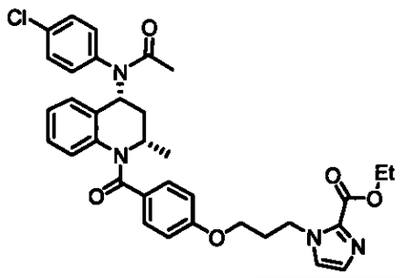
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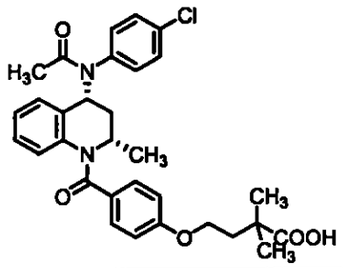
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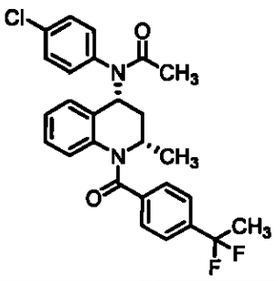
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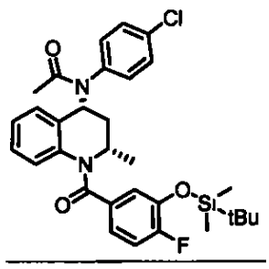
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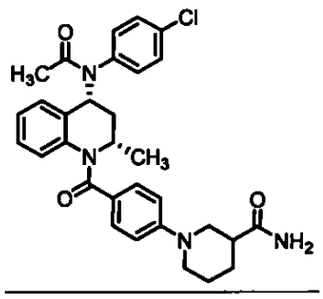
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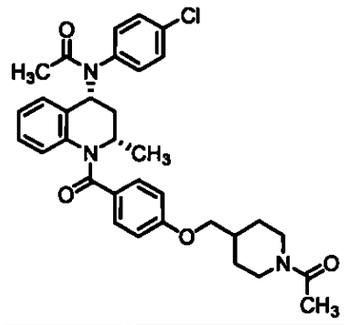
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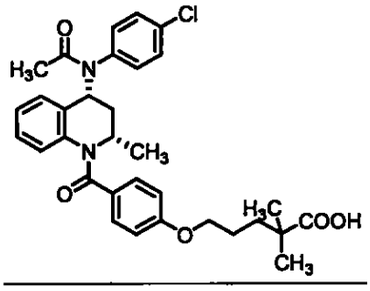
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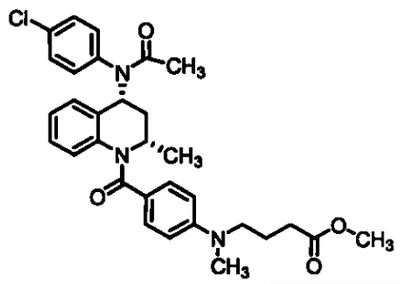
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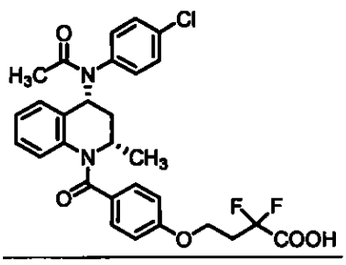
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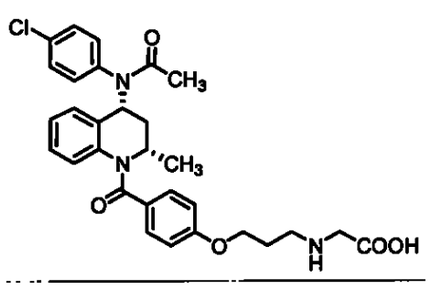
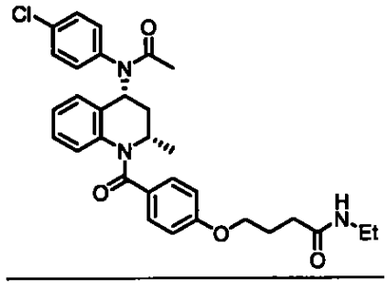
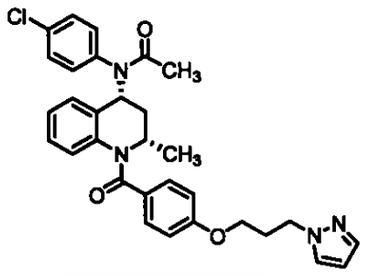
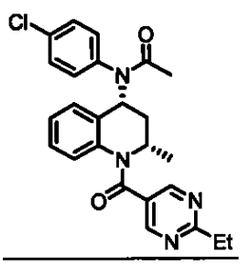
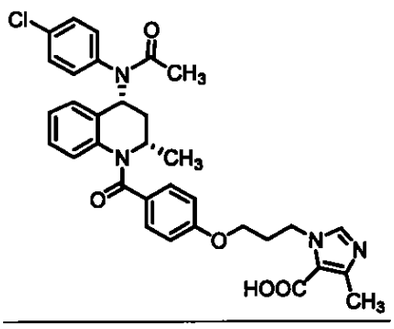
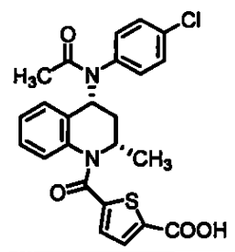
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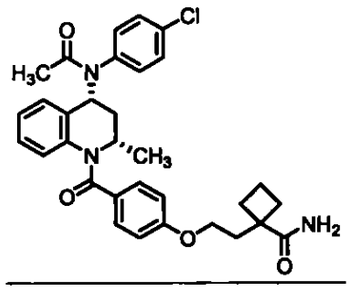


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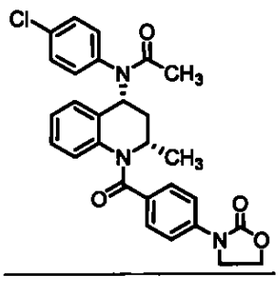


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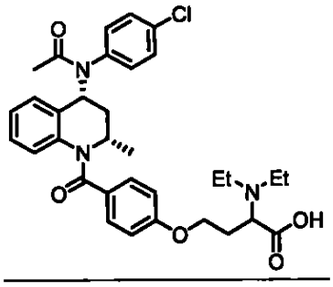
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 H-97	 H-98
 H-99	 H-100



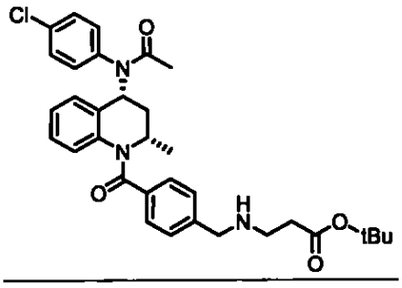
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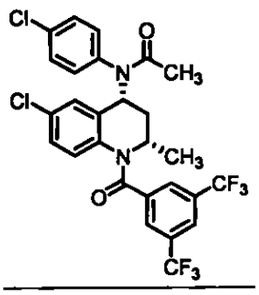
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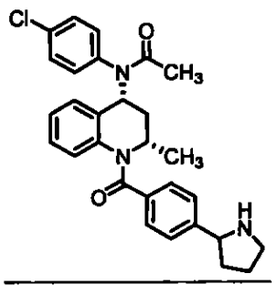
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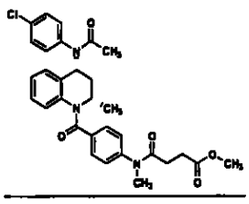
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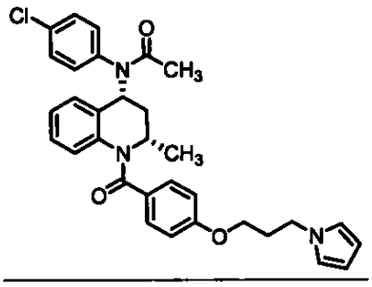
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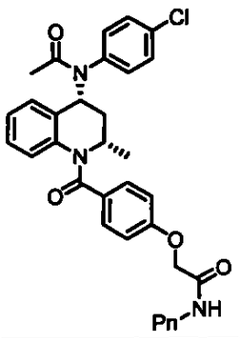
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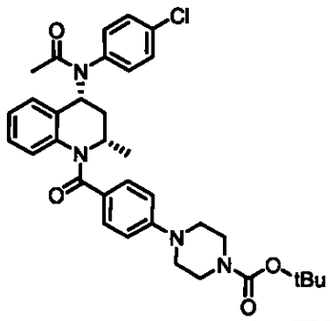
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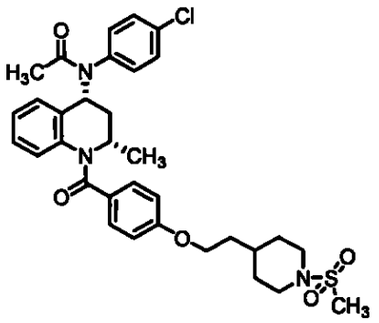
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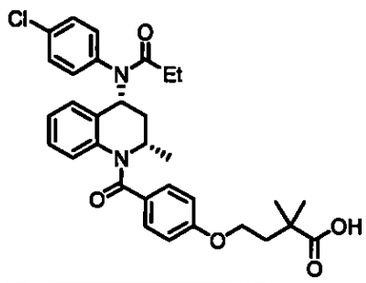
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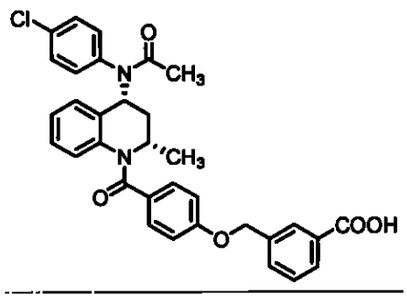
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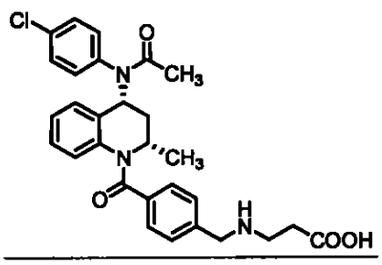
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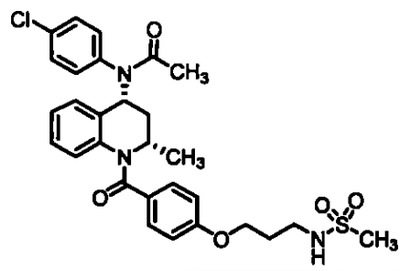
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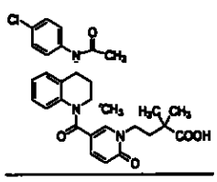
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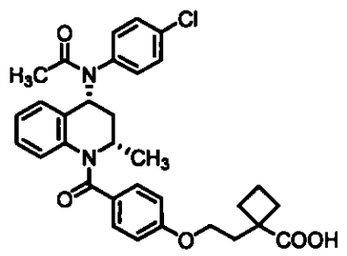
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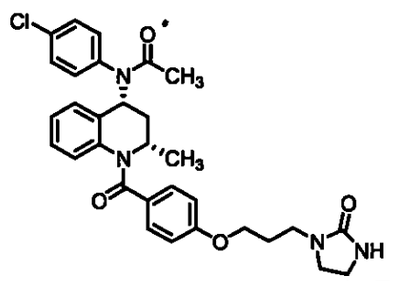
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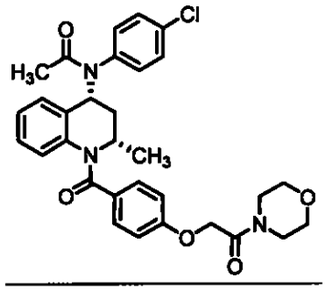
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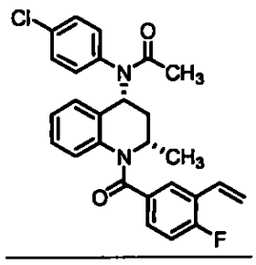
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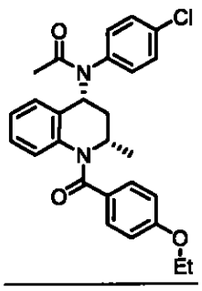
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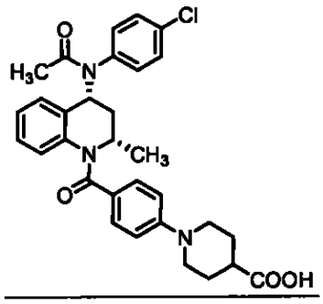
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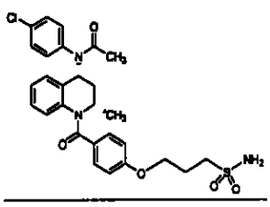
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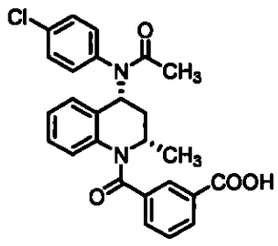
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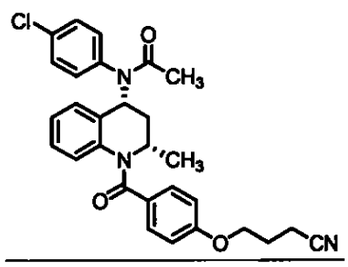
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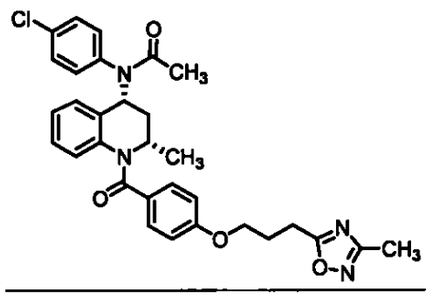
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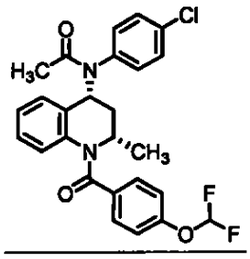
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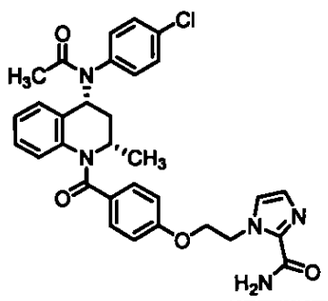
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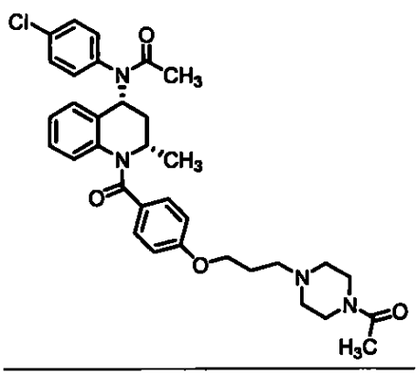
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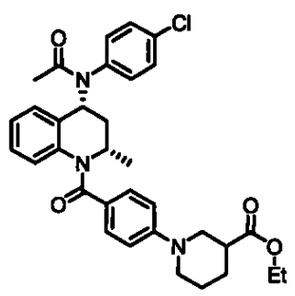
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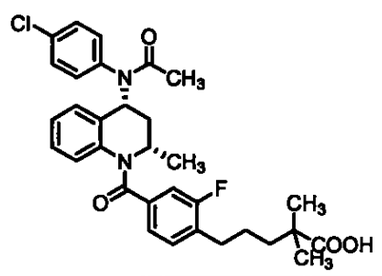
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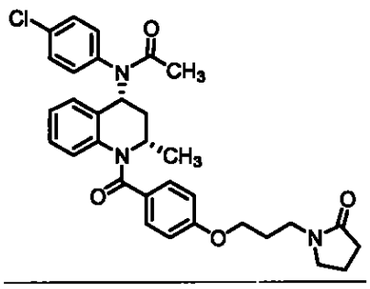
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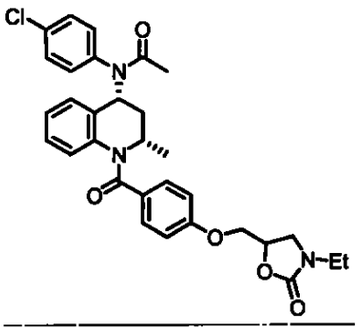
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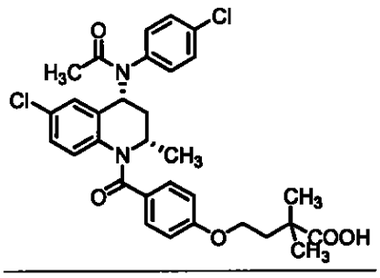
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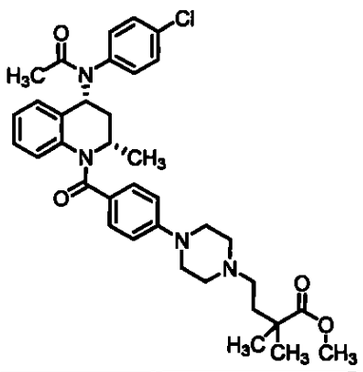
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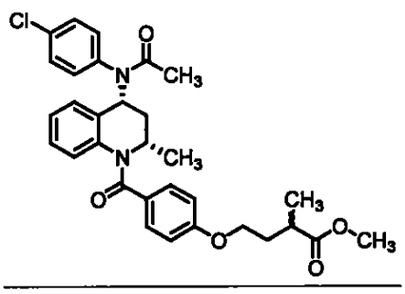
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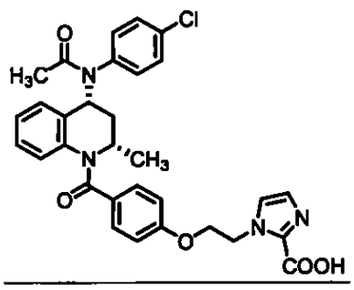
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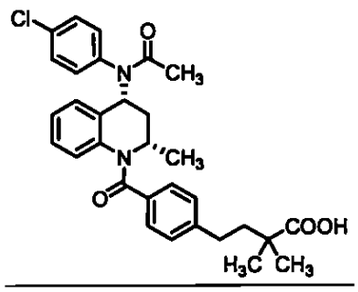
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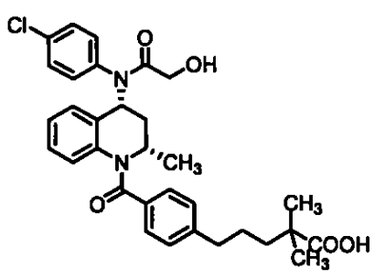
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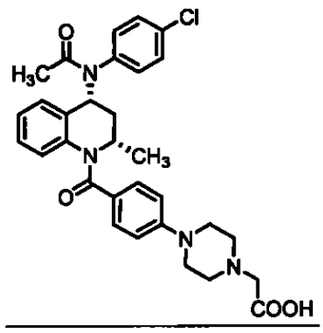
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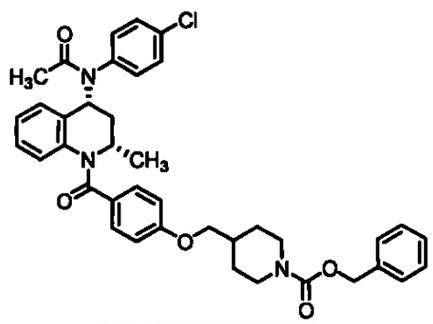
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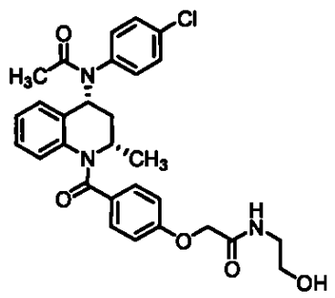
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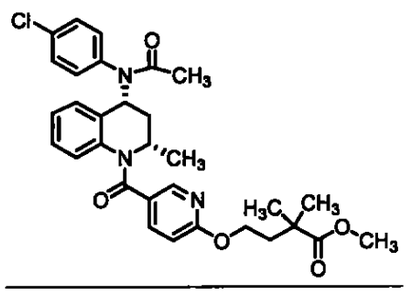
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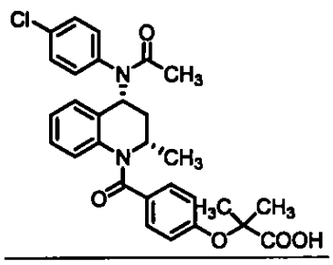
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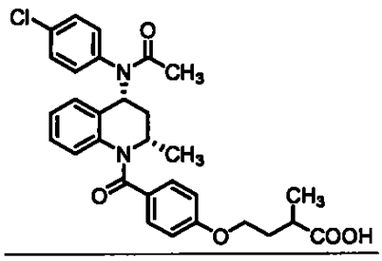
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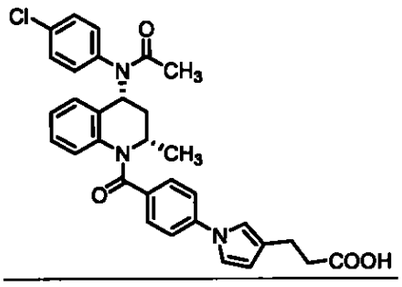
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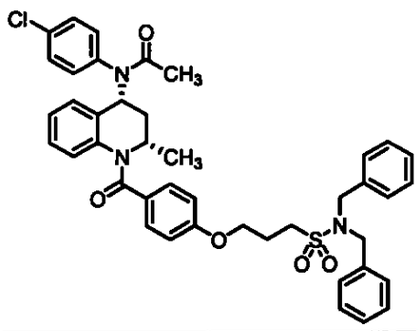
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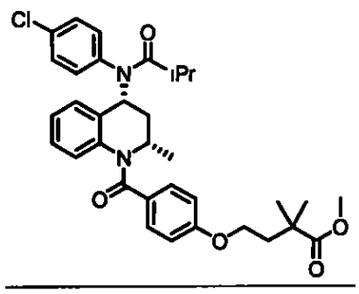
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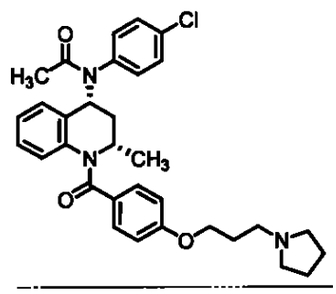
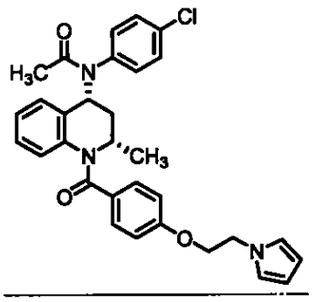
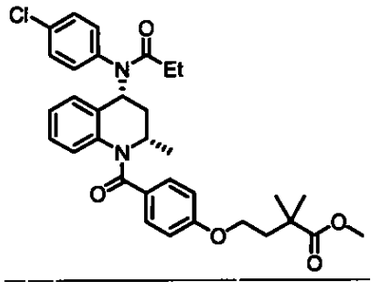
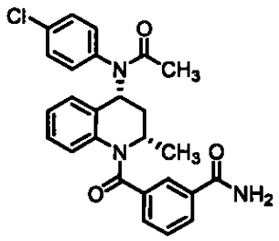
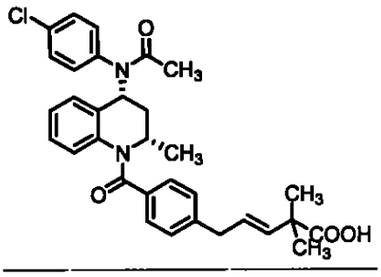
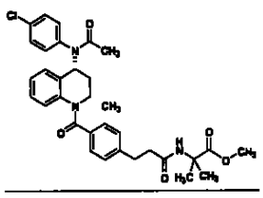
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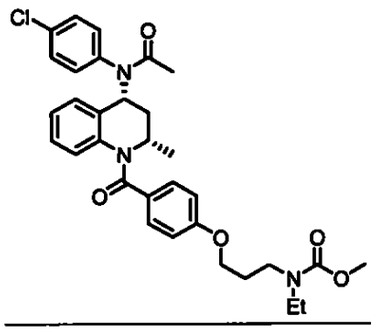


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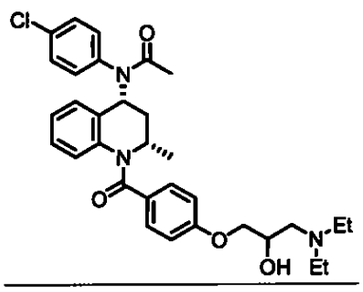


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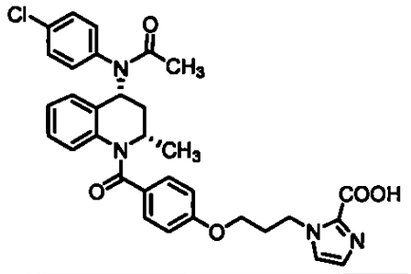
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 H-151	 H-152
 H-153	 H-154



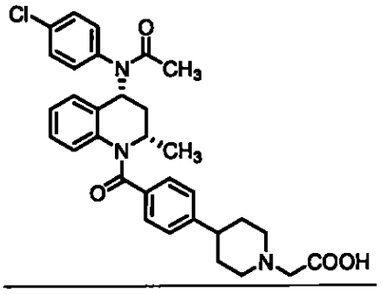
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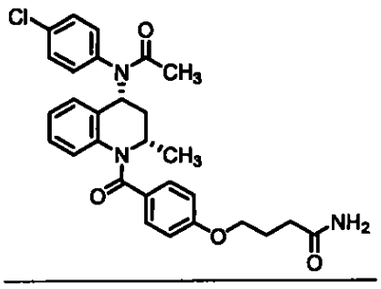
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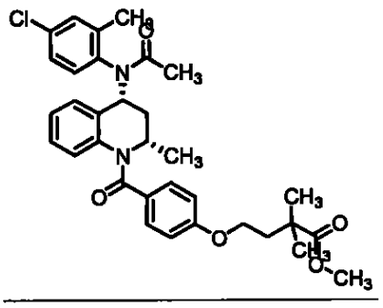
H-157



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H-160

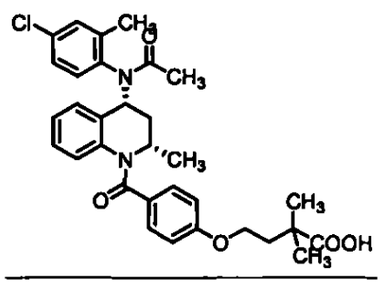
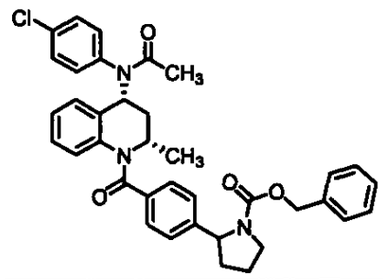
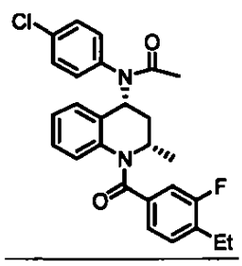
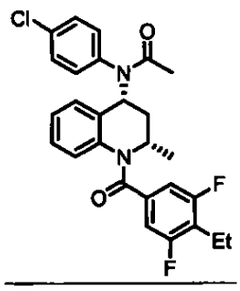
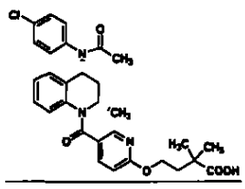
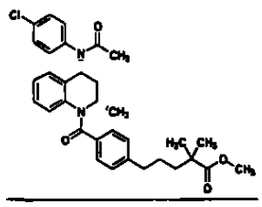
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 H-163	 H-164
 H-165	 H-166

Table 10: Chemical Names of Compounds Represented in Table 9:

H-1 3-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)amino]propanamide

H-2 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-

1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoic acid

H-3 Ethyl (4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)(fluoro)acetate

H-4 *N*-((2*S*,4*R*)-1-{4-[4-(2-Amino-2-oxoethyl)piperazin-1-yl]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-5 4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-6 2-{[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]amino}-2-methylpropanoic acid

H-7 *N*-[(2*S*,4*R*)-1-(4-*tert*-Butylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide

H-8 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(3-hydroxy-3-methylbutoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-9 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-iodobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-10 *N*-((2*S*,4*R*)-1-{4-[3-(Acetylamino)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-11 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[4,4,4-trifluoro-3-hydroxy-3-(trifluoromethyl)butoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-12 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)cyclohexanecarboxamide

H-13 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(1*H*-tetrazol-5-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-14 Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

H-15 Methyl 5-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoate

H-16 3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid

H-17 3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propane-1-sulfonic acid

H-18 Methyl 4-(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate

H-19 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-20 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-

3.51

1(2*H*)-yl]carbonyl}phenoxy)-*N*,*N*-diethylbutanamide

H-21 *N*-{(2*S*,4*R*)-6-Chloro-2-methyl-1-[(3-methylisoxazol-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide

H-22 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)cyclohexanecarboxylic acid

H-23 Methyl 5-(4-{[(2*S*,4*R*)-4-[[(acetyloxy)acetyl](4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate

H-24 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-1-methylpyrrolidine-2-carboxylic acid

H-25 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanamide

H-26 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(3-pyridin-3-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-27 5-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]-2-furamide

H-28 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(3-piperazin-1-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-29 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2,6-difluorophenoxy)-2,2-dimethylbutanoate

H-30 1-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-4-carboxamide

H-31 *N*-{(2*S*,4*R*)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide

H-32 2-{[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoic acid

H-33 Methyl 4-[5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoate

H-34 *N*-{(2*S*,4*R*)-1-[4-(Aminomethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide

H-35 *N*-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-2,2-dimethylpropanamide

H-36 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoate

H-37 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(2-oxoimidazolidin-1-yl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-38 4-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-

1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]butanoic acid

H-39 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[(4-hydroxy-4-methylpentyl)oxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-40 1-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-1*H*-imidazole-2-carboxamide

H-41 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[(2-oxo-1,3-oxazolidin-5-yl)methoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-42 5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid

H-43 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoate

H-44 3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid

H-45 *N*-(4-Aminophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-46 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethyl-*N*-(methylsulfonyl)butanamide

H-47 1-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-3-carboxylic acid

H-48 *N*-{(2*S*,4*R*)-6-Chloro-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide

H-49 4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(cyclopropylcarbonyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-50 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-51 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[3-(1*H*-imidazol-1-yl)-3-methylbutoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-52 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[(1-ethylpiperidin-4-yl)methoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-53 4-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]butanamide

H-54 (3*S*)-4-(4-{[(2*S*,4*R*)-4-Aacetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-3-hydroxybutanoic acid

H-55 3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpropanamide

H-56 *N*-((2*S*,4*R*)-1-{4-[2-(1-Acetylpiperidin-4-yl)ethoxy]benzoyl}-2-methyl-1,2,3,4-

tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-57 4-(5-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenoxy)-2,2-dimethylbutanoic acid

H-58 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[(methylsulfonyl)amino]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-59 (2*S*)-*N*-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-1-methylpyrrolidine-2-carboxamide

H-60 4-(4-{[(2*R*,4*S*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-61 *N*-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-*N*-ethylacetamide

H-62 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(4-hydroxy-4-methylpentyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-63 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-hydroxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-64 Methyl [3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]carbamate

H-65 Methyl 5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylate

H-66 5-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]-2-furoic acid

H-67 5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)pentanamide

H-68 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[(2-methylpyrimidin-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-69 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-dioxidoisothiazolidin-2-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-70 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-dichloro-4-ethylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-71 Ethyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)butanoate

H-72 Methyl 3-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]benzoate

H-73 Ethyl 1-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-4-carboxylate

H-74 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(6-ethylpyridin-3-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-75 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(3-{[(trifluoromethyl)sulfonyl]amino}propoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-76 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(2-oxo-1,3-oxazolidin-3-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-77 3-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)amino]propanoic acid

H-78 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(3,5-difluoro-4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-79 4-(4-{[(2*S*,4*R*)-4-[Acetyl(phenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-80 (4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)(fluoro)acetic acid

H-81 Ethyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)cyclohexanecarboxylate

H-82 (1*R*,2*R*)-2-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]cyclopentanecarboxylic acid

H-83 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{[6-(trifluoromethyl)pyridin-3-yl]carbonyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-84 *N*-[(2*S*,4*R*)-1-(4-{3-[(Aminocarbonyl)amino]propoxy}benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide

H-85 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[2-(1*H*-imidazol-1-yl)ethoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-86 Ethyl 1-[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-1*H*-imidazole-2-carboxylate

H-87 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-88 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(1,1-difluoroethyl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-89 *N*-[(2*S*,4*R*)-1-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-*N*-(4-chlorophenyl)acetamide

H-90 1-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-3-carboxamide

H-91 *N*-((2*S*,4*R*)-1-{4-[(1-Acetylpiperidin-4-yl)methoxy]benzoyl}-2-methyl-1,2,3,4-

tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-92 5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylpentanoic acid

H-93 Methyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)(methyl)amino]butanoate

H-94 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-difluorobutanoic acid

H-95 {[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]amino}acetic acid

H-96 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-*N*-ethylbutanamide

H-97 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(1*H*-pyrazol-1-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-98 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[(2-ethylpyrimidin-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-99 1-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-4-methyl-1*H*-imidazole-5-carboxylic acid

H-100 5-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}thiophene-2-carboxylic acid

H-101 1-[2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)ethyl]cyclobutanecarboxamide

H-102 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(2-oxo-1,3-oxazolidin-3-yl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-103 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-(diethylamino)butanoic acid

H-104 *tert*-Butyl 3-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzyl)amino]propanoate

H-105 *N*-{(2*S*,4*R*)-1-[3,5-bis(Trifluoromethyl)benzoyl]-6-chloro-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-*N*-(4-chlorophenyl)acetamide

H-106 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(4-pyrrolidin-2-ylbenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-107 Methyl 4-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)(methyl)amino]-4-oxobutanoate

H-108 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(1*H*-pyrrol-1-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-109 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[2-(isopropylamino)-2-oxoethoxy]benzoyl}-2-

methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-110 *tert*-Butyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperazine-1-carboxylate

H-111 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(4-{2-[1-(methylsulfonyl)piperidin-4-yl]ethoxy}benzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-112 4-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-113 3-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]benzoic acid

H-114 3-[(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzyl)amino]propanoic acid

H-115 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-2-methyl-1-(4-{3-[(methylsulfonyl)amino]propoxy}benzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-116 4-[5-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-oxopyridin-1(2*H*)-yl]-2,2-dimethylbutanoic acid

H-117 1-[2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)ethyl]cyclobutanecarboxylic acid

H-118 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(2-oxoimidazolidin-1-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-119 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(2-morpholin-4-yl-2-oxoethoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-120 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-fluoro-3-vinylbenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-121 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-122 1-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-4-carboxylic acid

H-123 *N*-((2*S*,4*R*)-1-{4-[3-(Aminosulfonyl)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-124 3-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzoic acid

H-125 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(3-cyanopropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-126 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(3-methyl-1,2,4-oxadiazol-5-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-127 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-1-[4-(difluoromethoxy)benzoyl]-2-methyl-1,2,3,4-

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tetrahydroquinolin-4-yl}acetamide

H-128 1-[2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)ethyl]-1*H*-imidazole-2-carboxamide

H-129 *N*-((2*S*,4*R*)-1-{4-[3-(4-Acetylpiperazin-1-yl)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-*N*-(4-chlorophenyl)acetamide

H-130 Ethyl 1-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidine-3-carboxylate

H-131 5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}-2-fluorophenyl)-2,2-dimethylpentanoic acid

H-132 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[3-(2-oxopyrrolidin-1-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-133 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[(3-ethyl-2-oxo-1,3-oxazolidin-5-yl)methoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-134 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-6-chloro-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-135 Methyl 4-[4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperazin-1-yl]-2,2-dimethylbutanoate

H-136 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylbutanoate

H-137 1-[2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)ethyl]-1*H*-imidazole-2-carboxylic acid

H-138 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylbutanoic acid

H-139 5-(4-{[(2*S*,4*R*)-4-[(4-Chlorophenyl)(glycoloyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpentanoic acid

H-140 [4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperazin-1-yl]acetic acid

H-141 Benzyl 4-[(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)methyl]piperidine-1-carboxylate

H-142 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-{2-[(2-hydroxyethyl)amino]-2-oxoethoxy}benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-143 Methyl 4-[(5-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoate

H-144 2-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2-methylpropanoic acid

H-145 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-

1(2*H*)-yl]carbonyl}phenoxy)-2-methylbutanoic acid

H-146 3-[1-(4-{[(2*S*,4*R*)-4-Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-1*H*-pyrrol-3-yl]propanoic acid

H-147 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-{3-[(dibenzylamino)sulfonyl]propoxy}benzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-148 Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(isobutyryl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

H-149 *N*-(4-Chlorophenyl)-*N*-{(2*S*,4*R*)-2-methyl-1-[4-(3-pyrrolidin-1-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide

H-150 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-2-methyl-1-{4-[2-(1*H*-pyrrol-1-yl)ethoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-151 Methyl 4-(4-{[(2*S*,4*R*)-4-[(4-chlorophenyl)(propionyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

H-152 3-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}benzamide

H-153 (3*E*)-5-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)-2,2-dimethylpent-3-enoic acid

H-154 Methyl 2-{[3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)propanoyl]amino}-2-methylpropanoate

H-155 Methyl [3-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]ethylcarbamate

H-156 *N*-(4-Chlorophenyl)-*N*-((2*S*,4*R*)-1-{4-[3-(diethylamino)-2-hydroxypropoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

H-157 1-[3-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)propyl]-1*H*-imidazole-2-carboxylic acid

H-158 [4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)piperidin-1-yl]acetic acid

H-159 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)butanamide

H-160 Methyl 4-(4-{[(2*S*,4*R*)-4-[acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate

H-161 4-(4-{[(2*S*,4*R*)-4-[Acetyl(4-chloro-2-methylphenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid

H-162 Benzyl 2-(4-{[(2*S*,4*R*)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenyl)pyrrolidine-1-carboxylate

H-163 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3-fluorobenzoyl)-2-methyl-1,2,3,4-

tetrahydroquinolin-4-yl]acetamide

H-164 *N*-(4-Chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-ethyl-3,5-difluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

H-165 4-[(5-{[(2*S*,4*R*)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}pyridin-2-yl)oxy]-2,2-dimethylbutanoic acid

H-166 Methyl 5-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-2,2-dimethylpentanoate

H-167 N-(4-Chlorophenyl)-N-((2S,4R)-1-{4-[3-(1H-imidazol-1-yl)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide

[001368] General Procedure J:

[001369] *N*-cyclopentyl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide

[001370] (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine was obtained following procedure G, substituting 4-methoxybenzoyl chloride for 4-fluorobenzoyl chloride The rest of the procedures were followed as indicated in general procedure G to afford (2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine in decent yield

[001371] To (2S,4R)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (200 mg, 0 67 mmol) in MeOH was added cyclopentanone (0 073 mL, 0.74 mmol) followed $Na(OAc)_3BH$ (284 mg, 1 34 mmol) and catalytic amount of HOAc The reaction mixture was stirred at room temperature over night. The reaction wash quenched by adding water. And the mixture was extracted with EtOAc 3 times. The organic layers were combined then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes- ethyl acetate system) to afford (2*S*,4*R*)-*N*-cyclopentyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine in decent yield

[001372] To a solution (2*S*,4*R*)-*N*-cyclopentyl-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-amine (100 mg, 02.7 mmol) in methylene chloride (5 mL) was added diisopropylethylamine (120 uL, 0.70 mmol) followed by acetyl chloride (90 uL, 1 27 mmol). The mixture was stirred at r.t. for 4 h. The reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate, washed with sat. aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford pure *N*-cyclopentyl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide (100 mg, 91%).

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 1.24-1.34 (m, 3H), 1.48-1.56 (m, 2H), 1.90-2.07 (m, 2H), 2 26-2 30 (s, 3H), 2 30-2.42 (m, 1H), 2 70-2 77 (m, 2H), 3.35-3.45 (m, 1H), 3 75 (s, 3H), 4 05-4 09 (m, 1H),

4 32-4 37 (m, 1 H), 4.82-4 88 (m, 1H), 6 50-6.58 (m, 1H), 6 65-6.68 (m, 2H), 6 86-6 89 (m, 1H), 6 95-7.15 (m, 5H), 7.24-7 28 (m, 2H)
MS m/z 407 (M+1).

[001373] ***N*-cyclopropyl-*N*-[2-methyl-1-(pyridin-3-ylcarbonyl)-1,2,3,4-tetrahydroquinolin-4-yl]acetamide**

[001374] At -5 °C to a solution of benzyl 2-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (1 g, 3 39 mmol) in DCM was added TEA (3.76 mL, 27.09 mmol), followed by cyclopropyl amine (0 24 mL, 3.39 mmol) Then $TiCl_4$ (2.4 mL, 3.39 mmol) was added. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The reaction mixture was conentrated under reduced pressure. The by- product percipiated out. After filtration the filtrate was concentrated Without purification it was directly used in next step

[001375] The crude product (895 1 mg, 3.48 mmol) from the previous step was dissolved in acetic acid (10 mL). $NaBH(OAc)_3$ (2.27 g, 10 7 mmol) was added The reaction was stirred at r t overnight. The reaction mixture was washed with brine The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford benzyl 4-(cyclopropylamino)-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate.

[001376] At to 0 °C to a solution of benzyl 4-(cyclopropylamino)-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (492.1 mg, 1.32 mmol) in methylene chloride (5 mL) was added acetyl chloride (0 11 mL, 1.57 mmol). Triethylamine (0 27 mL, 1.57 mmol) was added drop-wise over 30 min. A precipitate formed during this time An additional DCM was added to completely dissolve all the precipitate. The reaction was stirred at r.t. overnight The mixture was concentrated under reduced pressure, partitioned between ethyl acetate and 1N sodium hydroxide while cooled to 0 °C The aqueous layer was extracted 3 times with ethyl acetate washed with sat sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was directly used in the following step.

[001377] Benzyl-4-[acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate was dissolved in MeOH and a catalytic amount of Palladium on Carbon (10%) was added. The round bottom flask in which resided the resulting solution was evacuated and backfilled with hydrogen The reaction was stirred under the hydrogen atomosphere overnight. The mixture was carefully filtered through a Celite ® plug and concentrated to afford crude product. The crude residue was purified by silica gel chromatography (hexanes/ethyl acetate system) to afford *N*-cyclopropyl-*N*-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide.

[001378] To the solution of N-cyclopropyl-N-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (82 mg, 0.34 mmol) in DCM (5 mL) was added nicotinoyl chloride hydrochloride (71 mg,

0 40 mmol), followed by DIPEA (104 mg, 0 80 mmol) The reaction mixture was stirred at r.t. for overnight The mixture was concentrated under reduced pressure and dissolved in ethyl acetate (15 mL). The reaction mixture was washed with sat sodium bicarbonate and brine The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford slightly yellow solid product (81 mg, 68%)

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.70-0 81 (m, 4H), 1.24-1.26 (m, 3H), 1.31-1 37 (m, 1H), 1 75-2 05 (m, 1H), 2.34 (s, 3H), 2 67-2.89 (m, 1H), 4.84-4.86 (m, 1H), 5 50 (b, 1H), 6 42-6 46 (d, 1H), 6 82 (b, 1 H), 6 84-6 87 (t, 1H), 7.00-7.06 (t, 1H), 7.24-7.27 (m, 1H), 8.47-8 49 (m, 1H), 8.65 (b, 1H)

MS m/z: 350 (M+1).

[001379] ***N*-cyclopropyl-*N*-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide**

[001380] At -5 °C to a solution of benzyl 2-methyl-4-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (1 g, 3 39 mmol) in DCM was added TEA (3.76 mL, 27.09 mmol), followed by cyclopropyl amine (0.24 mL, 3.39 mmol). Then $TiCl_4$ (2 4 mL, 3.39 mmol) was added. The reaction mixture was allowed to warm to r t. and was stirred overnight. The reaction mixture was conentrated under reduced pressure. The by- product percipiated out. After filtration the filtrate was concentrated Without purification it was directly used in next step.

[001381] The crude product (895 1 mg, 3 48 mmol) from the previous step was dissolved in acetic acid (10 mL) $NaBH(OAc)_3$ (2 27 g, 10.7 mmol) was added. The reation was stirred at room temperature overnight. The reaction mixture was washed with brine The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford benzyl 4-(cyclopropylamino)-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate.

[001382] At 0 °C to a solution benzyl 4-(cyclopropylamino)-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate (492.1 mg, 1.32 mmol) in methylene chloride (5 mL) was added acetyl chloride (0 11 mL, 1 57 mmol). Triethylamine (0 27 mL, 1.57 mmol) was added dropwise over ~30 min. A precipitate formed during this time. An additional methylene chloride was added to completely dissolve all the precipitate. The reaction was stirred at r t. overnight. The mixture was concentrated under reduced pressure, partitioned between ethyl acetate and 1N sodium hydroxide while cooled to 0°C. The aqueous layer was extracted 3 times with ethyl acetate washed with sat. aqueous sodium bicarbonate, brine and dried over magnesium sulfate, filtered, and concentrated under reduced pressure The crude product was directly used in the following step

[001383] Benzyl-4-[acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinoline-1(2*H*)-carboxylate was dissolved in MeOH and a catalytic amount of Palladium on Carbon (10%) was added The round

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bottom flask in which resided the resulting solution was evacuated and backfilled with hydrogen The reaction was stirred under the hydrogen atmosphere overnight. The mixture was carefully filtered through a Celite ® plug and concentrated to afford crude product. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate system) to afford *N*-cyclopropyl-*N*-(2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide.

[001384] To the solution of N-cyclopropyl-N-(2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide (82 mg, 0 34 mmol) in DCM (5 mL) was added 4-methoxybenzoyl chloride (68 mg, 0.40 mmol), followed by DIPEA (104 mg, 0.80 mmol) The reaction mixture was stirred at r.t overnight. The mixture was concentrated under reduced pressure and dissolved in ethyl acetate The reaction mixture was washed with sat. sodium bicarbonate and brine. The organic phase was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (hexanes-ethyl acetate) to afford only the cis isomer as a slightly yellow solid product (81 mg, 68%). The mixture of two enantiomers was purified by chiral HPLC using the OD column and the two enatiomers were obtained:

[001385] ***N*-cyclopropyl-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide**

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0 75-0.86 (m, 2H), 1 24-1.36 (m, 2H), 1 56 (s, 3H), 2.03-2.07 (m, 1H), 2.39 (s, 1H), 2.68-2.69 (m, 1H), 3.72 (s, 3H), 4.78-4.86 (m, 1H), 5.50 (b, 1H), 6.47-6.50 (d, 1 H), 6 63-6.73 (d, 2H), 6.82-6.89 (m, 1H), 6 96-7 01 (m, 1H), 7.09-7 12 (m, 2H), 7 24-7.27 (m, 1H).
MS m/z: 379 (M+1)

[001386] ***N*-cyclopropyl-*N*-[(2*R*,4*S*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide**

^{1}H-NMR ($CDCl_3$, 300MHz) δ: 0.75-0.86 (m, 2H), 1 24-1 36 (m, 2H), 1 56 (s, 3H), 2.03-2.07 (m, 1H), 2.39 (s, 1H), 2 68-2.69 (m, 1H), 3.72 (s, 3H), 4.78-4 86 (m, 1H), 5.50 (b, 1H), 6.47-6.50 (d, 1 H), 6 63-6.73 (d, 2H), 6.82-6.89 (m, 1H), 6 96-7.01 (m, 1H), 7.09-7 12 (m, 2H), 7 24-7 27 (m, 1H).
MS m/z: 379 (M+1)

[001387] **4-(4-{[(2*S*,4*R*)-4-[Acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid**

[001388] 4-(4-{[(2*S*,4*R*)-4-[Acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid was synthesized according to general procedure I replacing *N*-(4-chlorophenyl)-*N*-[(2*S*,4*R*)-1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide with *N*-cyclopropyl-*N*-[1-(4-methoxybenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide and substituting 4-bromo-2,2-dimethylbutanoate for ethyl 4-bromoacetate. The rest of general procedure I was followed as indicated to afford methyl 4-(4-

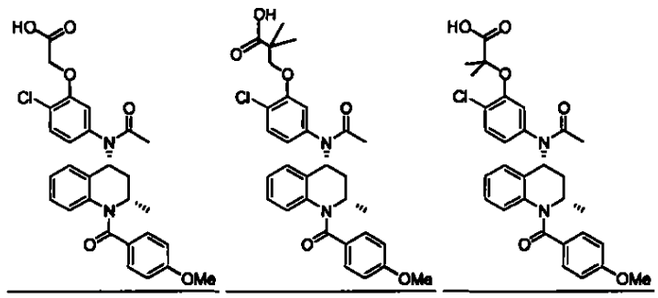
{[(2*S*,4*R*)-4-[acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoate.

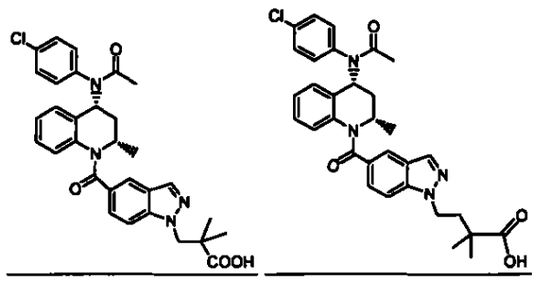
[001389] This material was dissolved in methanol/tetrahydrofuran/water (2/1/1) then sodium hydroxide (3 equivalents) was added and reaction mixture stirred at 40 °C overnight. The mixture was concentrated, the residue acidified with a 1N HCl aqueous solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, filtered and concentrated to give 4-(4-{[(2*S*,4*R*)-4-[acetyl(cyclopropyl)amino]-2-methyl-3,4-dihydroquinolin-1(2*H*)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid.

^{1}H-NMR (DMSO) δ 0.44-0.96 (br m, 4H), 1.01 (s, 6H), 1.14-1.22 (m, 1H), 1 26 (d, 3H), 1.76 (t, 2H), 2 02-2 05 (m, 1H), 2 29 (br s, 3H), 2.69-2.84 (m, 1H), 3.93 (t, 2H), 4 58-4.70 (m, 1H), 5 25-5.37 (m, 1H), 6.46 (d, 1H), 6.72 (d, 2H), 6.77-6.92 (m, 3H), 6.98 (d, 2H)

MS m/z 479 (M+1)

Table 11: Additional Exemplary Compounds Prepared According to the General Methods Detailed Above:





[001390] The Disclosed Compounds Inhibit Binding of PGD_2 to CRTH2

[001391] This radioligand membrane binding assay evaluates the ability of compounds to inhibit [^{3}H] Prostaglandin D_2 (PGD_2) binding to the cloned human CRTH2 receptor stably expressed in HEK-293 cells (expressing human CRTh2 receptor and α ?subunit or the heterotrimeric G protein 16 were prepared by Biosignal Company) using Scintillation Proximity Assay

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[001392] A binding buffer containing 50mM Tris-HCl (pH 7.5), 5mM $MgCl_2$ and 1mM EDTA was 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 [^{3}H] PGD_2 at twotimes the final assay concentration were prepared and stored on ice before adding to wells. Cold PGD_2 at twenty times the final assay concentration was prepared and stored on ice before adding to wells defining non-specific binding (NSB) corning plates #3653 were used for this assay

[001393] 10 mM stock concentrations of compounds in 100% DMSO were prepared and stored at room temperature A 10 point concentration response curve was then constructed for each compound, starting at 10 μM (final assay concentration). The compounds were prepared at 40 times final assay concenrations with nine consequent-3-fold dilutions.

[001394] 0 1 μl of each concentration of compound were added to the appropriate well of the 384 plate and 2 μl of cold PGD_2 was added into the wells defining NSB. 20 μl of [^{3}H] PGD_2 and then 20 μl of 2x of bead/membrane solution were then added to each well.

[001395] The plates were allowed to incubate at room temperature for approximately 2 hours and then counted on Packard Topcount using SPA tritium protocol for 1 minute/well.

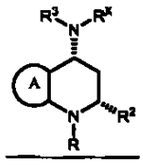
[001396] The percent inhibition of PGD_2 binding (PGD_2 used at the K_D value or lower) to the HEK-293 cell membranes was determined, the assay was always run as duplicate for n=1 for a total of n=2.

[001397] Compounds G-1 to G-34, H-1-H-22, H-24-35, H-37-H-63, H-65-H-89, H-91-H-106, H-105-H-167 have K_i <1 uM.

[001398] 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 of formula I-A:



I-A

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted monocyclic aromatic;

R is $-X_1-R^1$;

R^X is $-X_2-R^4$,

X_1 and X_2 are each independently $-S(O)_2-$, -C(O)-, or -C(O)NH-;

R^1 is:

A) an aromatic group or heteroaromatic group having 5-6 ring atoms, fused to a monocyclic non-aromatic heterocyclic ring or monocyclic aromatic or heteroaromatic ring wherein the non-aromatic heterocyclic ring, the aromatic ring, or the heteroaromatic ring are optionally substituted; or

B) an aromatic group or heteroaromatic group having 5-6 ring atoms, substituted by:

i) T^1-V-T-R^Y;

ii) T^1-V-T-M-R^Y, or

iii) V-R^9, wherein R^9 is an optionally substituted non-aromatic carbocyclic or heterocyclic group,

and wherein the aromatic or heteroaromatic group having 5-6 ring atoms optionally is further substituted by 1-2 independently selected groups represented by R^Z;

each R^Z is independently selected from halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$,

each R' is independently hydrogen, alkyl, $-C(O)OR^\circ$, $S(O)_2R^\circ$, or $-C(O)R^\circ$;

each R° is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group

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and aromatic group represented by R^o is optionally substituted with one or more independently selected groups represented by $R^{\#}$;

$R^{\#}$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$,

R^+ is –H, a C_1-C_3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine, or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated,

V is a covalent bond, -O-, -C(O)-, $-N(R')$-, -S-, -S(O)-, $-C(O)NR^5$-, $-NR^5C(O)$-, $-S(O)_2NR^5$-, $-NR^5S(O)_2$-, or $-S(O)_2$-,

T is C_{1-10} is a straight chain alkylene,

T^1 is a covalent bond, or a C_{1-10} straight chain alkylene, wherein T and T^1 together contain no more than 10 carbon atoms, and wherein T and T^1 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, O-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, alkoxy, or hydroxyl;

M is an optionally substituted group selected from monocyclic aromatic, heteroaromatic, monocyclic non-aromatic carbocyclic, or heterocyclic group,

R^Y is $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-S(O)R^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-OC(O)N(R^5)_2$, $-N(R^5)_2$, $-OR^5$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group,

provided that T is C_{2-10} when V is a covalent bond, and T is C_{2-10} when V is –O-, -S-, or $-N(R')$- and R^Y is –CN, –OH, -SH, $-N(R^5)_2$

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, $-C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or $-N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group;

R^2 is C_{1-3} alkyl,

R^3 is an optionally substituted monocyclic or bicyclic group selected from aromatic, heteroaromatic, non-aromatic carbocyclic, or non-aromatic heterocyclic; and

R^4 is optionally substituted C_{1-6}alkyl, C_{1-4}hydroxyalkyl, or optionally substituted C_{3-6}cycloalkyl,

provided that the compound of formula **I-A** is other than:

(±)-*Cis*-N-[1-(1H-indole-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-[1-(benzofuran-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid ethyl ester, (±)-*Cis*--{4-[2-Methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenoxy}-acetic acid, (±)-*Cis*-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide; (±)-*Cis*-N-[1-(4-carbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-{1-[4-(2-hydroxy-2-methyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide; (±)-*Cis*-N-[1-(4-dimethylcarbamoylmethoxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-[1-(benzo[b]thiophene-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-acetamide; (±)-*Cis*-N-[1-(benzo[b]thiophene-2-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-acetic acid, (±)-*Cis*-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-4-{4-[2-methyl-4-(phenyl-propionyl-amino)-3,4-dihydro-2H-quinoline-1-carbonyl]-phenyl}-piperidine-1-carboxylic acid ethyl ester; (±)-*Cis*-N-[2-methyl-1-(4-piperidin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-{1-[4-(1-acetyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide, (±)-*Cis*-N-{1-[4-(1-ethyl-piperidin-4-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide; (±)-*Cis*-N-{2-methyl-1-[4-(4-methyl-piperazin-1-yl)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-N-phenyl-propionamide; (±)-*Cis*-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-[2-Methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionic acid methyl ester; (±)-*Cis*-2-{4-[4-(acetyl-phenyl-amino)-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl]-phenylamino}-propionamide; (±)-*Cis*-N-[1-(2,3-dihydro-benzo[1,4]dioxine-6-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide, (±)-*Cis*-N-[1-(benzo[c]isoxazole-3-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-N-phenyl-propionamide; (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid ethyl ester; (±)-*Cis*-4-(4-{4-[(4-chloro-phenyl)-propionyl-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid,

(±)-*Cis*-N-(4-chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-propionamide, (±)-*Cis*-N-(4-chloro-phenyl)-N-{1-[4-(3-hydroxy-2,2-dimethyl-propoxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide, (±)-*Cis*-3-(4-{4-[acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-2,2-dimethyl-propionic acid methyl ester; (±)-*Cis*-N-(4-chloro-phenyl)-N-[1-(4-cyclopentyloxy-benzoyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (±)-*Cis*-N-{1-[4-(4-Acetyl-piperazin-1-yl)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-morpholin-4-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-[2-methyl-1-(6-morpholin-4-yl-pyridine-3-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S* ,4*R*)- 4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-piperidine-1-carboxylic acid ethyl ester; (2*S* ,4*R*)-N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(2-morpholin-4-yl-ethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide; (2*S* ,4*R*)-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-acetic acid; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(1H-tetrazol-5-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide; (2*S* ,4*R*)-N-{1-[4-(1-Acetyl-piperidin-4-yloxy)-benzoyl]-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl}-N-(4-chloro-phenyl)-acetamide; (2*S* ,4*R*)- N-(4-Chloro-phenyl)-N-{2-methyl-1-[4-(pyridin-4-ylmethoxy)-benzoyl]-1,2,3,4-tetrahydro-quinolin-4-yl}-acetamide, (2*S* ,4*R*)-4-(3-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenoxy)-butyric acid; (2*S*, 4*R*)-4-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-piperidine-1-carboxylic acid ethyl ester; (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-pyrrolidin-1-yl-benzoyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; (2*S*,4*R*)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-benzotriazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide, (2*S*,4*R*)- 3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-propionic acid; (2*S*,4*R*)-3-(4-{4-[Acetyl-(4-chloro-phenyl)-amino]-2-methyl-3,4-dihydro-2H-quinoline-1-carbonyl}-phenyl)-acrylic acid; N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-{(2R,4S)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-[(2S,4R)-2-methyl-1-(4-morpholin-4-ylbenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylpropanamide; N-[(2R,4S)-2-methyl-1-(4-morpholin-4-ylbenzoyl)-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylpropanamide; N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-{(2R,4S)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylpropanamide; N-{(2S,4R)-1-[4-(1-acetylpiperidin-4-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; (4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanoic acid; N-{(2S,4R)-1-[4-(2-amino-2-

oxoethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide, Ethyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)-3,6-dihydropyridine-1(2H)-carboxylate, N-[(2S,4R)-1-(1,3-benzodioxol-5-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-phenylacetamide; N-{(2S,4R)-2-methyl-1-[(3-methyl-1-benzofuran-2-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}-N-phenylacetamide, 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N-ethylbutanamide, N-(4-Chlorophenyl)-N-[(2S,4R)-1-(3-ethyl-4-fluorobenzoyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide; 4-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylbutanamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(4-oxo-4-pyrrolidin-1-ylbutoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, 4-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanamide, 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N-(methylsulfonyl)butanamide; Ethyl 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)butanoate; 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N-hydroxybutanamide, N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(3-cyanopropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[3-(1,2,4-oxadiazol-5-yl)propoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; 3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propanamide; N-{(2S,4R)-1-[4-(3-aminopropoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide, N-{(2S,4R)-1-[4-(2-amino-2-oxoethoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[2-(methylamino)-2-oxoethoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, 2-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-N,N-dimethylacetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(2-morpholin-4-yl-2-oxoethoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[2-(2-oxopyrrolidin-1-yl)ethoxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[2-(1H-imidazol-1-yl)ethoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(2-pyrrolidin-1-ylethoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-[(2S,4R)-1-(2,3-dihydro-1-benzofuran-5-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]acetamide; N-(4-Chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-pyrrolidin-1-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-morpholin-4-ylpropoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-((2S,4R)-2-methyl-1-{4-[(4-oxopentyl)oxy]benzoyl}-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; N-(4-Chlorophenyl)-N-{(2S,4R)-

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1-[4-(3-hydroxy-3-methylbutoxy)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-Chlorophenyl)-N-((2S,4R)-1-{4-[(4-hydroxy-4-methylpentyl)oxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide; N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[(1-ethylpiperidin-4-yl)methoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, N-(4-chlorophenyl)-N-((2S,4R)-1-{4-[3-(1H-imidazol-1-yl)propoxy]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, (2S,4R)-N-(4-Chloro-phenyl)-N-[2-methyl-1-(4-methyl-3,4-dihydro-2H-benzo[1,4]oxazine-7-carbonyl)-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[(4-methyl-3,4-dihydro-2H-1,4-benzoxazin-6-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(4-ethylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-{(2S,4R)-1-[4-(4-acetylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}-N-(4-chlorophenyl)acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-1-[4-(4-glycoloylpiperazin-1-yl)benzoyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-morpholin-4-ylprop-1-yn-1-yl)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)but-3-ynoic acid; N-[(2S,4R)-1-(1H-benzimidazol-2-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-(4-chlorophenyl)acetamide; N-[(2S,4R)-1-(1,3-benzothiazol-2-ylcarbonyl)-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl]-N-(4-chlorophenyl)acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[(1-methyl-1H-1,2,3-benzotriazol-5-yl)carbonyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, N-(4-chlorophenyl)-N-{(2S,4R)-1-[(1-isopropyl-1H-benzimidazol-5-yl)carbonyl]-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl}acetamide, [4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenyl)piperazin-1-yl]acetic acid, N-((2S,4R)-1-{4-[4-(2-amino-2-oxoethyl)piperazin-1-yl]benzoyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-N-(4-chlorophenyl)acetamide; 3-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)propanoic acid; 4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylbutanoic acid, {1-[(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)methyl]cyclopropyl}acetic acid, (2E)-4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)but-2-enoic acid; 3-(4-{[(2S,4R)-4-[Acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2,2-dimethylpropanoic acid; (2E)-4-(4-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}phenoxy)-2-methylbut-2-enoic acid, N-(4-chlorophenyl)-N-{(2S,4R)-2-methyl-1-[4-(3-{[(trifluoromethyl)sulfonyl]amino}propoxy)benzoyl]-1,2,3,4-tetrahydroquinolin-4-yl}acetamide; N-(4-chlorophenyl)-N-((2S,4R)-1-{[1-(2-hydroxyethyl)-2-methyl-1H-benzimidazol-5-yl]carbonyl}-2-methyl-1,2,3,4-tetrahydroquinolin-4-yl)acetamide, 5-{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}-2-methyl-1H-benzimidazol-1-yl)acetic acid, 3-(5-

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{[(2S,4R)-4-[acetyl(4-chlorophenyl)amino]-2-methyl-3,4-dihydroquinolin-1(2H)-yl]carbonyl}-1H-1,2,3-benzotriazol-1-yl)propanoic acid; (2S,4R)-N-(4-Chloro-phenyl)-N-[1-(1-isopropyl-1H-indazole-5-carbonyl)-2-methyl-1,2,3,4-tetrahydro-quinolin-4-yl]-acetamide; or (2S,4R)- N-(4-Chloro-phenyl)-N-(2-methyl-1-{4-[3-(1H-tetrazol-5-yl)-propoxy]-benzoyl}-1,2,3,4-tetrahydro-quinolin-4-yl)-acetamide.

2 The compound of claim 1, wherein:

Ring A is an optionally substituted monocyclic aromatic;

R is $-X_1-R^1$,

R^X is $-X_2-R^4$;

X_1 and X_2 are each independently $-S(O)_2-$, -C(O)-, or -C(O)NH-,

R^1 is A) an aromatic group or heteroaromatic group having 5-6 ring atoms, substituted by:

i) T^1-V-T-R^Y,

ii) T^1-V-T-M-R^Y, or

iii) V-R^9 wherein R^9 is an optionally substituted non-aromatic carbocyclic or heterocyclic group;

and wherein the aromatic or heteroaromatic group represented by R^1 optionally is further substituted by 1-2 independently selected groups represented by R^Z; or

B) an aromatic group or heteroaromatic group having 5-6 ring atoms, fused to a monocyclic non-aromatic heterocyclic ring or monocyclic aromatic ring wherein the non-aromatic heterocyclic ring or the aromatic ring are optionally substituted;

each R^Z is independently selected from halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$;

each R' is independently hydrogen, alkyl, $-C(O)OR^\circ$, $S(O)_2R^\circ$, or $-C(O)R^\circ$,

each R° is independently hydrogen or an alkyl group, non-aromatic heterocyclic group or aromatic group and the alkyl, non-aromatic heterocyclic group and aromatic group represented by R° is optionally substituted with one or more independently selected groups represented by $R^\#$,

$R^\#$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$,

R^+ is –H, a C_1-C_3 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine, or $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided

that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated;

R^Y is $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)NR^5{}_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2NR^5{}_2$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-S(O)R^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, $-CN$, $-NR^5C(O)NR^5{}_2$, $-OC(O)NR^5{}_2$, $-NR^5{}_2$, $-OR^5$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group,

V is a covalent bond, -O-, -C(O)-, $-N(R^{\cdot})-$, -S-, -S(O)-, $-C(O)NR^5-$, $-NR^5C(O)-$, $-S(O)_2NR^5-$, $-NR^5S(O)_2-$, or $-S(O)_2-$;

T is C_{1-10} is a straight chain alkylene, provided that T is C_{2-10} when V is a covalent bond, and T is C_{2-10} when V is –O-, -S-, or $-N(R^{\cdot})-$ and R^Y is –CN, –OH, -SH, $-N(R^5)_2$,

T^1 is a covalent bond, or a C_{1-10} straight chain alkylene, wherein T and T^1 together contain no more than 10 carbon atoms, and wherein T and T^1 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, amine, alkylamine, dialkylamine, or hydroxyl;

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, $-C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or $-N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group,

M is an optionally substituted monocyclic aromatic, heteroaromatic or an optionally substituted monocyclic non-aromatic carbocyclic or heterocyclic group;

R^2 is C_{1-3} alkyl;

R^3 is an optionally substituted aromatic group having 5-6 ring atoms, and

R^4 is C_{1-3} alkyl or C_{1-3} hydroxyalkyl

3. The compound of Claim 1, wherein:

Ring A is an optionally substituted phenyl group;

R^2 is methyl or ethyl,

R^3 is an optionally substituted phenyl group;

R^4 is methyl, ethyl, hydroxymethyl, hydroxyethyl, cyclopropyl, cyclobutyl, or isopropyl; and

X_1 and X_2 are -C(O)-.

4. The compound of Claim 2, wherein:

Ring A is an optionally substituted phenyl group;

R^2 is methyl or ethyl,

R^3 is an optionally substituted phenyl group,

R^4 is methyl, ethyl, hydroxymethyl, or hydroxyethyl, and

X_1 and X_2 are -C(O)-

5 The compound of Claim 3, wherein

R^1 is a phenyl ring substituted by V-T-R^Y, and optionally is further substituted by 1-2 independently selected groups represented by R^Z;

V is a covalent bond, -O- or -N(R')-; and

T 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, O-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, alkoxy, or hydroxyl.

6 The compound of Claim 4, wherein

R^1 is a phenyl ring substituted by V-T-R^Y, and optionally is further substituted by 1-2 independently selected groups represented by R^Z,

V is a covalent bond, -O- or -N(R')-, and

T 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, amine, alkylamine, dialkylamine, or hydroxyl

7 The compound of Claim 5 or 6, wherein·

R^Y is -C(O)OR^5, -C(O)N(R^5)$_2$, -NR^5C(O)R^5, -NR^5C(O)OR^5, -S(O)$_2$N(R^5)$_2$, -NR^5S(O)$_2$$R^5$, -O$R^5$, -CN, -N$R^5$C(O)N($R^5$)$_2$, -N($R^5$)$_2$, an optionally substituted non-aromatic heterocyclic group represented by R^7, or an optionally substituted heteroaryl group represented by R^8;

R^7 is an optionally substituted group selected from piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahyrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^8 is an optionally substituted group selected from furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl.

8 The compound of Claim 7, wherein:

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}, and

each R^{11} is independently selected from halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, -NO_2, -CN, -N(R')$_2$, -NR'CO_2R°, -NR'C(O)R°, -NR'NR'C(O)R°, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO_2R°, -C(O)C(O)R°, -C(O)CH_2C(O)R°, -CO_2R°,

-C(O)R°, -C(O)N(R°)$_2$, -OC(O)R°, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO$_2$N(R')$_2$, -S(O)R°, -NR'SO$_2$N(R')$_2$, -NR'SO$_2$R°, -C(=S)N(R')$_2$, -(CH$_2$)$_{1-4}$CO$_2$R°, -O(CH$_2$)$_{1-4}$CO$_2$R°, -(CH$_2$)$_{1-4}$CON(R°)$_2$, -O(CH$_2$)$_{1-4}$CON(R°)$_2$, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R°, -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R°, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R°)$_2$, -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R°)$_2$, or -C(=NH)-N(R')$_2$.

9. The compound of Claim 7, wherein

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, -NO$_2$, -CN, -N(R')$_2$, -NR'CO$_2$R°, -NR'C(O)R°, -NR'NR'C(O)R°, -N(R')C(O)N(R')$_2$, -NR'NR'C(O)N(R')$_2$, -NR'NR'CO$_2$R°, -C(O)C(O)R°, -C(O)CH$_2$C(O)R°, -CO$_2$R°, -C(O)R°, -C(O)N(R°)$_2$, -OC(O)R°, -OC(O)N(R°)$_2$, -S(O)$_2$R°, -SO$_2$N(R')$_2$, -S(O)R°, -NR'SO$_2$N(R')$_2$, -NR'SO$_2$R°, -C(=S)N(R')$_2$, or -C(=NH)-N(R')$_2$

10 The compound of claim 9, wherein:

R^Y is -C(O)OR^5, -C(O)N(R^5)$_2$, -NR^{5}C(O)R^5, -NR^{5}C(O)OR^5, -S(O)$_2$N(R^5)$_2$, -NR^{5}S(O)$_2$R^5, -NR^{5}C(O)N(R^5)$_2$, -OH, an optionally substituted non-aromatic heterocyclic group represented by R^7 or an optionally substituted heteroaryl group represented by R^8,

each R^5 is independently H or alkyl, or N(R^5)$_2$ is a nitrogen-containing non-aromatic heterocyclic group,

R^7 is an optionally substituted group selected from piperidinonyl, morpholinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl,

R^8 is an optionally substituted group selected from tetrazolyl, oxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, or imidazolyl;

V is a covalent bond, or -O-; and

T is a C_{1-5} straight chain alkylene optionally substituted at the carbon atom adjacent to R^Y with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, amine, dialkylamine, alkoxy, or hydroxyl

11. The compound of claim 9, wherein V is –O-

12 The compound of claim 9, wherein V is a covalent bond and T is a C_{1-5} straight chain alkylene substituted at the carbon atom adjacent to R^Y with alkyl, gem dialkyl, haloalkyl, spiro cycloalkyl, or an optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group

13. The compound of Claim 10, wherein

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R°$, -NR'C(O)R°, -NR'NR'C(O)R°, -$N(R')C(O)N(R')_2$, -NR'NR'C(O)$N(R')_2$, -NR'NR'$CO_2R°$, -C(O)C(O)R°, -$C(O)CH_2C(O)R°$, -$CO_2R°$, -C(O)R°, -$C(O)N(R°)_2$, -OC(O)R°, -$OC(O)N(R°)_2$, -$S(O)_2R°$, -$SO_2N(R')_2$, -S(O)R°, -$NR'SO_2N(R')_2$, -$NR'SO_2R°$, -C(=S)$N(R')_2$, and -C(=NH)-$N(R')_2$, $(CH_2)_nCO_2R°$, -$O(CH_2)_nCO_2R°$, -$(CH_2)_nOH$, -$(CH_2)_nOH$, -$(CH_2)_nC(O)N(R°)_2$, or -$O(CH_2)_nC(O)N(R°)_2$;

n is an integer from 1-4;

R^1 is a phenyl ring substituted at the *meta* or *para* positions by V-T-R^Y, and optionally is further substituted by 1-2 independently selected groups represented by R^Z;

each R^Z is independently selected from halogen, haloalkyl, -R°, -OR°, -O(haloalkyl), -$CO_2R°$, -$NR'SO_2R°$, -C(O)R°, -$C(O)N(R°)_2$, -OC(O)R°, and -$OC(O)N(R°)_2$,

each R^{11} is independently a substituent selected from halogen, haloalkyl, -R°, -OR°, -O(haloalkyl), 3,4-methylene-dioxy, 3,4-ethylene-dioxy, -$CO_2R°$, -C(O)R°, -$N(R')_2$, -$NR'SO_2R°$, -$C(O)N(R°)_2$, -OC(O)R°, and -$OC(O)N(R°)_2$;

each R' is independently H or alkyl; and

each R° is independently hydrogen, haloalkyl or an alkyl group

14 The compound of Claim 13, wherein:

R^Y is -$C(O)OR^5$, -$C(O)N(R^5)_2$, -OH, *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, *N*-substituted 2-imidazolidinyl, *N'*-substituted *N*-imidazolidinyl, *N*-substituted 4-imidazolidinyl, *N*-substituted 5-imidazolidinyl, *N*-imidazolidinonyl, 4-imidazolidinonyl, 5-imidazolidinonyl, *N*-substituted 4-imidazolidinonyl, *N*-substituted 5-imidazolidinonyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-pyrrolidin-2-onyl,, 3-pyrrolidin-2-onyl, 4-pyrrolidin-2-onyl, 5-pyrrolidin-2-onyl, *N*-substituted 3-pyrrolidin-2-only, *N*-substituted 4-pyrrolidin-2-only, *N*-substituted 5-pyrrolidin-2-onyl, *N*-pyrrolidin-3-onyl, 2-pyrrolidin-3-onyl, 4-pyrrolidin-3-onyl, 5-pyrrolidin-3-onyl, *N*-substituted 2-pyrrolidin-3-onyl *N*-substituted 4-pyrrolidin-3-onyl, *N*-substituted 5-pyrrolidin-3-onyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperidin-2-onyl, 3-piperidin-2-onyl, 4-piperidin-2-onyl, 5-piperidin-2-onyl, 6-piperidin-2-onyl, *N*-substituted 3-piperidin-2-onyl, *N*-substituted 4-piperidin-2-onyl, *N*-substituted 5-piperidin-2-onyl, *N*-substituted 6-piperidin-2-onyl, *N*-piperidin-3-onyl, 2-piperidin-3-onyl, 4-piperidin-3-onyl, 5-piperidin-3-onyl, 6-piperidin-3-onyl, *N*-substituted 2-piperidin-3-onyl, *N*-substituted 4-piperidin-3-onyl, *N*-substituted 5-piperidin-3-onyl, *N*-substituted 6-piperidin-3-onyl, *N*-piperidin-4-onyl, 2-piperidin-4-onyl, 3-piperidin-4-onyl, 5-piperidin-4-onyl, 6-piperidin-4-onyl, *N*-substituted 2-piperidin-4-onyl, *N*-substituted 3-piperidin-4-onyl, *N*-substituted 5-piperidin-4-onyl, *N*-substituted 6-piperidin-4-onyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-

substituted 2-piperazinyl, furanyl, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, 4-(1,2,3)oxadiazolyl, 5-(1,2,3)oxadiazolyl, 3-(1,2,4)oxadiazolyl, 5-(1,2,4)oxadiazolyl, 3-(1,2,5)oxadiazolyl, 4-(1,2,5)oxadiazolyl, 2-(1,3,4)oxadiazolyl, 5-(1,3,4)oxadiazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, *N*-substituted 2-pyrrolyl, *N*-substituted 3-pyrrolyl, *N*-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, *N*-substituted 3-pyrazolyl, *N*-substituted 4-pyrazolyl, *N*-substituted 5-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl,

V is -O-; and

T is a C_{1-3} straight chain alkylene substituted at the carbon adjacent to R^Y with fluoro, methyl, gem dimethyl, gem difluoro, fluoromethyl, spiro cyclopropyl, spiro cyclobutyl, optionally *N*-substituted spiro azetidinyl, optionally *N*- substituted spiro aziridinyl, optionally *N*- substituted spiro pyrrolidinyl, optionally *N*- substituted spiro piperidinyl, amine, methylamine, dimethylamine, or hydroxyl

15 The compound of Claim 14, wherein.

each R^Z is independently selected from halogen, haloalkyl, -R°, -OR°, and -O(haloalkyl);

R^3 is a phenyl group optionally substituted at the *meta* or *para* position by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently a substituent selected from halogen, haloalkyl, -R°, -OR°, -$N(R')_2$, -$NR'SO_2R^\circ$ and -O(haloalkyl).

16. The compound of Claim 15, wherein.

R^Y is -$C(O)OR^5$, -$C(O)N(R^5)_2$, -OH, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl, and

R^5 is –H, methyl, or ethyl

17. The compound of Claim 16, wherein

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, R°, -OR°, -CO_2R°, -$C(O)R^\circ$, -$C(O)N(R^\circ)_2$, -$OC(O)R^\circ$, -$(CH_2)_nCO_2R^\circ$, -$O(CH_2)_nCO_2R^\circ$, -$NHSO_2R^\circ$, -$NHCOR^\circ$, -CN, -$NHC(O)N(R^\circ)_2$, -$(CH_2)_nOH$, -$O(CH_2)_nOH$, -$(CH_2)_nC(O)N(R^\circ)_2$, or -$O(CH_2)_nC(O)N(R^\circ)_2$;

R^1 is a phenyl ring substituted at the *para* position by V-T-R^Y and optionally is further substituted at the *meta* position by R^Z;

R^Z is chloride, fluoride, bromide, -OR°, or -R°;

R^3 is a phenyl group optionally substituted at the *para* position by R^{11},

R^{11} is chloride, fluoride, bromide, -OR°, -$N(R')_2$, -$NR'SO_2R^\circ$ or -R°;

R' is independently hydrogen or a C_{1-3} alkyl group; and

R° is independently hydrogen, haloalkyl, or a C_{1-3} alkyl group.

18 The compound of Claim 3, wherein

R^1 is a phenyl ring substituted by V-R^9 wherein R^9 is an optionally substituted non-aromatic carbocyclic or heterocyclic group and optionally is further substituted by 1-2 independently selected groups represented by R^Z

19 The compound of Claim 18, wherein

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, R°, $-OR^{\circ}$, -O(haloalkyl), $-SR^{\circ}$, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^{\circ}$, $-NR'C(O)R^{\circ}$, $-NR'NR'C(O)R^{\circ}$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^{\circ}$, $-C(O)C(O)R^{\circ}$, $-C(O)CH_2C(O)R^{\circ}$, $-CO_2R^{\circ}$, $-C(O)R^{\circ}$, $-C(O)N(R^{\circ})_2$, $-OC(O)R^{\circ}$, $-OC(O)N(R^{\circ})_2$, $-S(O)_2R^{\circ}$, $-SO_2N(R')_2$, $-S(O)R^{\circ}$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^{\circ}$, $-C(=S)N(R')_2$, $-(CH_2)_{1-4}CO_2R^{\circ}$, $-O(CH_2)_{1-4}CO_2R^{\circ}$, $-(CH_2)_{1-4}CON(R^{\circ})_2$, $-O(CH_2)_{1-4}CON(R^{\circ})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{\circ}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{\circ}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{\circ})_2$, $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{\circ})_2$, or $-C(=NH)-N(R')_2$

20. The compound of Claim 18, wherein

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, R°, $-OR^{\circ}$, -O(haloalkyl), $-SR^{\circ}$, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^{\circ}$, $-NR'C(O)R^{\circ}$, $-NR'NR'C(O)R^{\circ}$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^{\circ}$, $-C(O)C(O)R^{\circ}$, $-C(O)CH_2C(O)R^{\circ}$, $-CO_2R^{\circ}$, $-C(O)R^{\circ}$, $-C(O)N(R^{\circ})_2$, $-OC(O)R^{\circ}$, $-OC(O)N(R^{\circ})_2$, $-S(O)_2R^{\circ}$, $-SO_2N(R')_2$, $-S(O)R^{\circ}$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^{\circ}$, $-C(=S)N(R')_2$, or $-C(=NH)-N(R')_2$.

21 The compound of Claim 19, wherein

R^9 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, 1,2,5-thiadiazolidine S, S-dioxide, or piperidinyl

22 The compound of Claim 20, wherein

R^9 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

23 The compound of Claim 18, wherein.

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R°$, -$NR'C(O)R°$, -$NR'NR'C(O)R°$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R°$, -$C(O)C(O)R°$, -$C(O)CH_2C(O)R°$, -$CO_2R°$, -$C(O)R°$, -$C(O)N(R°)_2$, -$OC(O)R°$, -$OC(O)N(R°)_2$, -$S(O)_2R°$, -$SO_2N(R')_2$, -$S(O)R°$, -$NR'SO_2N(R')_2$, -$NR'SO_2R°$, -$C(=S)N(R')_2$, and -$C(=NH)$-$N(R')_2$, $(CH_2)_nCO_2R°$, -$O(CH_2)_nCO_2R°$, -$(CH_2)_nOH$, -$(CH_2)_nOH$, -$(CH2)_nC(O)N(R°)_2$, or -$O(CH_2)_nC(O)N(R°)_2$;

n is an integer from 1-4;

R^1 is a phenyl ring, substituted at the *meta* or *para* position by a non-aromatic carbocyclic or heterocyclic group represented by V-R^9, and optionally is further substituted by 1-2 independently selected groups represented by R^Z,

each R^Z is independently selected from halogen, haloalkyl, -R°, -OR°, -O(haloalkyl), -$CO_2R°$, -$NR'SO_2R°$, -$C(O)R°$, -$C(O)N(R°)_2$, -$OC(O)R°$, and -$OC(O)N(R°)_2$,

V is a covalent bond or –O-;

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, -R°, -OR°, -O(haloalkyl), 3,4-methylene-dioxy, 3,4-ethylene-dioxy, -$CO_2R°$, -$N(R')_2$, -$C(O)R°$, -$C(O)N(R°)_2$, -$NR'SO_2R°$,-$OC(O)R°$, and -$OC(O)N(R°)_2$;

each R' is independently H or alkyl; and

each R° is independently hydrogen, haloalkyl or an alkyl group.

24. The compound of Claim 23, wherein

R^9 is oxazolidinyl, thiazolidinyl, tetrahydrofuranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl, each optionally substituted by alkyl, halide, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$, -$C(O)NR^{12}_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR°$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR°$ or -$N(R^{12})_2$,

n is an integer from 1-4, and

each R^{12} is independently -H, alkyl, haloalkyl, or hydroxyalkyl

25 The compound of Claim 24, wherein.

each R^Z is independently selected from halogen, haloalkyl, -R°, -OR°, and -O(haloalkyl);

R^3 is a phenyl group optionally substituted at the *meta* or *para* position by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently a substituent selected from halogen, haloalkyl, -R°, -OR°, -N(R')$_2$, -NR'SO_2R° and -O(haloalkyl).

26 The compound of Claim 25, wherein

R^9 is *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-substituted 2-piperazinyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, or -C(O)N(R^{12})$_2$, and wherein the *N*-substituents are alkyl, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -(CH_2)$_n$$CO_2$H, -($CH_2$)$_n$C(O)NR°, -($CH_2$)$_n$C($CH_3$)$_2$$CO_2$H, -($CH_2$)$_n$C($CH_3$)$_2$C(O)NR° or -C(O)N($R^{12}$)$_2$; and

n is an integer from 1-4.

27. The compound of Claim 26, wherein.

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, R°, -OR°, -CO_2R°, -C(O)R°, -C(O)N(R°)$_2$, -OC(O)R°, -(CH_2)$_n$$CO_2$R°, -O($CH_2$)$_n$$CO_2$R°, -$NHSO_2$R°, -NHCOR°, -CN, -NHC(O)N(R°)$_2$, -(CH_2)$_n$OH, -O(CH_2)$_n$OH, -(CH_2)$_n$C(O)N(R°)$_2$, or -O(CH_2)$_n$C(O)N(R°)$_2$;

n is an integer from 1-4;

R^1 is a phenyl ring substituted at the *para* position by a non-aromatic carbocyclic or heterocyclic group represented by V-R^9, and optionally is further substituted at the *meta* position by R^Z,

R^Z is chloride, fluoride, bromide, -OR°, or -R°;

R^3 is a phenyl group optionally substituted at the *para* position by R^{11},

R^{11} is chloride, fluoride, bromide, -OR°, -N(R')$_2$, -NR'SO_2R° or -R°;

R' is independently hydrogen or a C_{1-3} alkyl group, and

R° is independently hydrogen, haloalkyl or a C_{1-3} alkyl group.

28. The compound of Claim 27, wherein

R^9 is *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, or *N*-substituted 2-piperazinyl, and is optionally substituted by at any substitutable carbon

atom by chloride, fluoride, bromide, methyl, ethyl, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-C(O)R^{12}$ or $C(O)NH_2$, and wherein the *N*-substituents are methyl, ethyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-(CH_2)_nCO_2H$, $-(CH_2)_nC(O)NR^\circ$, $-(CH_2)_nC(CH_3)_2CO_2H$, $-(CH_2)_nC(CH_3)_2C(O)NR^\circ$, or $-C(O)NH_2$,

n is an integer from 1-4; and

each R^{12} is independently -H, methyl, or ethyl.

29. The compound of Claim 3, wherein:

R^1 is a phenyl group fused to an optionally substituted monocyclic non-aromatic heterocyclic ring represented by R^{10}, or a monocyclic aromatic ring represented by R^{13}

30 The compound of Claim 29, wherein:

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R^\circ$, $-O(CH_2)_nCO_2R^\circ$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)N(R^\circ)_2$, $-O(CH_2)_nC(O)N(R^\circ)_2$,

n is an integer from 1-4;

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$, $-(CH_2)_{1-4}CO_2R^\circ$, $-O(CH_2)_{1-4}CO_2R^\circ$, $-(CH_2)_{1-4}CON(R^\circ)_2$, $-O(CH_2)_{1-4}CON(R^\circ)_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^\circ$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^\circ$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^\circ)_2$, $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^\circ)_2$, or $-C(=NH)-N(R')_2$.

31. The compound of Claim 29, wherein:

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, haloalkyl, R°, $-OR^\circ$, -O(haloalkyl), $-SR^\circ$, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, -

$NR'SO_2R^o$, -C(=S)N(R')$_2$, and -C(=NH)-N(R')$_2$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)N(R^o)_2$, $-O(CH_2)_nC(O)N(R^o)_2$;

n is an integer from 1-4,

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}, and

each R^{11} is independently selected from halogen, haloalkyl, $-R^o$, $-OR^o$, -O(haloalkyl), $-SR^o$, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, -CN, -N(R')$_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, -C(=S)N(R')$_2$, and -C(=NH)-N(R')$_2$.

32 The compound of Claim 31, wherein

R^{10} is oxazolidinyl, oxazolidinonyl, dioxolanyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrothienyl, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dithiolanyl, pyrrolidinyl, piperazinyl, piperidinyl, piperidinyl, tetrahydrothienyl S,S dioxide, thiomorpholinyl S,S dioxide, or tetrahydrothiopyranyl S,S dioxide, each of which are optionally substituted, and

R^{13} is pyrazolyl, triazolyl, imidazolyl, furanyl, pyrrolyl, thienyl, cyclopentadienyl, or thienyl S,S dioxide, each of which are optionally substituted.

33. The compound of Claim 32, wherein.

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11};

each R^{11} is independently a substituent selected from halogen, haloalkyl, $-R^o$, $-OR^o$, -O(haloalkyl), 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-CO_2R^o$, $-C(O)R^o$, -N(R')$_2$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-NR'SO_2R^o$ and $-OC(O)N(R^o)_2$,

each R' is independently H or alkyl; and

each R^o is independently hydrogen, haloalkyl or an alkyl group.

34. The compound of Claim 33, wherein

R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_0$-

$_3(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}-$, $-C(O)N(R^{12})_2$,

R^{13} is triazolyl, imidazolyl, furanyl, pyrrolyl, thienyl, each of which is optionally substituted at any substitutable ring carbon atom with alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)OR^{12}-$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-N(R^{12})_2$, $-(CH_2)_{1-4}CO_2R^{12}$, $-O(CH_2)_{1-4}CO_2R^{12}$, $-(CH_2)_{1-4}CON(R^{12})_2$, $-O(CH_2)_{1-4}CON(R^{12})_2$, $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$; and

each R^{12} is independently H, alkyl, haloalkyl, or hydroxyalkyl.

35 The compound of Claim 34, wherein:

R^3 is a phenyl group optionally substituted at the *meta* or *para* position by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently a substituent selected from halogen, haloalkyl, $-R^o$, $-OR^o$, $-N(R')_2$, $-NR'SO_2R^o$ and -O(haloalkyl).

36 The compound of Claim 35, wherein

R^{10} is piperidinyl, piperazinyl, dioxolanyl, tetrahydrofuranyl, or morpholinyl, each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, or $-C(O)N(R^{12})_2$, each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, or $-C(O)N(R^{12})_2$; and

R^{13} is triazolyl, imidazolyl, or pyrrolyl each optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, or $-C(O)N(R^{12})_2$, and each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, $C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$

37 The compound of Claim 36, wherein:

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, R^o, $-OR^o$, $-CO_2R^o$, $-C(O)R^o$, $-CN$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-NHSO_2R^o$, $-NHCOR^o$, $-NHC(O)NR^o{}_2$, $-(CH_2)_nOH$, $-O(CH_2)_nOH$, $-(CH_2)_nC(O)N(R^o)_2$, or $-O(CH_2)_nC(O)N(R^o)_2$;

n is an integer from 1-4;

R^3 is a phenyl group optionally substituted at the *para* position by R^{11};

R^{11} is chloride, fluoride, bromide, -OR°, -$N(R')_2$, -$NR'SO_2R^{\circ}$ or -R°;

R' is independently hydrogen or a C_{1-3} alkyl group; and

R° is independently hydrogen, haloalkyl, or a C_{1-3} alkyl group

38 The compound of Claim 37, wherein:

R^{10} is piperidinyl, piperazinyl, or morpholinyl and is optionally *N*-substituted by methyl, ethyl, isopropyl, -$C(O)OR^{12}$, $C(O)NH_2$ or -$C(O)R^{12}$;

R^{13} is triazolyl and is optionally *N*-substituted by methyl, ethyl, -$C(O)OR^{12}$, $C(O)NH_2$ or -$C(O)R^{12}$; and

each R^{12} is independently -H, methyl, or ethyl

39. The compound of Claim 29, wherein

R^{10} is tetrahydrofuranyl, tetrahydropyranyl, morpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$, -$N(R^{12})_2$, -$(CH_2)_{1-4}CO_2R^{12}$, -$O(CH_2)_{1-4}CO_2R^{12}$, -$(CH_2)_{1-4}CON(R^{12})_2$, -$O(CH_2)_{1-4}CON(R^{12})_2$, -$(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, -$O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, -$(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or -$O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, and each of which is optionally substituted at any substitutable ring nitrogen atom with alkyl, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$;

each R^{12} is independently H, alkyl, haloalkyl, or hydroxyalkyl;

R^{13} is pyrazolyl, triazolyl, imidazolyl, or pyrrolyl, each of which is *N*-substituted with T^2-R^{Y1} and optionally further substituted at any one or more ring carbon atoms alkyl, halide, haloalkyl, hydroxyalkyl, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$, -$N(R^{12})_2$, -$(CH_2)_{1-4}CO_2R^{12}$, -$O(CH_2)_{1-4}CO_2R^{12}$, -$(CH_2)_{1-4}CON(R^{12})_2$, -$O(CH_2)_{1-4}CON(R^{12})_2$, -$(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, -$O(CH_2)_{0-3}(C(CH_3)_2)CO_2R^{12}$, -$(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$, or -$O(CH_2)_{0-3}(C(CH_3)_2)CON(R^{12})_2$,

T^2 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, O-containing spiro non-aromatic heterocyclic group, amine, alkylamine, dialkylamine, or hydroxyl;

R^{Y1} is -$C(O)OR^5$, -$C(O)N(R^5)_2$, -$NR^5C(O)R^5$, -$NR^5C(O)OR^5$, -$S(O)_2N(R^5)_2$, -$NR^5S(O)_2R^5$, -OR^5, -CN, -$NR^5C(O)N(R^5)_2$, -$N(R^5)_2$, an optionally substituted non-aromatic heterocyclic group represented by R^7, or an optionally substituted heteroaryl group represented by R^8;

R^7 is an optionally substituted piperidinonyl, oxazolidinyl, oxazolidinonyl, thiazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, thiazolidinyl, tetrahyrothiophene, morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, dioxanyl, dioxolanyl, dithiolanyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl; and

R^8 is an optionally substituted furanyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, pyrimidyl, thiazolyl, thienyl, or imidazolyl

40. The compound of Claim 39, wherein:

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R°$, -NR'C(O)R°, -NR'NR'C(O)R°, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R°$, -C(O)C(O)R°, $-C(O)CH_2C(O)R°$, $-CO_2R°$, -C(O)R°, $-C(O)N(R°)_2$, -OC(O)R°, $-OC(O)N(R°)_2$, $-S(O)_2R°$, $-SO_2N(R')_2$, -S(O)R°, $-NR'SO_2N(R')_2$, $-NR'SO_2R°$, $-C(=S)N(R')_2$, and $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R°$, $-O(CH_2)_nCO_2R°$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)N(R°)_2$, or $-O(CH_2)_nC(O)N(R°)_2$;

n is an integer from 1-4;

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11}; and

each R^{11} is independently selected from halogen, haloalkyl, R°, -OR°, -O(haloalkyl), -SR°, 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R°$, -NR'C(O)R°, -NR'NR'C(O)R°, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R°$, -C(O)C(O)R°, $-C(O)CH_2C(O)R°$, $-CO_2R°$, -C(O)R°, $-C(O)N(R°)_2$, -OC(O)R°, $-OC(O)N(R°)_2$, $-S(O)_2R°$, $-SO_2N(R')_2$, -S(O)R°, $-NR'SO_2N(R')_2$, $-NR'SO_2R°$, $-C(=S)N(R')_2$, $-(CH_2)_{1-4}CO_2R°$, $-O(CH_2)_{1-4}CO_2R°$, $-(CH_2)_{1-4}CON(R°)_2$, $-O(CH_2)_{1-4}CON(R°)_2$ $-(CH_2)_{0-3}(C(CH_3)_2)CO_2R°$, $-O(CH_2)_{0-3}(C(CH_3)_2)CO_2R°$, $-(CH_2)_{0-3}(C(CH_3)_2)CON(R°)_2$, $-O(CH_2)_{0-3}(C(CH_3)_2)CON(R°)_2$, or $-C(=NH)-N(R')_2$.

41. The compound of Claim 40, wherein:

R^3 is a phenyl group optionally substituted by one or more independently selected groups represented by R^{11};

each R^{11} is independently a substituent selected from halogen, haloalkyl, -R°, -OR°, -O(haloalkyl), 3,4-methylene-dioxy, 3,4-ethylene-dioxy, $-CO_2R°$, -C(O)R°, $-N(R')_2$, $-C(O)N(R°)_2$, -OC(O)R°, $-NR'SO_2R°$ and $-OC(O)N(R°)_2$,

each R' is independently H or alkyl; and

each R° is independently hydrogen, haloalkyl or an alkyl group.

42. The compound of Claim 41, wherein:

R^{Y1} is -C(O)OR^5, -C(O)N(R^5)$_2$, -NR^{5}C(O)R^5, -NR^{5}C(O)OR^5, -S(O)$_2$N(R^5)$_2$, -NR^{5}S(O)$_2$R^5, -NR^{5}C(O)N(R^5)$_2$, -OH, an optionally substituted non-aromatic heterocyclic group represented by R^7 or an optionally substituted heteroaryl group represented by R^8;

each R^5 is independently H or alkyl, or N(R^5)$_2$ is a nitrogen-containing non-aromatic heterocyclic group,

R^7 is piperidinonyl, morpholinyl, imidazolidinonyl, pyrrolidinyl, pyrrolidinonyl, piperazinyl, or piperidinyl,

R^8 is tetrazolyl, oxazolyl, oxadiazolyl, pyrrolyl, pyrazolyl, pyridinyl, or imidazolyl,

T^2 is a C_{1-5} straight chain alkylene optionally substituted at the carbon atom adjacent to R^Y with halide, alkyl, gem dialkyl, gem dihalo, haloalkyl, spiro cycloalkyl, optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group, amine, dialkylamine, or hydroxyl;

the group represented by R^{10} is morpholinyl, thiomorpholinyl, imidazolidinyl, imidazolidinonyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon ring atom with alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, -C(O)OR^{12}-, -C(O)N(R^{12})$_2$, -NR^{12}C(O)R^{12}, -NR^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, -S(O)$_2$COR^{12}, -S(O)$_2$N(R^{12})$_2$, -S(O)$_2$OR^{12}, -S(O)OR^{12}, -OR^{12}, -SR^{12}, -CN, -NR^{12}C(O)N(R^{12})$_2$, -OC(O)N(R^{12})$_2$, -N(R^{12})$_2$, -(CH$_2$)$_{1-4}$CO$_2$R^{12}, -O(CH$_2$)$_{1-4}$CO$_2$R^{12}, -(CH$_2$)$_{1-4}$CON(R^{12})$_2$, -O(CH$_2$)$_{1-4}$CON(R^{12})$_2$, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R^{12}, -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R^{12}, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R^{12})$_2$, or -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R^{12})$_2$, and

the group represented by R^{13} is triazolyl, imidazolyl, or pyrrolyl, each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable ring carbon atom with alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, -C(O)OR^{12}-, -C(O)N(R^{12})$_2$, -NR^{12}C(O)R^{12}, -NR^{12}C(O)OR^{12}, -S(O)$_2$R^{12}, -S(O)$_2$COR^{12}, -S(O)$_2$N(R^{12})$_2$, -S(O)$_2$OR^{12}, -S(O)OR^{12}, -OR^{12}, -SR^{12}, -CN, -NR^{12}C(O)N(R^{12})$_2$, -OC(O)N(R^{12})$_2$, -N(R^{12})$_2$, -(CH$_2$)$_{1-4}$CO$_2$R^{12}, -O(CH$_2$)$_{1-4}$CO$_2$R^{12}, -(CH$_2$)$_{1-4}$CON(R^{12})$_2$, -O(CH$_2$)$_{1-4}$CON(R^{12})$_2$, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R^{12}, -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CO$_2$R^{12}, -(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R^{12})$_2$, or -O(CH$_2$)$_{0-3}$(C(CH$_3$)$_2$)CON(R^{12})$_2$.

43. The compound of Claim 42, wherein:

R^3 is a phenyl group optionally substituted at the *meta* or *para* position by one or more independently selected groups represented by R^{11}, and

each R^{11} is independently a substituent selected from halogen, haloalkyl, -R°, -OR°, -N(R')$_2$, -NR'SO$_2$R° and -O(haloalkyl).

44. The compound of Claim 43 wherein.

R^{Y1} is -C(O)OR^5, -C(O)N(R^5)$_2$, -OH, *N*-morpholinyl, 2-morpholinyl, 3-morpholinyl, *N*-substituted 2-morpholinyl, *N*-substituted 3-morpholinyl, *N*-imidazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 5-imidazolidinyl, *N*-substituted 2-imidazolidinyl, *N'*-substituted *N*-imidazolidinyl, *N*-

substituted 4-imidazolidinyl, *N*-substituted 5-imidazolidinyl, *N*-imidazolidinonyl, 4-imidazolidinonyl, 5-imidazolidinonyl, *N*-substituted 4-imidazolidinonyl, *N*-substituted 5-imidazolidinonyl, *N*-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, *N*-substituted 2-pyrrolidinyl, *N*-substituted 3-pyrrolidinyl, *N*-pyrrolidin-2-onyl,, 3-pyrrolidin-2-onyl, 4-pyrrolidin-2-onyl, 5-pyrrolidin-2-onyl, *N*-substituted 3-pyrrolidin-2-only, *N*-substituted 4-pyrrolidin-2-only, *N*-substituted 5-pyrrolidin-2-onyl, *N*-pyrrolidin-3-onyl, 2-pyrrolidin-3-onyl, 4-pyrrolidin-3-onyl, 5-pyrrolidin-3-onyl, *N*-substituted 2-pyrrolidin-3-onyl *N*-substituted 4-pyrrolidin-3-onyl, *N*-substituted 5-pyrrolidin-3-onyl, *N*-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, *N*-substituted 2-piperidinyl, *N*-substituted 3-piperidinyl, *N*-substituted 4-piperidinyl, *N*-piperidin-2-onyl, 3-piperidin-2-onyl, 4-piperidin-2-onyl, 5-piperidin-2-onyl, 6-piperidin-2-onyl, *N*-substituted 3-piperidin-2-onyl, *N*-substituted 4-piperidin-2-onyl, *N*-substituted 5-piperidin-2-onyl, *N*-substituted 6-piperidin-2-onyl, *N*-piperidin-3-onyl, 2-piperidin-3-onyl, 4-piperidin-3-onyl, 5-piperidin-3-onyl, 6-piperidin-3-onyl, *N*-substituted 2-piperidin-3-onyl, *N*-substituted 4-piperidin-3-onyl, *N*-substituted 5-piperidin-3-onyl, *N*-substituted 6-piperidin-3-onyl, *N*-piperidin-4-onyl, 2-piperidin-4-onyl, 3-piperidin-4-onyl, 5-piperidin-4-onyl, 6-piperidin-4-onyl, *N*-substituted 2-piperidin-4-onyl, *N*-substituted 3-piperidin-4-onyl, *N*-substituted 5-piperidin-4-onyl, *N*-substituted 6-piperidin-4-onyl, *N*-piperazinyl, 2-piperazinyl, *N'*-substituted *N*-piperazinyl, *N*-substituted 2-piperazinyl, furanyl, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, 4-(1,2,3)oxadiazolyl, 5-(1,2,3)oxadiazolyl, 3-(1,2,4)oxadiazolyl, 5-(1,2,4)oxadiazolyl, 3-(1,2,5)oxadiazolyl, 4-(1,2,5)oxadiazolyl, 2-(1,3,4)oxadiazolyl, 5-(1,3,4)oxadiazolyl, *N*-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, *N*-substituted 2-pyrrolyl, *N*-substituted 3-pyrrolyl, *N*-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl, *N*-substituted 3-pyrazolyl, *N*-substituted 4-pyrazolyl, *N*-substituted 5-pyrazolyl, 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl;

T^2 is a C_{1-4} straight chain alkylene substituted with fluoro, methyl, gem dimethyl, gem difluoro fluoromethyl, spiro cyclopropyl, spiro cyclobutyl, optionally *N*-substituted spiro azetidinyl, optionally *N*-substituted spiro azirindinyl, optionally *N*-substituted spiro pyrrolidinyl, optionally *N*-substituted spiro piperidinyl, amine, methylamine, dimethylamine, or hydroxyl,

the group represented by R^{10} is morpholinyl, pyrrolidinyl, piperazinyl, or piperidinyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}; and

the group represented by R^{13} is imidazolyl, or pyrrolyl each of which is *N*-substituted with T^2-R^{Y1} and further optionally substituted at any substitutable carbon atom by alkyl, halide, haloalkyl, hydroxyalkyl, -C(O)OR^{12}, -C(O)R^{12}, -OC(O)R^{12}, or -C(O)N$(R^{12})_2$, and each optionally substituted at any substitutable nitrogen atom by alkyl, haloalkyl, hydroxyalkyl, C(O)OR^{12}, -C(O)R^{12}, -R^{12}C(O)OR^{12}, -$S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, -C(O)N$(R^{12})_2$.

45 The compound of Claim 44, wherein

Ring A is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halogen, R°, $-OR^{\circ}$, $-CO_2R^{\circ}$, $-C(O)R^{\circ}$, -CN, $-C(O)N(R^{\circ})_2$, $-OC(O)R^{\circ}$, $-(CH_2)_nCO_2R^{\circ}$, $-O(CH_2)_nCO_2R^{\circ}$, $-NHSO_2R^{\circ}$, $-NHCOR^{\circ}$, $-NHC(O)N(R^{\circ})_2$, $-(CH_2)_nOH$, $O(CH_2)_nOH$, $-(CH_2)_nC(O)N(R^{\circ})_2$, or $-O(CH_2)_nC(O)N(R^{\circ})_2$,

n is an integer from 1-4,

R^3 is a phenyl group optionally substituted at the *para* position by R^{11},

R^{11} is chloride, fluoride, bromide, $-OR^{\circ}$, $-N(R')_2$, $-NR'SO_2R^{\circ}$ or $-R^{\circ}$;

R' is independently hydrogen or a C_{1-3} alkyl group; and

R° is independently hydrogen, haloalkyl, or a C_{1-3} alkyl group

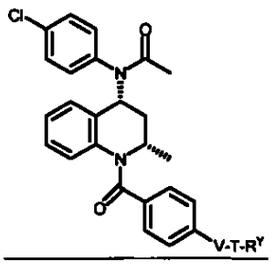
46. The compound of Claim 45, wherein:

R^{Y1} is $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-tetrazolyl, 5-tetrazolyl, *N*-substituted 5-tetrazolyl, *N*-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl; *N*-substituted 2-imidazolyl, *N*-substituted 4-imidazolyl, or *N*-substituted 5-imidazolyl;

the group represented by R^{10} is piperidinyl, piperazinyl, or morpholinyl, *N*-substituted with T^2-R^{Y1} and further optionally substituted at the carbon alpha to the nitrogen atom with methyl or gem dimethyl, and

the group represented by R^{13} is triazolyl *N*-substituted with T^2-R^{Y1} and further optionally substituted at the carbon alpha to the nitrogen atom with methyl.

47. A compound represented by the following structural formula



or a pharmaceutically acceptable salt thereof, wherein:

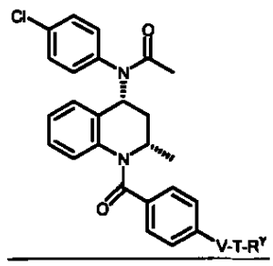
V is a covalent bond or –O-,

T is an unsubstituted straight chained C_{1-10} alkylene,

R^Y is R^Y is $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-OC(O)N(R^5)_2$, $-N(R^5)_2$, $-OR^5$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group;

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, $-C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or $-N(R^5)_2$ is a nitrogen-containing non-aromatic heterocyclic group.

48 A compound represented by the following structural formula



or a pharmaceutically acceptable salt thereof, wherein

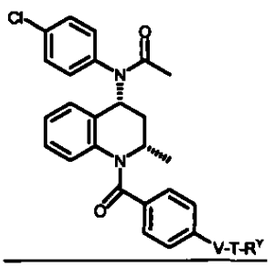
V is a covalent bond or –O-;

T is an straight chained C_{1-10} alkylene substituted with alkyl, gem dialkyl, haloalkyl, spiro cycloalkyl, or an optionally *N*-substituted nitrogen containing spiro non-aromatic heterocyclic group,

R^Y is R^Y is $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-OC(O)N(R^5)_2$, $-N(R^5)_2$, $-OR^5$, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group; and

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, $-C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, benzyl, pyrrolidinyl, morpholinyl, or $-N(R^5)_2$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group

49. A compound represented by the following structural formula:



or a pharmaceutically acceptable salt thereof, wherein:

V is–O-,

T is an straight chained C_{1-10} alkylene optionally 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, amine, alkylamine, dialkylamine, or hydroxyl;

R^Y is -C(O)OR^5, -C(O)R^5, -OC(O)R^5, -C(O)N$(R^5)_2$, -NR^5C(O)R^5, -NR^5C(O)OR^5, -S$(O)_2R^5$, -S$(O)_2$COR^5, -S$(O)_2$N$(R^5)_2$, -NR^5S$(O)_2$, -NR^5S$(O)_2R^5$, S$(O)_2OR^5$, -S(O)OR^5, -SR^5, -C(O)NR^5S$(O)_2R^5$, -CN, -NR^5C(O)N$(R^5)_2$, -OC(O)N$(R^5)_2$, -N$(R^5)_2$, -OR^5, an optionally substituted non-aromatic heterocyclic group or an optionally substituted heteroaryl group; and

each R^5 is independently -H, alkyl, haloalkyl, hydroxyalkyl, carboxyalkyl, -C(O)O$CH_2C_6H_5$, S$(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, C(O)NH_2, benzyl, pyrrolidinyl, morpholinyl, or -N$(R^5)_2$ is an optionally substituted nitrogen-containing non-aromatic heterocyclic group

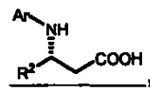
50 A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and a compound of claim 1, 2, 47, 48, or 49.

51 A method of treating an inflammatory disease, disorder or symptom in a subject in need of treatment, comprising the step of administering to the subject an effective amount of a compound represented by the compound of Claim 1, 2, 47, 48, or 49

52 The method of Claim 51 where the inflammatory disease, disorder or symptom is allergic rhinitis, rheumatoid arthritis, chronic obstructive pulmonary disorder, atopic dermatitis, or allergic asthma.

53. The method of Claim 51 where the inflammatory disease, disorder or symptom is allergic rhinitis or allergic asthma.

54. A method of preparing a compound represented by the following structural formula:





comprising the step of reacting Ar-NH_2 with ;

wherein Ar is an optionally substituted monocyclic aromatic group and R^2 is C_1-C_3 alkyl.

55 The method of Claim 54 wherein Ar is an optionally substituted phenyl group and R^2 is methyl or ethyl.

56 The method of Claim 55 wherein Ar is a phenyl group optionally substituted *meta* or *para* with R^{14};

each R^{14} is independently halo, cyano, R^o, $-OR^{30}$, $-CO_2R^{31}$, $-C(O)R^o$, $-C(O)N(R^x)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)NR^x_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)NR^o_2$, $O(CH_2)_nC(O)N(R^x)_2$;

n is an integer from 1-4,

R^o is independently hydrogen, C_1-C_3 haloalkyl or a C_{1-3} alkyl group;

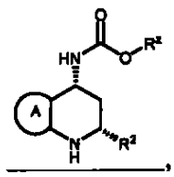
one R^x is –H or C_1-C_3 alkyl and the other is an amine protecting group;

R^{30} is an alcohol protecting group; and

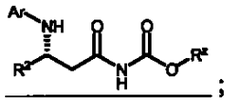
R^{31} is a carboxylic acid protecting group

57 The method of Claim 56 wherein Ar is a phenyl group.

58 A method of preparing a product compound represented by the following structural formula:



from a starting compound represented by the following structural formula



;

said method comprising the step of reducing the amide carbonyl of the starting compound to form an intermediate and then cyclizing the intermediate to form the product compound, wherein $-C(O)OR^z$ is an amide protecting group.

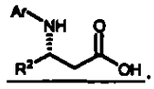
59 The method of Claim 58 wherein R^z is a substituted or unsubstituted alkyl group, allyl group or aromatic group.

60 The method of Claim 59 wherein the amide carbonyl of the starting compound is reduced by reacting the starting compound with sodium borohydride and a Lewis acid and the intermediate is cyclized in the presence of acid

61. The method of Claim 60 wherein Ar is an optionally substituted phenyl group and R^2 is methyl or ethyl

62. The method of Claim 60 wherein R^z is benzyl, methyl, ethyl, allyl, 2,2,2,-trichloromethyl, 2,2,2-trichloro-*tert*-butyl, *tert*-butyl or fluorenylmethyl.

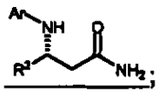
63 The method of Claim 58 wherein the starting compound is prepared by amidating an amino acid with $H_2NC(O)OR^z$, wherein said amino acid is represented by represented by the following structural formula:



64. The method of Claim 63 wherein said amidation is carried out by reacting the amino acid with a carboxylic acid activating reagent to form an activated intermediate and then reacting the activated intermediate with $H_2NC(O)OR^z$

65. The method of Claim 64 wherein the carboxylic acid activating agent is a carbonyldiimidazole.

66. The method of Claim 63 wherein said amidation is carried out by reacting the amino acid with a carboxylic acid activating reagent to form an activated intermediate and then reacting the activated intermediate with NH_3 or a functional equivalent thereof to form a carboxamide intermediate represented by the following structural formula·



reacting the carboxamide intermediate with X-C(O)OR^z, wherein X is a leaving group

67 The method of Claim 63 wherein the amino acid is prepared by reacting Ar-NH_2 with



68. The method of Claim 67 wherein Ar is an optionally substituted phenyl group and R^2 is methyl or ethyl.

69 The method of Claim 68 wherein Ar is a phenyl group optionally substituted at the six and seven positions with R^{14};

each R^{14} is independently halo, cyano, R^o, $-OR^{30}$, $-CO_2R^{31}$, $-C(O)R^o$, $-C(O)N(R^x)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)N(R^x)_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)N(R^x)_2$, $O(CH_2)_nC(O)N(R^x)_2$;

n is an integer from 1-4;

R^o is independently hydrogen, C_{1-3} haloalkylgroup or a C_{1-3} alkyl group;

one R^x is –H or C_1-C_3 alkyl and the other is an amine protecting group;

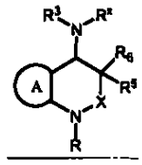
R^{30} is an alcohol protecting group, and

R^{31} is a carboxylic acid protecting group.

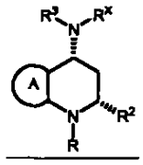
70 The method of Claim 69 wherein Ar is a phenyl group

ABSTRACT OF THE DISCLOSURE

Disclosed herein are compounds represented by Structural Formula (I) and (I-A):



I



I-A

Also disclosed is the use of such compounds for inhibiting the G-protein coupled receptor referred to as chemoattractant receptor-homologous molecule expressed on Th2, or simply "CRTH2" for the treatment of inflammatory disorders The variables in Structural Formula (I) and (I-A) are defined herein.

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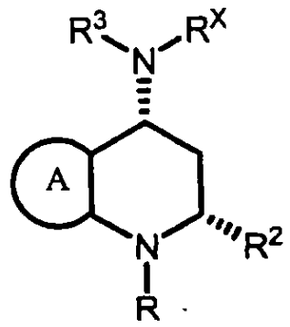
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(54) Título: **ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO DE ENFERMEDADES INFLAMATORIAS.**

(57 Resumen En este documento se describen compuestos representados por la Formula Estructural (I):



También se describe el uso de dichos compuestos para inhibir el receptor acoplado a proteína G mencionados como molécula homóloga al receptor de quimioatracción expresada en Th2 o simplemente "CRTH2" para el tratamiento de trastornos inflamatorios. Las variables en la Fórmula Estructural (I) se definen en este documento.

ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO DE ENFERMEDADES INFLAMATORIAS

ANTECEDENTES DE LA INVENCIÓN

Las células auxiliares inmunes del tipo Th2 están implicadas en la orquestación de la respuesta alérgica. Los mecanismos por los cuales las células Th2 llevan a cabo una respuesta inmune están empezando ahora a ser entendidos. Por ejemplo, recientemente se ha publicado que las células Th2 expresan un receptor conjugado con una proteína G en particular denominado como "molécula homóloga al receptor de quimioatracción expresada en Th2" (véase Tanaka et al., J Immunol 164:2277 (2000)), o simplemente "CRTH2" Otra publicación reciente describe que la prostaglandina PGD2 es un ligando de CRTH2 y que los agentes que actúan como antagonistas de la interacción entre PGD2 y CRTH2 inhibirán las respuestas mediadas por PGD2 (véase la Publicación de la Solicitud de Patente de Estados Unidos Nº US2002/0022218).

PGD2 está implicada en numerosas respuestas biológicas, incluyendo la quimiotáxis de células inmunes que media en las respuestas inflamatorias. De esta manera, PGD2 juega un papel clave en trastornos tales como rinitis alérgica, asma alérgica, dermatitis atópica y trastornos inflamatorios sistémicos. Se espera, por tanto, que los antagonistas de CRTH2 sean útiles en el tratamiento de estos trastornos mediados por PGD2. Desafortunadamente, se conocen pocos inhibidores de CRTH2. En consecuencia, los médicos serán incapaces de explotar estos avances hasta que no se desarrollen nuevos inhibidores de CRTH2.

SUMARIO DE LA INVENCIÓN

Ahora se ha encontrado que ciertas 1,2,3,4-tetrahidro-quinolin-4-il)aminas son potentes inhibidores de CRTH2. Por ejemplo, los compuestos (1)-(39) inhiben de forma eficaz la unión de PGD2 a células HEK-293 que expresan de forma estable CRTH2 a una concentración de 25 μM y muchas

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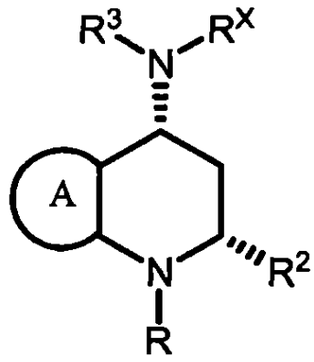
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con una Ki de menos de 1,0 µM (véase la Tabla 14 del Ejemplo 18). En base a este descubrimiento, se describen en este documento inhibidores de CRTH2, composiciones farmacéuticas que comprenden estos inhibidores y métodos de inhibición de la actividad CRTH2 en un sujeto que necesita de este tratamiento

Una realización de las presentes invenciones es un compuesto representado por la Fórmula Estructural (I):



(I)

El anillo A es un aromático monocíclico sustituido o no sustituido, preferiblemente un anillo opcionalmente sustituido con fenilo;

R es $-X_1-R^1$;

R^X es $-X_2-R^4$,

cada uno de X_1 y X_2 son independientemente $-S(O)_2-$, -C(O)- o -C(O)NH- y, preferiblemente, X1 y X2 son ambos –C(O)-.

R^1 es un grupo aromático o heteroaromático que tiene 5-6 átomos en el anillo, sustituido con T^1-V-T-R^Y, T^1-V-T-M-R^Y; o V-R^9, y además está opcionalmente sustituido con 1-2 grupos seleccionados independientemente representados por R^Z, o R1 es un grupo aromático o un grupo heteroaromático que tiene 5-6 átomos en el anillo, condensado con un anillo heterocíclico monocíclico no aromático o anillo monocíclico aromático sustituido o no sustituido.

R^9 es un grupo carbocíclico o heterocíclico no aromático opcionalmente sustituido;

R^Z se selecciona independientemente entre halógeno, haloalquilo, R^o, -OR^o, -O(haloalquilo), -SR^o, -NO_2, -CN, -$N(R')_2$, -$NR'CO_2R^o$, -$NR'C(O)R^o$, -$NR'NR'C(O)R^o$, -$N(R')C(O)N(R')_2$, -$NR'NR'C(O)N(R')_2$, -$NR'NR'CO_2R^o$, -$C(O)C(O)R^o$, -$C(O)CH_2C(O)R^o$, -CO_2R^o, -$C(O)R^o$, -$C(O)N(R^o)_2$, -$OC(O)R^o$, -$OC(O)N(R^o)_2$, -$S(O)_2R^o$, -$SO_2N(R')_2$, -$S(O)R^o$, -$NR'SO_2N(R')_2$, -$NR'SO_2R^o$, -$C(=S)N(R')_2$ y -$C(=NH)$-$N(R')_2$;

R^Y es -$C(O)OR^5$, -$C(O)R^5$, -$OC(O)R^5$, -$C(O)N(R^5)_2$, -$NR^5C(O)R^5$, -$NR^5C(O)OR^5$, -$S(O)_2R^5$, -$S(O)_2COR^5$, -$S(O)_2N(R^5)_2$, -$NR^5S(O)_2R^5$, -$NR^5S(O)_2R^5$, $S(O)_2OR^5$, -$S(O)OR^5$, -$S(O)R^5$, -SR^5, -$C(O)NR^5S(O)_2R^5$, -CN, -$NR^5C(O)NR^5_2$, -$OC(O)NR^5_2$, -NR^5_2, -OR^5, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido;

V es un enlace covalente, -O-, -C(O)-, -N(R')-, -S-, -S(O)-, -$C(O)NR^5$-, -$NR^5C(O)$-, -$S(O)_2NR^5$-, -$NR^5S(O)_2$- o -$S(O)_2$-;

T es alquileno C_{1-10} de cadena lineal, con la condición de que T sea C_{2-10} cuando V es un enlace covalente, y T es C_{2-10} cuando V es -O-, -S- o –H(R')- y R^Y es –CN, -OH, -SH, -$N(R^5)_2$.

T^1 es un enlace covalente o un alquileno C_{1-10} de cadena lineal, donde T y T^1 juntos no contienen más de 10 átomos de carbono y donde T y T^1 están opcional e independientemente sustituidos en cualquiera de uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, nitrógeno opcionalmente *N*-sustituido que contiene un grupo heterocíclico no aromático espiro, amina, alquilamina, dialquilamina, alcoxi o hidroxilo,

R^5 es independientemente -H, alquilo, haloalquilo, hidroxialquilo, carboxialquilo, -$C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, bencilo, pirrolidinilo, morfolinilo o -NR^5_2 es un grupo heterocíclico no aromático que contiene nitrógeno,

M es un grupo opcionalmente sustituido seleccionado entre grupo aromático monocíclico, heteroaromático, carbocíclico monocíclico no aromático

o heterocíclico. Las secciones que a continuación definen las expresiones "carbociclo no aromático" y "grupo heterocíclico no aromático" proporcionan ejemplos específicos de valores adecuados para M. Los sustituyentes adecuados para los anillos aromáticos representados por M son como los definidos para R^{11}, los sustituyentes adecuados para carbociclos y no aromáticos son como se describen en las secciones en las que a continuación se definen sustituyentes adecuados para estos dos grupos

R^2 es alquilo C_{1-3}.

R^3 es un grupo aromático opcionalmente sustituido que tiene 5-6 átomos en el anillo Preferiblemente R^3 es un grupo fenilo opcionalmente sustituido ; y

R^4 es alquilo C_1-C_3 o hidroxialquilo C_1-C_3. Preferiblemente R^4 es metil, etil, hidroximetil o hidroxietil.

Otra realización de la presente invención es un método para inhibir CRTH2 en un sujeto que necesita de la inhibición de CRTH2. El método comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto de la presente invención

Aún otra realización de la presente invención es una composición farmacéutica. La composición farmacéutica comprende un vehículo o diluyente farmacéuticamente aceptable y un compuesto de la invención. Las composiciones farmacéuticas pueden usarse en terapia, por ejemplo, para inhibir la actividad de CRTH2 en un sujeto que necesita de este tratamiento

Aún otra realización de la presente invención es el uso de un compuesto de la invención para la fabricación de un medicamento para inhibir la actividad de CRTH2 en un sujeto que necesita de este tratamiento El medicamento comprende una cantidad efectiva de un compuesto de la invención.

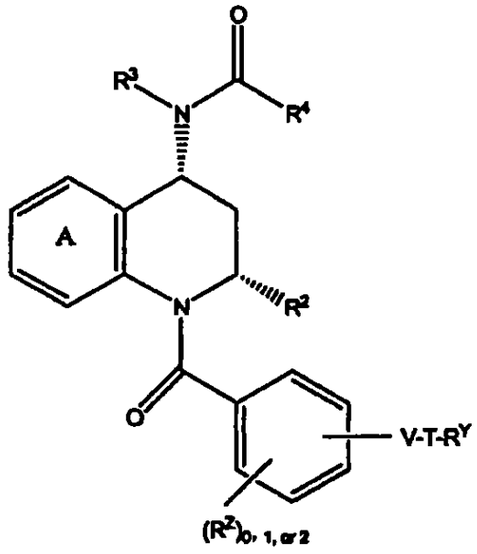
Los compuestos descritos son inhibidores eficaces de la actividad de CRTH2 y, como tal, se espera que sean útiles para el tratamiento y prevención de enfermedades mediadas por la actividad CRTH2, incluyendo, pero no de forma limitante, enfermedades inflamatorias tales como asma alérgica, dermatitis atópica, rinitis alérgica, anafilaxis sistémica o respuestas de hipersensibilidad, alergias a fármacos (por ejemplo, a la penicilina,

cefalosporinas), alergias a la picadura de insectos y dermatosis inflamatorias tales como dermatitis, eccema, dermatitis alérgica y urticaria por contacto, restenosis, miositis (incluyendo polimiositis, dermatomiositis).

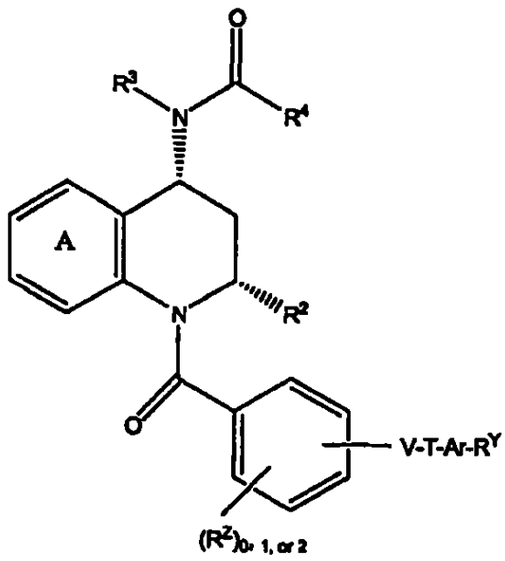
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención se dirige a inhibidores de la molécula homóloga al receptor de quimioatracción expresada en células Th2, también denominada en este documento como "CRTH2" La prostaglandina PGD2 es un ligando natural de CRTH2, donde se une e induce al menos alguna de sus actividades proinflamatoria. De esta manera, los compuestos descritos pueden usarse para inhibir la actividad de CRTH2; para inhibir la actividad de PGD2 y para inhibir o tratar (de forma terapéutica o profiláctica) trastornos inflamatorios y afecciones alérgicas mediadas por CRTH2 y/o PGD2. Las células del sistema inmune que expresan CRTH2 incluyen células Th2, eosinófilos y basófilos. De esta manera, los compuestos descritos pueden usarse de forma ventajosa para inhibir trastornos inflamatorios y afecciones alérgicas mediadas por estas células.

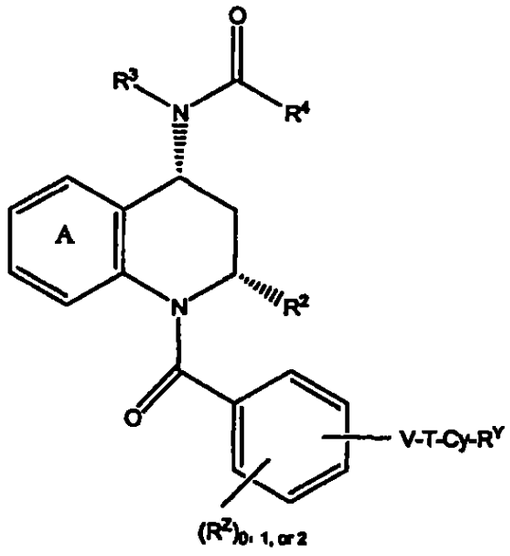
En una realización, la presente invención es un compuesto representado por las Fórmulas Estructurales **(II)**, **(III)** o **(IV)**.



(II)



(III)



(IV)

Ar en la Fórmula Estructural (III) es un anillo aromático monocíclico. Cy en la Fórmula Estructural (IV) es un grupo carbocíclico o heterocíclico no

aromático El resto de variables en las Fórmulas Estructurales (II)-(IV) son como se han descrito para la Fórmula Estructural (I) Preferiblemente, V en las Fórmulas Estructurales (II)-(IV) es un enlace covalente, -O- o -N(R')-, y T en las Fórmulas Estructurales (II)-(IV) es un alquileno C_{1-6} de cadena lineal opcionalmente sustituido en cualquiera de uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, alquilamina, dialquilamina o hidroxilo.

Como alternativa, en las Fórmulas Estructurales (II)-(IV) V es un enlace covalente, -NR'- o -O-; y T es un alquileno C_{1-10} de cadena lineal (preferiblemente C_{1-5}, más preferiblemente C_{1-3}) opcionalmente mono-sustituido en cualquier átomo de carbono sustituible con haluro, alquilo, haloalquilo, amina, dialquilamina o hidroxilo

Preferiblemente, R^Y en las Fórmulas Estructurales (I) y (II) es $-C(O)OR^5$, $-C(O)NR^5_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)NR^5_2$, $-NR^5_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8. R^7 es un piperidinonilo opcionalmente sustituido, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo. R^8 es un furanilo opcionalmente sustituido, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo y el resto de variables son como se han descrito en el párrafo anterior

Más preferiblemente, R^Y en las Fórmulas Estructurales (I) y (II) es $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8. R^7 es piperidinonilo, morfolinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo. R^8 es tetrazolilo, oxazolilo,

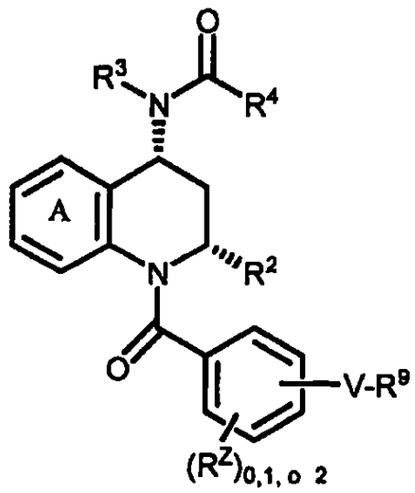
oxadiazolilo, pirrolilo, pirazolilo, piridinilo o imidazolilo. R^5 es independientemente H o alquilo o $N(R^5)_2$ es un grupo heterocíclico no aromático que contiene nitrógeno. V es un enlace covalente o -O-; y T es un alquileno C_{1-5} de cadena lineal opcionalmente sustituido en el átomo de carbono adyacente a R^Y con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, dialquilamina o hidroxilo.

Más preferiblemente, R^1 en las Fórmulas Estructurales (I)-(III) es un anillo fenilo opcionalmente sustituido en las posiciones *meta* y *para* (más preferiblemente *para*) con V-T-R^Y o V-T-M-R^Y. Aún más preferiblemente R^Y es -C(O)OR^5, -C(O)$N(R^5)_2$, -OH, *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, *N*-sustituido 2-morfolinilo, *N*-sustituido 3-morfolinilo, *N*-imidazolidinilo, 2-imidazolidinilo, 4-imidazolidinilo, 5-imidazolidinilo, *N*-sustituido 2-imidazolidinilo, *N*-imidazolidinilo *N'*-sustituido, 4-imidazolidinilo *N*-sustituido, 5-imidazolidinilo *N*-sustituido, *N*-imidazolidinonilo, 4-imidazolidinonilo, 5-imidazolidinonilo, 4-imidazolidinonilo *N*-sustituido, 5-imidazolidinonilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-pirrolidin-2-onilo, 3-pirrolidin-2-onilo, 4-pirrolidin-2-onilo, 5-pirrolidin-2-onilo, 3-pirrolidin-2-onilo *N*-sustituido, 4-pirrolidin-2-onilo *N*-sustituido, 5-pirrolidin-2-onilo *N*-sustituido, *N*-pirrolidin-3-onilo, 2-pirrolidin-3-onilo, 4-pirrolidin-3-onilo, 5-pirrolidin-3-onilo, 2-pirrolidin-3-onilo *N*-sustituido, 4-pirrolidin-3-onilo *N*-sustituido, 5-pirrolidin-3-onilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperidin-2-onilo, 3-piperidin-2-onilo, 4-piperidin-2-onilo, 5-piperidin-2-onilo, 6-piperidin-2-onilo, 3-piperidin-2-onilo *N*-sustituido, 4-piperidin-2-onilo *N*-sustituido, 5-piperidin-2-onilo *N*-sustituido, 6-piperidin-2-onilo *N*-sustituido, *N*-piperidin-3-onilo, 2-piperidin-3-onilo, 4-piperidin-3-onilo, 5-piperidin-3-onilo, 6-piperidin-3-onilo, *N*-sustituido 2-piperidin-3-onilo, 4-piperidin-3-onilo *N*-sustituido, 5-piperidin-3-onilo *N*-sustituido, 6-piperidin-3-onilo *N*-sustituido, *N*-piperidin-4-onilo, 2-piperidin-4-onilo, 3-piperidin-4-onilo, 5-

piperidin-4-onilo, 6-piperidin-4-onilo, 2-piperidin-4-onilo *N*-sustituido, 3-piperidin-4-onilo *N*-sustituido, 5-piperidin-4-onilo *N*-sustituido, 6-piperidin-4-onilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, 2-piperazinilo *N*-sustituido, furanilo, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, 4-(1,2,3)oxadiazolilo, 5-(1,2,3)oxadiazolilo, 3-(1,2,4)oxadiazolilo, 5-(1,2,4)oxadiazolilo, 3-(1,2,5)oxadiazolilo, 4-(1,2,5)oxadiazolilo, 2-(1,3,4)oxadiazolilo, 5-(1,3,4)oxadiazolilo, *N*-pirrolilo, 2-pirrolilo, 3-pirrolilo, 2-pirrolilo *N*-sustituido, 3-pirrolilo *N*-sustituido, *N*-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 3-pirazolilo *N*-sustituido, 4-pirazolilo *N*-sustituido, 5-pirazolilo *N*-sustituido, 2-piridinilo, 3-piridinilo, 4-piridinilo, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo, 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido. V es -O- y T es un alquileno C_{1-3} de cadena lineal sustituido en el átomo de carbono adyacente a R^Y con flúor, metilo, gem dimetilo, gem difluorofluorometilo, espiro ciclopropilo, espiro ciclobutilo, espiro azetidinilo opcionalmente *N*-sustituido, espiro aziridinilo opcionalmente *N*-sustituido, espiro pirrolidinilo opcionalmente *N*-sustituido, espiro piperidinilo opcionalmente *N*-sustituido, amina, metilamina, dimetilamina o hidroxilo.

Aún más preferiblemente R^Y es $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido. R^5 es -H, metilo o etilo. R^1 en las Fórmulas Estructurales (I)-(III) es un anillo fenilo opcionalmente sustituido en la posición *para* con V-T-R^Y o V-T-M-R^Y.

En otra realización preferida, la presente invención es un compuesto representado por la Fórmula Estructural (V):



(V)

Todas las variables de la Fórmula Estructural (V) son como se han descrito para la Fórmula Estructural (I). Preferiblemente, R^9 en la Fórmula Estructural (V) es un ciclohexanilo opcionalmente sustituido, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo, S,S-dióxido de isotiazolidinilo o piperidinilo. R^9 es preferiblemente *meta o para* al átomo de carbono unido al carbonilo, más preferiblemente *para*. V es preferiblemente un enlace covalente o -O-, más preferiblemente un enlace covalente.

Más preferiblemente, R^9 en la Fórmula Estructural (V) es oxazolidinilo, tiazolidinilo, tetrahidrofuranilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo, cada uno opcionalmente sustituido con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, -

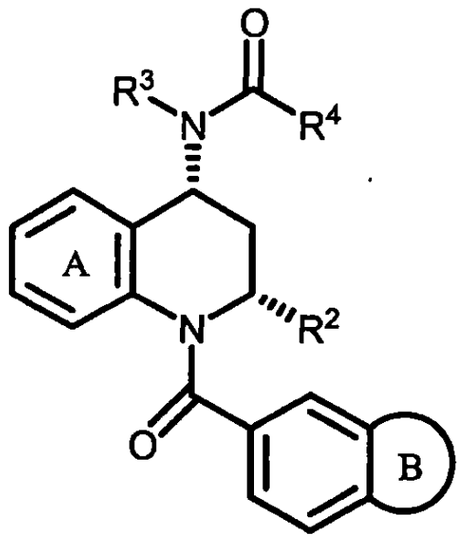
$S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$, $-(CH_2)_nCO_2H$, $-(CH_2)_nC(O)NR^o$, $-(CH_2)_nC(CH_3)_2CO_2H$, $-(CH_2)_nC(CH_3)_2C(O)NR^o$ o $-NR^{12}{}_2$, n es un número entero de 1 a 4 y cada R^{12} es independientemente -H, alquilo, haloalquilo o hidroxialquilo, y el resto de variables son como se han descrito en el párrafo anterior Como alternativa, para aquellos grupos representados por R^9 que tiene un nitrógeno del anillo sustituible, el grupo está *N*-sustituido con T^2-R^{Y1}, que se define a continuación o opcionalmente sustituido en uno o más átomos de carbono del anillo sustituibles con uno o más grupos listados anteriormente en este párrafo

Más preferiblemente, R^9 en la Fórmula Estructural (V) es *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, 2-morfolinilo *N*-sustituido, 3-morfolinilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, 2-piperazinilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, cada uno opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)N(R^{12})_2$ y donde los sustituyentes *N* son alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-(CH_2)_nCO_2H$, $-(CH_2)_nC(O)NR^o$, $-(CH_2)_nC(CH_3)_2CO_2H$, $-(CH_2)_nC(CH_3)_2C(O)NR^o$ o $-C(O)N(R^{12})_2$. Para estos grupos representados por R^9 que tiene un N del anillo sustituible, un sustituyente N preferido es T^2-R^{Y1}, que es como se define a continuación.

Aún más preferiblemente, R^9 en la Fórmula Estructural (V) es *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido o 2-piperazinilo *N*-sustituido y esta opcionalmente sustituido en cualquier átomo de carbono sustituible con cloruro, fluoruro, bromuro, metilo, etilo, $-C(O)OR^{12}$, $-OC(O)R^{12}$, $-C(O)R^{12}$ o $C(O)NH_2$ y donde los sustituyentes N son metilo, etilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-(CH_2)_nCO_2H$, $-(CH_2)_nC(O)NR^o$, $-(CH_2)_nC(CH_3)_2CO_2H$, $-(CH_2)_nC(CH_3)_2C(O)NR^o$ o $-C(O)NH_2$ y

cada R^{12} es independientemente -H, metilo o etilo Para estos grupos representados por R^9 que tiene un N del anillo sustituible, un sustituyente N preferido es T^2-R^{Y1}, que es como se define a continuación.

En otra realización preferida, la presente invención es un compuesto representado por la Fórmula Estructural (VI):



(VI)

B es un anillo heterocíclico monocíclico no aromático opcionalmente sustituido representado por R^{10} o un anillo aromático monocíclico (preferiblemente heteroaromático) representado por R^{13}; el resto de variables de la Fórmula Estructural (VI) son como se han descrito para la Fórmula Estructural (I).

Preferiblemente, R^{10} en la Fórmula Estructural (VI) es oxazolidinilo, oxazolidinonilo, dioxolanilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, ditiolanilo, pirrolidinilo, piperazinilo, piperidinilo, piperidinilo, S,S-dióxido de tetrahidrotienilo, S,S-dióxido de tiomorfolinilo, S,S-dióxido de tetrahidrotiopiranilo, cada uno de los cuales está opcionalmente

sustituido. R^{13} es pirazolilo, triazolilo, imidazolilo, furanilo, pirrolilo, tienilo, ciclopentadienilo y S,S-dióxido de tienilo, cada uno de los cuales está opcionalmente sustituido. El resto de variables de la Fórmula Estructural (VI) son como se han descrito en el párrafo anterior.

Otros ejemplos de valores adecuados para R^{10} incluyen tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales opcionalmente sustituido en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$ o $-N(R^{12})_2$ y cada uno de los cuales opcionalmente sustituido en cualquier átomo de nitrógeno del anillo sustituible con alquilhaloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$; y otros ejemplos de valores adecuados para R^{13} incluyen triazolilo, imidazolilo, furanilo, pirrolilo, tienilo, cada uno de los cuales opcionalmente sustituido en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)NR^{12}_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2NR^{12}_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, $-CN$, $-NR^{12}C(O)NR^{12}_2$, $-OC(O)NR^{12}_2$ o $-NR^{12}_2$ y cada uno de los cuales opcionalmente sustituido en cualquier átomo de nitrógeno del anillo sustituible con alquilhaloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$ Cada R^{12} es independientemente H, alquilo, haloalquilo o hidroxialquilo.

Aún más preferiblemente, en la Fórmula Estructural (VI) R^{10} es dioxolanilo, tetrahidrofuranilo, morfolinilo, cada opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)NR^{12}_2$ o cada opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$ o $-C(O)NR^{12}_2$. R^{13} es

triazolilo, imidazolilo o pirrolilo cada opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$ o -$C(O)NR^{12}_2$ y cada opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $C(O)OR^{12}$, -$C(O)R^{12}$, -$R^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, $S(O)_2NR^{12}_2$, -$C(O)NR^{12}_2$

Aún más preferiblemente, en la Fórmula Estructural (VI) R^{10} es morfolinilo y esta opcionalmente *N*-sustituido con metilo, etilo, -$C(O)OR^{12}$, $C(O)NH_2$ o -$C(O)R^{12}$, R^{13} es triazolilo y esta opcionalmente *N*-sustituido con metilo, etilo, -$C(O)OR^{12}$, $C(O)NH_2$ o -$C(O)R^{12}$ y cada R^{12} es independientemente -H, metilo o etilo.

En otra realización preferida, en la Fórmula Estructural (VI), el Anillo B es un heterocicio monocíclico no aromático o un grupo heteroarilo monocíclico que comprende un átomo de nitrógeno en el anillo que está sustituido con T^2-R^{Y1} Estos grupos monocíclico no aromático y heteroarilo están opcionalmente sustituidos. Preferiblemente, el anillo heterocíclico monocíclico no aromático se representa por R^{10}, Preferiblemente, el anillo heteroaromático monocíclico se representa por R^{13}. Los ejemplos de valores adecuados para R^{10} incluyen oxazolidinilo, oxazolidinonilo, tiazolidinilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo, cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquiera de uno o más átomos de carbono del anillo con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)NR^{12}_2$, -$OC(O)NR^{12}_2$ o $-NR^{12}_2$ Los ejemplos de valores adecuados para R^{13} incluyen pirazolilo, triazolilo, imidazolilo o pirrolilo, cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquiera de uno o más átomo de carbono del anillo con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -

$S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)NR^{12}_2$, $-OC(O)NR^{12}_2$ o $-NR^{12}_2$. Cada R^{12} es independientemente H, alquilo, haloalquilo o hidroxialquilo. El resto de variables son como se han descrito anteriormente para la Fórmula Estructural (VI).

Preferiblemente, T^2 en la Fórmula Estructural (VI) es un alquileno C_{1-6} de cadena lineal opcionalmente sustituido en cualquiera de uno o más átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, alquilamina, dialquilamina o hidroxilo. R^{Y1} es $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2NR^5_2$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)NR^5_2$, $-NR^5_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8. R^7 es un piperidinonilo opcionalmente sustituido, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo R^8 es un furanilo opcionalmente sustituido, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo.

Otros ejemplos de valores adecuados para R^{10} incluyen morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2NR^{12}_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)NR^{12}_2$, $-OC(O)NR^{12}_2$ o $-NR^{12}_2$. Otros ejemplos de valores adecuados para R^{13} incluyen triazolilo, imidazolilo o pirrolilo, cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, -

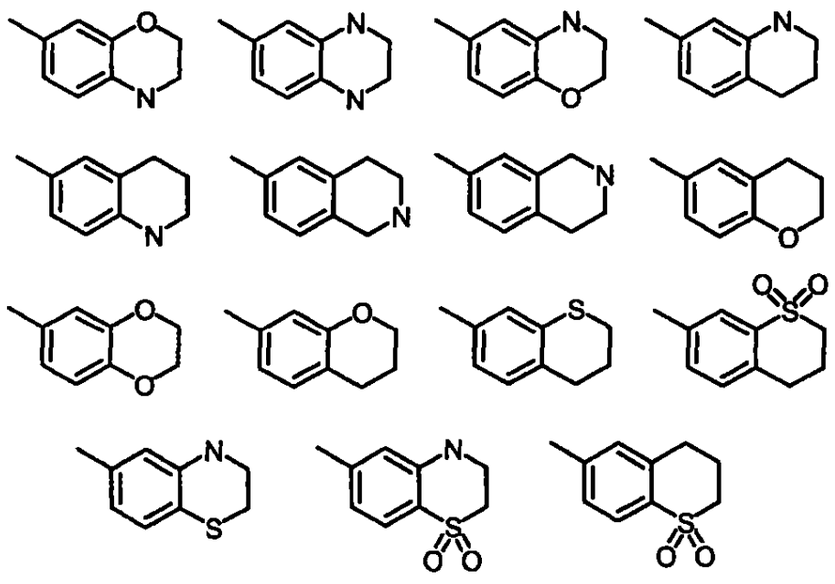
$NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2N(R^{12})_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)N(R^{12})_2$ o $-N(R^{12})_2$. R^{Y1} es $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8. Cada R^5 es independientemente H o alquilo o $N(R^5)_2$ es un grupo heterocíclico no aromático que contiene nitrógeno. R^7 es piperidinonilo, morfolinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo R^8 es tetrazolilo, oxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo o imidazolilo T^2 es un alquileno C_{1-5} de cadena lineal opcionalmente sustituido en el átomo de carbono adyacente a R^Y con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, dialquilamina o hidroxilo.

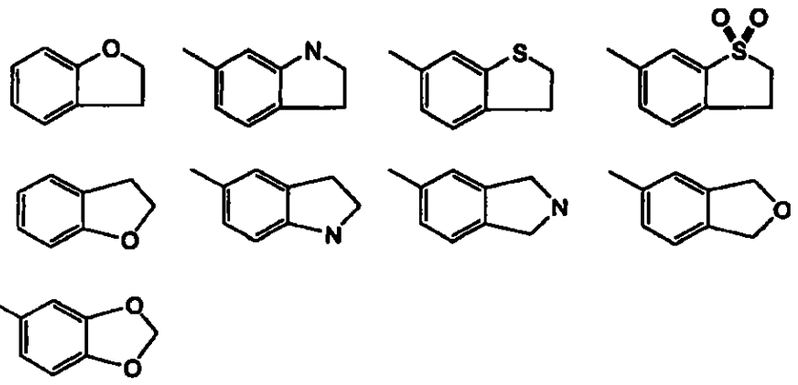
Preferiblemente, otros ejemplos de valores adecuados para R^{10} incluyen morfolinilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$. Otros ejemplos de valores adecuados para R^{13} incluyen imidazolilo o pirrolilo cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)NR^{12}{}_2$ y cada opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$. R^{Y1} es $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, 2-morfolinilo *N*-sustituido, 3-morfolinilo *N*-sustituido, *N*-imidazolidinilo, 2-imidazolidinilo, 4-imidazolidinilo, 5-imidazolidinilo, 2-imidazolidinilo *N*-sustituido, *N*-imidazolidinilo *N'*-sustituido, 4-imidazolidinilo *N*-sustituido, 5-imidazolidinilo *N*-sustituido, *N*-imidazolidinonilo, 4-imidazolidinonilo, 5-imidazolidinonilo, 4-imidazolidinonilo *N*-sustituido, 5-imidazolidinonilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-

pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-pirrolidin-2-onilo, 3-pirrolidin-2-onilo, 4-pirrolidin-2-onilo, 5-pirrolidin-2-onilo, 3-pirrolidin-2-onilo *N*-sustituido, 4-pirrolidin-2-onilo *N*-sustituido, 5-pirrolidin-2-onilo *N*-sustituido, *N*-pirrolidin-3-onilo, 2-pirrolidin-3-onilo, 4-pirrolidin-3-onilo, 5-pirrolidin-3-onilo, 2-pirrolidin-3-onilo *N*-sustituido, 4-pirrolidin-3-onilo *N*-sustituido, 5-pirrolidin-3-onilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperidin-2-onilo, 3-piperidin-2-onilo, 4-piperidin-2-onilo, 5-piperidin-2-onilo, 6-piperidin-2-onilo, 3-piperidin-2-onilo *N*-sustituido, 4-piperidin-2-onilo *N*-sustituido, 5-piperidin-2-onilo *N*-sustituido, 6-piperidin-2-onilo *N*-sustituido, *N*-piperidin-3-onilo, 2-piperidin-3-onilo, 4-piperidin-3-onilo, 5-piperidin-3-onilo, 6-piperidin-3-onilo, 2-piperidin-3-onilo *N*-sustituido, 4-piperidin-3-onilo *N*-sustituido, 5-*piperidin*-3-onilo *N*-sustituido, 6-*piperidin*-3-onilo *N*-sustituido, *N*-piperidin-4-onilo, 2-piperidin-4-onilo, 3-piperidin-4-onilo, 5-piperidin-4-onilo, 6-piperidin-4-onilo, 2-piperidin-4-onilo *N*-sustituido, 3-piperidin-4-onilo *N*-sustituido, 5-piperidin-4-onilo *N*-sustituido, 6-piperidin-4-onilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N'*-sustituido *N*-piperazinilo, 2-piperazinilo *N*-sustituido, furanilo, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, 4-(1,2,3)oxadiazolilo, 5-(1,2,3)oxadiazolilo, 3-(1,2,4)oxadiazolilo, 5-(1,2,4)oxadiazolilo, 3-(1,2,5)oxadiazolilo, 4-(1,2,5)oxadiazolilo, 2-(1,3,4)oxadiazolilo, 5-(1,3,4)oxadiazolilo, *N*-pirrolilo, 2-pirrolilo, 3-pirrolilo, 2-pirrolilo *N*-sustituido, 3-pirrolilo *N*-sustituido, *N*-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 3-pirazolilo *N*-sustituido, 4-pirazolilo *N*-sustituido, 5-pirazolilo *N*-sustituido, 2-piridinilo, 3-piridinilo, 4-piridinilo, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido. T^2 es un alquileno C_{1-3} de cadena lineal sustituido con flúor, metilo, gem dimetilo, gem difluoro fluorometilo, espiro ciclopropilo, espiro ciclobutilo, espiro azetidinilo opcionalmente *N*-sustituido, opcionalmente espiro aziridinilo *N*-sustituido, espiro pirrolidinilo opcionalmente *N*-sustituido, espiro piperidinilo opcionalmente *N*-sustituido, amina, metilamina, dimetilamina o hidroxilo.

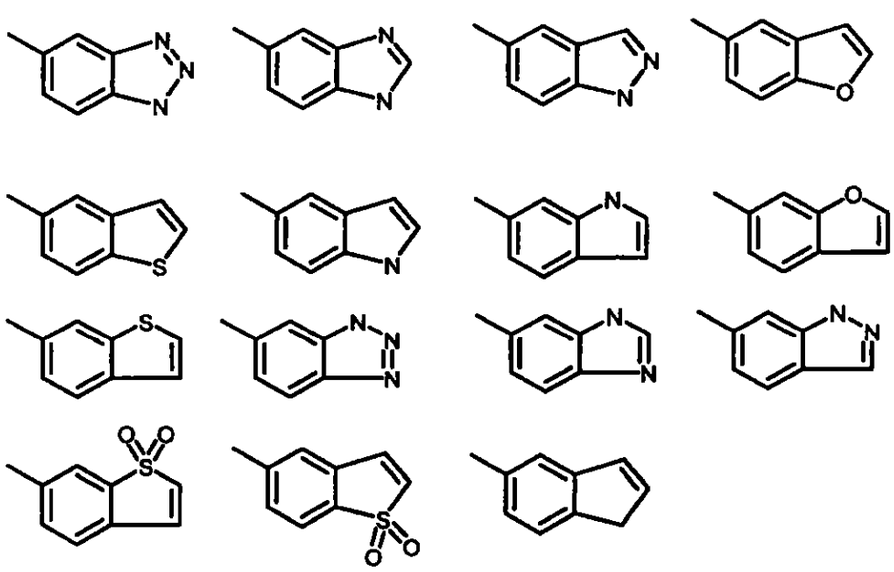
Más preferiblemente, otros ejemplos de valores adecuados para R^{10} incluyen morfolinilo, *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en el carbono alfa del átomo de nitrógeno con metilo o gem dimetilo. Otros ejemplos de valores adecuados para R^{13} incluyen imidazolilo *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido además en el carbono alfa del átomo de nitrógeno con metilo o gem dimetilo. R^{Y1} es -C(O)OR^5, -C(O)$N(R^5)_2$, -OH, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo, 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido

En una realización, en la Fórmula Estructural (VI) R^1 es un anillo fenilo opcionalmente sustituido condensado al grupo representado por R^{10} como se representa por las siguientes Fórmulas Estructurales:





En una realización de la Fórmula Estructural (VI), R^1 es un anillo fenilo opcionalmente sustituido condensado al grupo representado por R^{13} como se representa por las siguientes Fórmulas Estructurales:



Las Fórmulas Estructurales mostradas anteriormente para los anillos bicíclicos condensados también pueden estar opcionalmente sustituidas en cualquiera de uno o más átomos de carbono o átomos de nitrógeno Los ejemplos de sustituyentes adecuados son los que se han descrito anteriormente para los grupos representados por R^{10} y R^{13}. En una realización

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más específica, cualquier sistema de anillo bicíclico condensado mostrado anteriormente que tiene átomos de nitrógeno asimétricos está *N*-sustituido con T^2-R^{Y1} T^2-R^{Y1} es como se ha descrito anteriormente

Como se ha descrito anteriormente, el Anillo A (preferiblemente el anillo fenilo A) en las Fórmulas Estructurales (I)-(VI) está opcionalmente sustituido (preferiblemente en las posiciones seis y siete) con uno o más grupos representados por R^{14}; En las Fórmulas Estructurales (I)-(V), R^1 es un grupo aromático (preferiblemente un anillo fenilo) opcionalmente sustituido con 1-2 grupos seleccionados independientemente representados por R^Z, y en las Fórmulas Estructurales (I)-(VI), R^3 es un grupo aromático (preferiblemente, por ejemplo, un grupo fenilo) opcionalmente sustituido con uno o más grupos representados por R^{11} Los valores adecuados para R^{14}, R^Z y R^{11} son aquellos que no disminuyen sustancialmente la capacidad del compuesto de la invención para inhibir CRTH2 Los ejemplos de sustituyentes adecuados son halógeno, haloalquilo, R°, $-OR^\circ$, -O(haloalquilo), $-SR^\circ$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^\circ$, $-NR'C(O)R^\circ$, $-NR'NR'C(O)R^\circ$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^\circ$, $-C(O)C(O)R^\circ$, $-C(O)CH_2C(O)R^\circ$, $-CO_2R^\circ$, $-C(O)R^\circ$, $-C(O)N(R^\circ)_2$, $-OC(O)R^\circ$, $-OC(O)N(R^\circ)_2$, $-S(O)_2R^\circ$, $-SO_2N(R')_2$, $-S(O)R^\circ$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^\circ$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$ Otros valores R^{11} incluyen 3,4-metileno-dioxi y 3,4-etileno-dioxi.

Cada R' es independientemente hidrógeno, alquilo, $-C(O)OR^\circ$, $S(O)_2R^\circ$ o $-C(O)R^\circ$. Cada R° es independientemente hidrógeno o un grupo alquilo, grupo heterocíclico no aromático o grupo aromático y el alquilo, el grupo heterocíclico no aromático y el grupo aromático representado por R° esta opcionalmente sustituido con uno o más grupos seleccionados independientemente representados por $R^\#$. $R^\#$ es R^+, $-OR^+$, -O(haloalquilo), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$ o $-C(=NH)-N(R^+)_2$ R^+ es -H, un grupo alquilo C_1-C_3, un grupo heteroarilo monocíclico, un grupo heterocíclico no aromático o un grupo

fenilo opcionalmente sustituido con alquilo, haloalquilo, alcoxi, haloalcoxi, halo, -CN, $-NO_2$, amina, alquilamina o dialquilamina; o $-N(R^+)_2$ es un grupo heterocíclico no aromático, con la condición de que los grupos heterocíclicos no aromáticos representados por R^+ y $-N(R^+)_2$ que comprenden una amina de anillo secundario están opcionalmente acilados o alquilados.

Los valores preferidos para R^Z y R^{11} son halógeno, haloalquilo, $-R^o$, $-OR^o$, $-O$(haloalquilo), $-CO_2R^o$, $-C(O)R^o$, $-NR'SO_2R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$ y $-OC(O)N(R^o)_2$ 3,4-metileno-dioxi y 3,4-etileno-dioxi y $-N(R')_2$ también son valores preferidos para R^{11} Cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo, cada R' es independientemente H o alquilo

Preferiblemente, R^3 es un anillo fenilo opcionalmente sustituido en las posiciones *meta o para* con uno o más grupos representados por R^{11} Los valores más preferidos para R^{11} y R^Z son halógeno, haloalquilo, $-R^o$, $-OR^o$ y $-O$(haloalquilo). $-NR'SO_2R^o$ y $-N(R')_2$ también son valores preferidos para R^{11}

Más preferiblemente, R^3 es un anillo fenilo opcionalmente sustituido en la posición *para* con R^{11}. R^1 es un anillo fenilo opcionalmente sustituido en la posición *meta* con R^Z. Los valores aún más preferidos para R^Z y R^{11} son cloruro, fluoruro, bromuro, $-OR^o$ o R^o $-NR'SO_2R^o$ y $-N(R')_2$ también son valores preferidos para R^{11} Cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo C1-C3 Cada R' es independientemente hidrógeno o un grupo alquilo C1-C3

R^{14} es un sustituyente opcional, preferiblemente en las posiciones seis y siete del anillo fenilo A; los valores preferidos son halógeno R^o, $-OR^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, -CN, $-OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, $NHC(O)NR^o_2$, $(CH_2)_nOH$, $O(CH_2)_nOH$, $(CH_2)_nC(O)NR^o_2$ o $O(CH_2)_nC(O)NR^o_2$. R^o es hidrógeno, haloalquilo o un grupo alquilo C1-C3.

En ciertos aspectos los siguientes compuestos están excluidos de la presente invención:

Cuando R^1 es fenilo *para* sustituido con $V\text{-}T\text{-}R^Y$, R^2 es metilo, R^3 es *para* clorofenil, R^x es $C(O)CH_3$, X_1 es $-C(O)$ y V es $-O-$, $T\text{-}R^Y$ es $-CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}CONH_2$, $-CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}OH$, $-CH_2\text{-}CH_2\text{-}CH_2\text{-}C(CH_3)_2\text{-}OH$, $-CH_2\text{-}CH_2\text{-}$

$C(CH_3)_2$-COOH, $-CH_2$-C (espiro ciclopropil)-CH_2-COOH o $-CH_2-C(CH_3)_2$-COOH).

Cuando R^1 es fenilo *para* sustituido con V-T-R^Y, R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es –C(O) y V es un enlace covalente entonces, T-R^Y es $-CH_2-CH_2-COOH$

Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es fenilo *para* sustituido con V-R^9 en el que R^9 es un grupo heterocíclico no aromático opcionalmente sustituido, V es un enlace covalente, R^1 es *N*-morfolinilo, *N*-etoxicarbonil-4-piperidinilo, *N*-acetil-4-piperdinilo, *N*-etoxicarbonil-4-piperidi-3-enilo, *N*-pirrolidinilo, *N*-etil-*N'*-piperazinilo, *N*-acetil-*N'*-pierazinilo o N-($CH_2C(O)NH_2$)-*N'*-piperazinilo

Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X^1 es C(O) y R^1 fenilo *para* sustituido con V-R^9 en el que R^9 es un grupo heterocíclico no aromático opcionalmente sustituido, V es –O-, R^1 es *N*-etoxicarbonil-4-piperdinilo o *N*-acetil-4-piperdinilo

Cuando R^2 es metilo, R^3 es fenilo, R^x es $C(O)CH_2CH_3$, X^1 es C(O) y R1 es fenilo *para* sustituido con un grupo heterocíclico no aromático, R^1 es *N*-acetil-4-piperdinilo o *N*-morfolinilo

Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X^1 es C(O) y R^1 fenilo condensado con un grupo heterocíclico no aromático opcionalmente sustituido, R^1 es tetrahidrofuranilo n N'-metilmorfolinilo.

Cuando R^2 es metilo, R^3 es fenilo, R^x es $C(O)CH_3$, X^1 es C(O) y R1 es piridinilo *para* sustituido con un grupo heterocíclico no aromático, R^1 es *N*-morfolinilo.

Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es fenilo condensado con un grupo aromático opcionalmente sustituido, R^1 es *N*-isopropil triazolilo, *N*-metil triazolilo, *N*-isopropil imidazolilo, 2, metil *N* hidroxietil imidazolilo, 2, metil *N* carboximetil imidazolilo, *N* carboxietil triazolil *N*-isopropil pirazolilo.

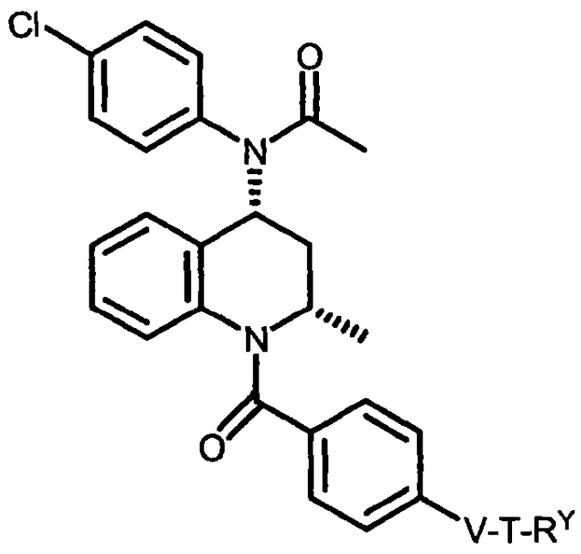
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Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es imidazolilo condensado con un grupo aromático opcionalmente sustituido, R^1 es fenilo

Cuando R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es tiazolilo condensado con un grupo aromático opcionalmente sustituido, R^1 es fenilo.

Quedan excluidos de esta invención los compuestos descritos en la Solicitud de Patente de Estados Unidos 10/678.872 presentada el 4 de octubre de 2003 (cuyos contenidos íntegros se incorporan en este documento como referencia).

Otra realización de la presente invención es un compuesto representado por la Fórmula Estructural (X):



(X)

V es un enlace covalente o -O-

T es un alquileno C_{1-10} no sustituido de cadena lineal

R^Y es $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2$, $-NR^5S(O)_2R^5$,

$S(O)_2OR^5$, $-S(O)OR^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)NR^5_2$, $-OC(O)NR^5_2$, $-NR^5_2$, $-OR^5$, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido.

El compuesto de Fórmula Estructural (X), sin embargo, excluye los compuestos en los que T-R^Y es $-CH_2R^{20}$, $-CH_2CH_2R^{21}$ o $-(CH_2)_3R^{22}$ R^{20} es -COOH, $-C(O)NH_2$, $-C(O)NHCH_3$, $C(O)N(CH_3)_2$, 5-tetrazolilo, 4-piridinilo, *N*-etil-4-piperidinilo o C(O)*N*-morfolinilo R^{21} es -COOH, *N*-morfolinilo, $C(O)NH_2$, *N*-pirrolidin-2-onilo, *N*-imidazolilo o *N*-pirrolidinilo R^{22} es -COOH, $C(O)N(CH_2CH_3)_2$, $C(O)NH(CH_2CH_3)$, $C(O)NH_2$, $C(O)NHS(O)_2CH_3$, C(O)NHOH, $C(O)OCH_2CH_3$, NH_2, $C(O)CH_3$, CN, $NHS(O)_2CF_3$, C(O)*N*-pirrolidinilo, *N*-pirrolidinilo, 5-tetrazolilo, 5-(1,2,4)oxadiazolilo, *N*-morfolinilo o *N*-imidazolilo.

El término "alquileno" como se usa en este documento se refiere a un hidrocarburo de cadena lineal que está completamente saturado Un grupo alquileno es típicamente C_{1-10}, más típicamente C_{1-6}, más preferiblemente C_{1-5} y aún más preferiblemente C_{1-3} Un "alquileno sustituido" es un grupo alquileno en el que uno o más átomos de hidrógeno del metileno se remplazan con un sustituyente. Los sustituyentes adecuados son como se describen a continuación para un grupo alquilo sustituido. Los sustituyentes preferidos para el grupo alquileno representado por T son flúor, metilo, gem dimetilo, gem difluorofluorometilo, espiro ciclopropilo, espiro ciclobutilo, espiro azetidinilo opcionalmente *N*-sustituido, espiro aziridinilo opcionalmente *N*-sustituido, espiro pirrolidinilo opcionalmente *N*-sustituido, espiro piperidinilo opcionalmente *N*-sustituido, amina, metilamina, dimetilamina o hidroxilo. Un "átomo de carbono del alquileno sustituible" es un átomo de carbono del alquileno que se une a uno o más átomos de hidrógeno. Por lo tanto, los átomos de hidrógeno pueden reemplazarse opcionalmente con el sustituyente

Los términos "alquilo", "hidroxialquilo", "carboxialquilo", "haloalquilo", "alquilamina", "dialquilamina", usados solos o como parte de un resto mayor incluyen cadenas saturadas lineales y ramificadas que contienen de uno a diez átomos de carbono, preferiblemente de uno a seis, más preferiblemente de uno a cinco y aún más preferiblemente de uno a tres

El término "alilo" como se usa en este documento tiene la fórmula -$CH_2CH=CH_2$ y puede estar opcionalmente sustituido en cualquier átomo de carbono sustituible. Un "átomo de carbono sustituible del alilo" es un átomo de carbono del alilo que se une a uno o más átomos de hidrógeno Por lo tanto, el átomo de hidrógeno puede reemplazarse opcionalmente con el sustituyente Los sustituyentes adecuados son como se han descrito para el grupo alquilo

Las expresiones "gem dialquilo" y "gem dihalo" incluyen compuestos en los que dos sustituyentes alquilo o dos sustituyentes halo, respectivamente, se unen al mismo átomo de carbono, por ejemplo, -$C(CH_3)_2$- o $C(F)_2$-.

Un grupo "espiro cicloalquilo" o "espiro heterocíclico no aromático" es un grupo cicloalquilo o heterocíclico no aromático que comparte un átomo de carbono del anillo con un átomo de carbono de un grupo alquileno o grupo alquilo

Las expresiones "carbocíclico no aromático" o "cicloalifático" incluirán hidrocarburos C_{3-10} cíclicos que están completamente saturados o que contienen una o más unidades de insaturación, pero que no son aromáticos Los grupos cicloalifáticos son típicamente C_{3-10}, más típicamente C_{3-7}.

"Alcoxi" significa (alquil)-O, "haloalcoxi" significa (haluro)-O-, "alcoxialquileno" significa (alquil)-O-(alquileno) tal como metoximetileno (CH_3OCH_2), "hidroxialquilo" significa un grupo alquilo sustituido con hidroxi, acilado significa "-C(O)-(alquilo").

El término "heteroátomo" se refiere a nitrógeno, oxígeno o azufre e incluye cualquier forma oxidada de nitrógeno o azufre, y la forma cuaternizada de cualquier nitrógeno básico El término "nitrógeno" también incluye un nitrógeno sustituible de un anillo heterocíclico. Como ejemplo, 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)

La expresión "grupo aromático" incluye grupos de anillo aromático carbocíclico y grupos de anillo heteroarilo. El término "grupo aromático" puede

usarse de forma intercambiable con los términos "arilo", "anillo arilo" o "anillo aromático".

Los grupos de anillo carbocíclico aromático tienen sólo átomos de carbono en el anillo e incluyen anillos aromáticos monocíclicos tales como fenilo y sistemas de anillos aromáticos policíclicos condensados en los que dos o más anillos aromáticos carbocíclicos se condensan uno a otro Los ejemplos incluyen 1-naftilo, 2-naftilo, 1-antracilo y 2-antracilo. También se incluye dentro del alcance del término "anillo aromático carbocíclico", como se usa en este documento, un grupo en el que un anillo aromático se condensa a uno o más anillos no aromáticos (alifáticos o heterocíclicos), tal como en un indanilo, ftalimidilo, naftimidilo, fenantridinilo o tetrahidronaftilo, donde el radical o punto de unión está en el anillo aromático

El término "heteroarilo" o "heteroaromático" se refiere a grupos de anillo heteroaromático que tienen de cinco a catorce miembros, incluyendo anillos heteroaromáticos monocíclicos y anillos aromáticos policíclicos en los que un anillo aromático monocíclico se condensa a uno o más de otros anillos aromáticos carbocíclicos o heteroaromáticos Los ejemplos de anillos heteroarilo incluyen 2-furanilo, 3-furanilo, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo, 3-isoxazolilo, 4-isoxazolilo, 5-isoxazolilo, oxadiazolilo, 2-oxadiazolilo, 5-oxadiazolilo, 2-oxazolilo, 4-oxazolilo, 5-oxazolilo, *N*-pirrolilo, 2-pirrolilo, 3-pirrolilo, pirazolilo, 2-piridinilo, 3-piridinilo, 4-piridinilo, 2-pirimidilo, 4-pirimidilo, 5-pirimidilo, 3-piridazinilo, 2-tiazolilo, 4-tiazolilo, 5-tiazolilo, 2-triazolilo, 5-triazolilo, tetrazolilo, 2-tienilo, 3-tienilo, carbazolilo bencimidazolilo, benzotienilo, benzofuranilo, indolilo, quinolinilo, benzotriazolilo, benzotiazolilo, benzooxazolilo, bencimidazolilo, isoquinolinilo, indolilo, isoindolilo, acridinilo o benzoisazolilo

También se incluye dentro del alcance del término "heteroarilo", como se usa en este documento, un grupo en el que un anillo heteroarilo se condensa a uno o más grupos heterocíclicos cicloalifáticos o no aromáticos donde el radical o punto de unión está en el anillo heteroaromático Los ejemplos incluyen tetrahidroquinolinilo, tetrahidroisoquinolinilo y pirido[3,4-d]pirimidinilo El término

"heteroarilo" puede usarse de forma intercambiable con el término "anillo heteroarilo" o el término "heteroaromático".

El término "grupo heterocíclico no aromático" o "anillo heterocíclico no aromático" se refiere a sistemas de anillo no aromáticos que tienen típicamente de tres a catorce miembros, preferiblemente de tres a seis, donde uno o más carbonos del anillo, preferiblemente de uno a cuatro, se reemplazan cada uno con un heteroátomo tal como N, O o S. Los ejemplos de anillos heterocíclicos no aromáticos incluyen 3-tetrahidrofuranilo, 2-tetrahidropiranilo, 3-tetrahidropiranilo, 4-tetrahidropiranilo, [1,3]-dioxalanilo, [1,3]-ditiolanilo, [1,3]-dioxanilo, 2-tetrahidrotiofenilo, 3-tetrahidrotiofenilo, 2-morfolinilo, 3-morfolinilo, *N*-morfolinilo, 2-tiomorfolinilo, 3-tiomorfolinilo, 4-tiomorfolinilo, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, *N*-piperazinilo, 2-piperazinilo, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, piperidinonilo, 4-tiazolidinilo, diazolonilo, diazolonilo *N*-sustituido, oxazolidinilo, tetrahidrotienilo, imidazolidinilo, imidazolidinonilo, pirrolidinonilo, S,S-dióxido de isotiazolidinilo, pipendinilo, 1-ftalimidinilo, 3-1*H*-bencimidazol-2-ona, benzoxanilo, benzopirrolidinilo, benzopipendinilo, benzoxolanilo, benzotiolanilo y benzotianilo

Un grupo "aromático sustituido" es un grupo aromático con un sustituyente en uno o más átomos de carbono del anillo o átomos de nitrógeno del anillo sustituibles. Cada sustituyente se selecciona independientemente. Los ejemplos de sustituyentes adecuados sobre un átomo de carbono insaturado o átomo de carbono sustituible de un grupo aromático son como se han descrito anteriormente para R^Z, R^{11} y R^{14}.

Un "átomo de carbono del anillo sustituible" en un anillo aromático (incluyendo los grupos aromáticos representados por el Anillo A, anillo fenilo A, R^1 y R^3) es un átomo de carbono del anillo que se une a un átomo de hidrógeno. Por lo tanto, el átomo de hidrógeno puede reemplazarse opcionalmente con el sustituyente. Por tanto, el término "átomo de carbono del anillo sustituible" en un anillo aromático excluye los átomos de carbono del

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anillo que se condensan con otros anillos o que se representan como ya unidos aun sustituyente.

Un grupo alquilo o un heterociclo o carbociclo no aromático puede contener uno o más sustituyentes en cualquier átomo de carbono sustituible. Un "átomo de carbono del alquilo sustituible" es un átomo de carbono del alquilo que se une a uno o más átomos de hidrógeno. Por lo tanto, los átomos de hidrógeno pueden reemplazarse opcionalmente con el sustituyente. Los ejemplos de sustituyentes adecuados sobre el carbono saturado de un grupo alquilo o un heterociclo no aromático incluyen aquellos listados anteriormente para el carbono insaturado de un grupo aromático y, en los átomos de carbono internos de un grupo alquilo o sobre los átomos de carbono del anillo de un grupo heterocíclico no aromático, los siguientes: =O, =S, =NNHR*, =NN(R*)$_2$, =NNHC(O)R*, =NNHCO$_2$(alquilo), =NNHSO$_2$(alquilo) o =NR*. Cada R* se selecciona independientemente entre hidrógeno, un grupo alquilo no sustituido o un grupo alquilo sustituido Los ejemplos de sustituyentes sobre el grupo alquilo representado por R* incluyen amino, alquilamino, dialquilamino, aminocarbonilo, halógeno, alquilo, alquilaminocarbonilo, dialquilaminocarbonilo, alquilaminocarboniloxi, dialquilaminocarboniloxi, alcoxi, nitro, ciano, carboxi, alcoxicarbonilo, alquilcarbonilo, hidroxi, haloalcoxi o haloalquilo.

Los sustituyentes adecuados sobre el nitrógeno sustituible de un grupo heteroarilo o heterocíclico aromático incluyen-R^{12}, -N(R^{12})$_2$, -C(O)R^{12}, -CO$_2R^{12}$, -C(O)C(O)R^{12}, -C(O)CH$_2$ C(O)R^{12}, -SO$_2R^{12}$, -SO$_2$N(R^{12})$_2$, -C(=S)N(R^{12})$_2$, -C(=NH)-N(R^{12})$_2$ y -NR^{12}SO$_2R^{12}$, donde R^{12} es hidrógeno, un grupo alquilo, un grupo alquilo sustituido, fenilo (Ph), Ph sustituido, -O(Ph), -O(Ph) sustituido, CH$_2$(Ph) o un anillo heteroarilo o heterocíclico no aromático no sustituido Los ejemplos de sustituyentes sobre el grupo alquilo o el anillo fenilo representado por R^{12} incluyen amino, alquilamino, dialquilamino, aminocarbonilo, halógeno, alquilo, alquilaminocarbonilo, dialquilaminocarboniloxi, alcoxi, nitro, ciano, carboxi, alcoxicarbonilo, alquilcarbonilo, hidroxi, haloalcoxi o haloalquilo Un "átomo de nitrógeno del anillo sustituible" en un grupo heteroarilo o heterocíclico no aromático que contiene nitrógeno es un átomo de nitrógeno del

anillo que se une a un átomo de hidrógeno. Por lo tanto, el átomo de hidrógeno puede reemplazarse opcionalmente con el sustituyente Por lo tanto, el término "átomo de nitrógeno del anillo sustituible" excluye los átomos de nitrógeno del anillo que se representan como ya unidos a un sustituyente, y los átomos de nitrógeno del anillo que son átomos del anillo en dos anillos condensados (como en, por ejemplo, indolizina) y los átomos de nitrógeno del anillo que tienen tres enlaces covalentes a otros átomos del anillo (como por ejemplo piridina).

En ciertos casos, los compuestos de la presente invención pueden asociarse en forma aislada con disolvente o agua, como en un "solvato" o "hidrato". Las referencias a los compuestos o fórmulas estructurales descritas que representan los compuestos descritos pretenden incluir tales solvatos e hidratos.

De forma adicional, las sales farmacéuticamente aceptables de los compuestos descritos en este documento también se incluyen en la presente invención y pueden usarse en las composiciones y métodos descritos en este documento Por ejemplo, puede obtenerse una sal de ácido de un compuesto que contiene un resto amina y otro básico haciendo reaccionar el compuesto con un ácido orgánico o inorgánico adecuado, tal como ácido clohídrico, ácido bromhídrico, ácido acético, ácido perclórico y similares. Los compuestos con un resto de amonio cuaternario también contiene un contraión tal como cloro, bromo, yodo, acetato, perclorato y similares. Otros ejemplos de estas sales incluye clorhidratos, bromhidratos, sulfatos, metanosulfonatos, nitratos, maleatos, acetatos, citratos, fumaratos, tartratos [por ejemplo (+)-tartratos, ( ) tartratos o mezcla de los mismos incluyendo mezclas racémicas], succinatos, bernzoatos y sales con aminoácidos tales como ácido glutámico

Las sales de los compuestos que contienen un ácido carboxílico u otro resto funcional ácido pueden prepararse por reacción con una base adecuada. Esta sal farmacéutica aceptable puede hacerse con una base que proporciona un catión farmacéuticamente aceptable, el cual incluye sales de metales alcalinos (especialmente de sodio y potasio), sales de metales alcalinoterreos

(especialmente calcio y magnesio), sales de aluminio y sales de amonio, así como sales hechas a partir de bases orgánicas fisiológicamente aceptables tales como trimetilamina, trietilamina, morfolina, piridina, piperidina, picolina, diciclohexilamina, N,N'-dibenziletilendiamina, 2-hidroxietilamiona, bis-(2-hidroxietil)amina, tri-(2-hidroxietil)amina, procaina, dibenzilpiperidina, deshidroabietilamina, N,N'-bisdeshidroabietilamino, glucamina, N-metilglucamina, colidina, quinina, quinolina y aminoácidos básicos tales como lisina y arginina.

Los compuestos, composiciones farmacéuticas y métodos descritos pueden usarse para inhibir la actividad CRTH2, para inhibir la actividad de PGD2 y para inhibir o tratar (de forma terapéutica o profiláctica) trastornos con un componente inflamatorio y afecciones alérgicas mediadas por células Th2, eosinófilos y basófilos

Los ejemplos de afecciones alérgicas para las que se cree que los compuestos, composiciones farmacéuticas y métodos descritos son particularmente eficaces incluyen asma alérgica, dermatitis atópica y rinitis alérgica Otras afecciones alérgicas incluyen anafilaxis sistémica o respuestas de hipersensibilidad, alergias a fármacos (por ejemplo, a penicilina, cefalosporinas), alergias a picaduras de insectos y dermatosis tales como dermatitis, eccema, dermatitis atópica, dermatitis alérgica y urticaria por contacto.

Los ejemplos de enfermedades con un componente inflamatorio para las que se cree que los compuestos, composiciones farmacéuticas y métodos descritos son particularmente eficaces incluyen artritis reumatoide, osteoartritis, enfermedad inflamatoria del intestino [por ejemplo, tal como colitis ulcerativa, enfermedad de Crohn, ileítis, enfermedad celíaca, esprue no tropical, enteritis, enteropatía asociada con artropatías seronegativas, colitis microscópica o colagenosa, gastroenteritis eosinofílica o pouchitis como resultado de proctocolectomía, y anastomosis ileoanal] y trastornos de la piel [por ejemplo, psoriasis, eritema, pruritis y acné].

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Muchas enfermedades autoinmunes también tienen un componente inflamatorio. Los ejemplos incluyen esclerosis múltiple, lupus eritematoso sistémico, miastenia gravis, diabetes de comienzo juvenil, glomerulonefritis y otras nefritis, tiroiditis autoinmune, enfermedad de Behcet y rechazo a injerto (incluyendo rechazo a aloinjerto o enfermedad injerto-contra-hospedador) Se cree que el componente inflamatorio de estos trastornos se media, al menos en parte, por CRTH2

Las enfermedades caracterizadas por la reperfusión tienen un componente inflamatorio que se cree que se media, al menos en parte, por CRTH2 Los ejemplos incluyen apoplejía, isquemia cardiaca y similar Los compuestos y composiciones descritas también pueden usarse para tratar estos trastornos.

Otras enfermedades y afecciones con un componente inflamatorio que se cree que se media 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 dan como resultado fibrosis intersticial, tales como enfermedades intersticiales del pulmón (ILD) (por ejemplo, fibrosis pulmonar idiopática, o ILD asociada con artritis reumatoide, u otras afecciones autoinmunes), neumonitis de hipersensibilidad, enfermedades de colágeno y sarcoidosis Otras enfermedades o afecciones más con componentes inflamatorios que pueden tratarse de acuerdo con los métodos descritos en este documento incluyen vasculitis (por ejemplo, vasculitis necrotizante, cutánea y de hipersensibilidad), espondiloartropatías, escleroderma, ateroesclerosis, restenosis y miositis (incluyendo polimiositis, dermatomiositis), pancreatitis y diabetes mellitus dependiente de insulina.

Un sujeto con una de las enfermedades o afecciones nombradas anteriormente se dice que "necesita de la inhibición de CRTH2". El sujeto con una enfermedad o afección de este tipo se "trata" cuando al menos se alivia uno de los síntomas asociados con la enfermedad o afección (tratamiento

terapéutico) o se inhibe o previene (tratamiento profiláctico), en su totalidad o en parte

Un "sujeto" es un mamífero, preferiblemente un humano, pero también puede ser un animal que necesita un tratamiento veterinario, por ejemplo, animales de compañía (por ejemplo, perros, gatos y similares), animales de granja (por ejemplo, vacas, ovejas, cerdos, caballos y similares) y animales de laboratorio (por ejemplo, ratas, ratones, cobayas y similares) Como se indica anteriormente, un "sujeto que necesita de inhibición de CRTH2" es un sujeto en quien puede obtenerse un efecto terapéutico o profiláctico beneficioso inhibiendo la función o actividad de CRTH2.

Una "cantidad eficaz" de los inhibidores de CRTH2 descritos es la cantidad que inhibe la actividad de CRTH2 en un sujeto que necesita de esta inhibición, o la que, cuando se administra a un sujeto que tiene un afección o enfermedad que puede tratarse de forma profiláctica o terapéutica inhibiendo la actividad de CRTH2, mejora los síntomas de la enfermedad, retrasa la aparición de los síntomas y/o aumento la longevidad. La cantidad precisa de inhibidor de CRTH2 administrada al sujeto dependerá del tipo y gravedad de la enfermedad o afección y de las características del sujeto, tales como estado general de salud, edad, sexo, peso corporal y tolerancia a fármacos. La dosificación también puede variar de acuerdo con la vía de administración, que incluye oral, aerosol, rectal, transdérmica, subcutánea, intravenosa, intramuscular, intraperitoneal e intranasal.

El especialista será capaz de determinar dosificaciones apropiadas dependiente de estos y otros factores. Una "cantidad eficaz" típicamente oscila entre aproximadamente 0,01 mg/kg/día a aproximadamente 100 mg/kg/día, preferiblemente entre aproximadamente 0,5 mg/kg/día a aproximadamente 50 mg/kg/día

Los inhibidores de CRTH2 descritos en este documento y las sales farmacéuticamente aceptables de los mismos pueden usarse en preparaciones farmacológicas en combinación con un vehículo o diluyente farmacéuticamente aceptable Los vehículos farmacéuticamente aceptables incluyen cargas o

diluyentes sólidos inertes y soluciones acuosas u orgánicas estériles El inhibidor de CRTH2 se presentará en estas composiciones farmacéuticas en cantidades suficientes como para proporcionar la cantidad de dosificación deseada en el intervalo descrito en este documento. Las técnicas para formulación y administración de los compuestos de la presente invención pueden encontrarse en Remington the Science and Practice of Pharmacy, 19ª edición, Marck Publishing Co , Easton, PA (1995)

Para administración oral, puede combinarse el inhibidor de CRTH2 o sales del mismo con un vehículo o diluyente sólido o líquido adecuado para formar cápsulas, comprimidos, píldoras, polvos, jarabes, soluciones, suspensiones y similares.

Los comprimidos, píldoras, cápsulas y similares contiene de aproximadamente el 1 a aproximadamente el 99 por ciento del peso del ingrediente activo y un aglutinante tal como la goma de tragacanto, goma arábiga, almidón de maíz o gelatina, excipientes tales como fosfato dicálcico; un agente desintegrante tal como almidón de maiz, almidón de patata, ácido algínico, un lubricante tal como estearato de magnesio; y un agente edulcorante tal como sacarosa, lactosa o sacarina. Cuando la forma de unidad de dosificación es una cápsula, ésta puede contener, además de materiales del tipo anterior, un vehículo líquido tal como un ácido graso.

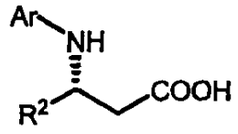
Pueden estar presentes otros materiales diversos como recubrimientos o para modificar la forma física de la unidad de dosificación. Por ejemplo, los comprimidos puede recubrirse con goma, azúcar o ambos, Un jarabe o elixir puede contener, además del ingrediente activo, sacarosa como agente edulcorante, metil y propilparabenos como conservantes, un colorante y un aromatizante tal como aroma de cereza o de naranja.

Para la administración parenteral, el inhibidor de CRTH2 descrito, o sales del mismo, puede combinarse con medios acuosos u orgánicos estériles para formar soluciones o suspensiones inyectables. Por ejemplo, pueden usarse soluciones en aceite de sésamo o de cacahuete, propilenglicol acuoso y similares, así como soluciones acuosas de sales farmacéuticamente

aceptables de los compuestos solubles en agua También pueden prepararse dispersiones en glicerol, polietilenglicoles líquidos y mezcla de los mismos en aceites En condiciones normales de almacenamiento y uso, estas preparaciones contienen un conservante para prevenir el crecimiento de microorganismos.

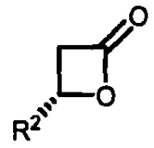
Además de las formulaciones descritas previamente, los compuestos también pueden formularse como una preparación de almacenamiento Estas formulaciones de actuación a largo plazo pueden administrarse por implantación por vía, por ejemplo, subcutánea o intramuscular o por inyección intramuscular. De esta manera, por ejemplo, como una emulsión en un aceite aceptable, o resina de intercambio iónico como derivados solubles en pequeñas cantidades, por ejemplo, como pequeñas cantidades de sales solubles.

Otra realización de la presente invención es un método para preparar un compuesto aminoácido representado por la Fórmula Estructural (XI):



(XI)

El método comprende la etapa de hacer reaccionar Ar-NH_2 con una lactona representada por la Fórmula Estructural (XXII).



(XII)

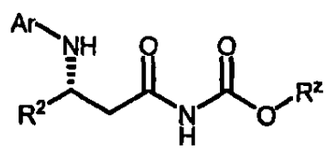
Ar es un grupo aromático monocíclico opcionalmente sustituido y R^2 es alquilo C1-C3 Preferiblemente, Ar es un grupo fenilo opcionalmente sustituido y R^2 es metilo o etilo. Los sustituyentes adecuados para Ar son como se han descrito anteriormente para el anillo A o el Anillo Fenilo A, con la condición, sin embargo, de que se protejan los grupos funcionales que pueden interferir con la reacción Los grupos funcionales que requieren protección serán obvios para el especialista en la técnica e incluyen aminas, alcoholes, ácidos carboxílicos y

similares. Los ejemplos de sustituyentes preferidos incluyen halo, ciano, R^o, -OR^{30}, -CO_2R^{31}, -$C(O)R^o$, -$C(O)N(R^x)_2$, -$OC(O)R^o$, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)NR^x_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)NR^x_2$, $O(CH_2)_nC(O)NR^x_2$; n es un número entero de 1-4, R^o es independientemente hidrógeno, C_{1-3} haloalquilo o un grupo alquilo C1-C3, un R^x es -H o alquilo C_1-C_3 y el otro es un grupo protector de amina; R^{30} es un grupo protector de alcohol, y R^{31} es un grupo protector de ácido carboxílico Los grupos protectores adecuados se conocen bien en la técnica y se describen, por ejemplo, en Greene y Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991) Las enseñanzas completas de Greene y Wits se incorporan en este documento como referencia. Ar es un grupo fenilo

También se incluye dentro de la presente invención la reacción correspondiente con el enantiómero del compuesto aminoácido representado por la Fórmula Estructural (XII), formando de esta manera el enantiómero del compuesto representado por la Fórmula Estructural (XI).

La reacción de la arilamina y la lactona cíclica anterior puede realizarse en disolventes en los que ambos reactivos son solubles Los ejemplos incluyen disolventes próticos (tales como agua y metanol) y disolventes apróticos polares (dimetilformamida, dimetilsulfóxido, hexametilfosforamida y similares) Puede usarse un exceso de un reactivo en relación con el otro (por ejemplo, un exceso de hasta diez veces), sin embargo, son más típicas las cantidades equimolares. La reacción se realiza típicamente al punto de ebullición del disolvente que se usa, pero también puede realizarse normalmente a temperaturas que varían de la temperatura ambiente a temperaturas de hasta 200°C Las temperaturas de 70°C a 90°C son las más comúnmente usadas

Otra realización es un método para preparar un compuesto intermedio representado por la Fórmula Estructural (XIII) a partir del compuesto aminoácido representado por la Fórmula Estructural (XI)



(XIII)

El método comprende la etapa de amidar el grupo ácido carboxílico del compuesto aminoácido con $NH_2C(O)OR^z$. El grupo $-C(O)OR^z$ es un grupo protector de amina que tomado junto con $-NH_2$ forma un carbamato De esta manera, R^z es un grupo alquilo, alilo o arilo sustituido o no sustituido Los sustituyentes que pueden estar presentes en el grupo alquilo, alilo o arilo representado por R^z son aquellos que no interfieren en las reacciones que se realizan y se reconocen fácilmente por el especialista. Los ejemplos incluyen alquilo, halógeno y alcoxi De esta manera, los valores adecuados para R^z se conocen bien por los especialistas y se describen, por ejemplo, en Green y Wuts, "Protective Groups in Organic Synthesis", John Wiley & Sons (1991) Los ejemplos específicos incluyen, aunque sin limitación, bencilo, metilo, etilo, alilo, 2,2,2,-triclorometilo, 2,2,2-tricloro-*terc*-butilo, *terc*-butilo o fluorenilmetilo

La expresión "amidación con un ácido carboxílico con $NH_2C(O)OR^z$" se refiere a convertir un ácido carboxílico (-COOH) en la amida $-C(O)NHC(O)OR^z$ en una o más etapas de reacción. Se conocen en la técnica muchos métodos para convertir un ácido carboxílico en una amida Típicamente, el ácido carboxílico se convierte primero en un grupo que puede desplazarse más fácilmente con una amina o amida que -OH. De esta manera, -OH se convierte en un mejor grupo saliente Un "grupo saliente" es un grupo que puede desplazarse fácilmente mediante un nucleófilo. En la presente invención, el compuesto aminoácido puede convertirse directamente en el compuesto intermedio activando el ácido carboxílico del compuesto aminoácido y después haciéndose reaccionar con $NH_2C(O)OR^z$ Como alternativa, el ácido carboxílico puede convertirse primero en la carboxamida ($-C(O)NH_2$) activando el grupo ácido carboxílico del compuesto aminoácido y después haciéndolo reaccionar con NH_3 o un grupo funcional equivalente del mismo (por ejemplo, NH_4Cl) y después protegiendo la carboxamida resultante. Cuando se usa $NH_2C(O)OR^z$

como nucleófilo, la amidación se realiza preferiblemente en presencia de al menos un equivalente de una base no nucleófila tal como un alcóxido (*terc*-butóxido de litio, *terc*-butóxido potásico, isopropóxido de litio e isopropóxido de potasio) o base de amida (Por ejemplo, isopropilamida de litio o potasio o hexametilpiperidida)

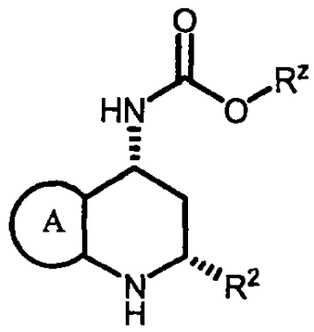
En un ejemplo, -OH del ácido carboxílico se convierte en un grupo saliente mejor reemplazándolo con un halógeno, típicamente con cloruro. El ácido carboxílico se convierte por tanto en un haluro de ácido, por ejemplo, un cloruro de ácido. Los reactivos adecuados para preparar cloruros de ácido a partir de ácidos carboxílicos se conocen bien en la técnica e incluyen cloruro de tionilo, cloruro de oxalilo, tricloruro de fósforo y pentacloruro de fósforo Típicamente, cada grupo ácido carboxílico se hace reaccionar con aproximadamente un equivalente o un ligero exceso de cloruro de tionilo, cloruro de oxalilo, tricloruro de fósforo y pentacloruro de fósforo en un disolvente inerte tal como un disolvente etéreo (por ejemplo, éter dietílico, tetrahidrofurano o 1,4-dioxano), un disolvente halogenado (por ejemplo, cloruro de metileno o 1,2-dicloroetano) o disolvente aromático (por ejemplo, benceno o tolueno) CUando se usa cloruro de oxalilo, normalmente se añade una amina terciaria para acelerar la reacción en cantidades que varían de una cantidad catalítica a aproximadamente un equivalente en relación con el cloruro de oxalilo.

Como alternativa, el ácido carboxílico se convierte primero en un "éster activado" Un éster -COOR se dice que es "activado" cuando -OR se desplaza fácilmente mediante una amina o amida que -OH -OR es más fácilmente desplazable según R se vuelve más fáciles de retirar electrones Algunos ésteres activados son suficientemente estables como para aislarse, por ejemplo, ésteres en los que R es fenilo o fenilo sustituido. Por ejemplo, puede prepararse malonato de difenilo a partir de cloruro de malonilo y fenol, ambos disponibles en el mercado por Aldrich Chemical Co., Milwaukee, WI., mediante los procedimientos anteriores. Otros ésteres activados son más reactivos y se preparan generalmente y se usan in situ

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La formación de un éster activado in situ requiere un "agente de acoplamiento", también denominado "agente activante de ácido carboxílico", que es un reactivo que reemplaza al grupo hidroxilo de un ácido carboxílico con un grupo que es susceptible de desplazamiento nucleófilo. Los ejemplos de agentes de acoplamiento incluyen 1,1'-carbonildiimidazol (CDI), cloroformiato de isobutilo, dimetilaminopropiletil-carbodiimida (EDC), diciclohexilcarbodiimida (DCC) Cuando se amida por generación in situ de un éster activado, puede usarse un exceso del ácido carboxílico o amina (típicamente un exceso de 50%, más típicamente un exceso de aproximadamente 10-15%). Sin embargo, es más común cuando se realiza la presente invención usar cantidades equimolares de ambos reactivos Generalmente, se usan de aproximadamente 1,0 equivalentes a aproximadamente 10 equivalentes de agente de acoplamiento en relación con cada grupo de ácido carboxílico, preferiblemente de aproximadamente 1,0 equivalentes a 1,5 equivalentes. Cuando se usa DCC, normalmente se añade un ácido débil tal como 1-hidroxibenzotriazol (HOBt) para acelerar la reacción. Típicamente, se usan entre uno y aproximadamente 1,5 equivalentes de HOBt en relación con DCC, preferiblemente entre uno y aproximadamente 1,2 equivalentes. La reacción se realiza generalmente en disolventes apróticos inertes, por ejemplo, disolventes halogenados tales como cloruro de metileno, dicloroetano y cloroformo, disolventes etéreos tales como tetrahidrofurano, 1,4-dioxano y éter dietílico y dimetilformamida. La temperatura de reacción adecuada generalmente varía de aproximadamente 0°C a aproximadamente 100°C, pero la reacción se realiza preferiblemente a temperatura ambiente.

Otra realización más de la presente invención es un método para preparar un compuesto producto representado por la Fórmula Estructural (XIV):



(XIV)

El método comprende la etapa de reducir el carbonilo de la amida del compuesto intermedio para formar un segundo intermedio y después ciclar el segundo intermedio para formar el compuesto producto Las variables de la Fórmula Estructural (XIV) son como se han descrito anteriormente para las Fórmulas Estructurales (XI)-(XIII). El "carbonilo de la amida" se entiende como el carbonilo que está entre el carbono metileno y el átomo de nitrógeno y no el carbonilo que se une a un átomo de nitrógeno y otro de oxígeno.

Para realizar la etapa de reducción, se usa un agente reductor que puede reducir el carbonilo de la amida pero no el grupo carbamato Un ejemplo común es borohidruro sódico junto con un Ácido de Lewis tal como cloruro de magnesio o cloruro de calcio. La etapa de reducción se realiza típicamente en un disolvente alcohólico tal como metanol o etanol. Puede usarse un exceso de borohidruro sódico y Ácido de Lewis de hasta 50%, pero típicamente se usan de 0,5 a 1,0 equivalentes de borohidruro sódico y de 0,5 a 2,0 equivalentes de Ácido de Lewis.

La etapa de ciclación se realiza en ácido acuoso o alcohólico diluido, usando, por ejemplo, HCl de 0,1 N a 10 N, H_2SO_4, H_3PO_4 o un ácido sulfónico tal como ácido metanosulfónico, ácido toluenosulfónico o ácido fenilsulfónico Más típicamente, se usa ácido entre 0,8 N y 1,2 N. Comúnmente, también está presente un ácido orgánico, tal como ácido acético, ácido benzoico, ácido cítrico y similares, por ejemplo entre 0,5 equivalentes y 10 equivalentes Típicamente, se usa un co-disolvente inmiscible en agua o alcohol. Los co-disolventes comunes incluyen disolventes halogenados tales como

diclorometano o cloroformo y disolventes etéreos tales como tetrahidrofurano y éter dietílico

Otra realización de la presente invención es un método para preparar el compuesto producto representado por la Fórmula Estructural (XIV) a partir de la lactona cíclica representada por la Fórmula Estructural (XII) El método comprende combinar las tres etapas de reacción descritas anteriormente. Como alternativa, el enantiómero del compuesto representado por la Fórmula Estructural (XIV) se prepara usando las tres mismas etapas de reacción, con la condición, sin embargo, de que se usa el enantiómero de la lactona de partida representada por la Fórmula Estructural (XII)

Otra realización más de la presente invención es un compuesto representado por cualquiera de las Fórmulas Estructurales (XI)-(XIV)

La invención se ilustra mediante los siguientes ejemplos que no pretenden ser limitantes de ningún modo

EJEMPLIFICACIÓN

General. Todas las reacciones que implican reactivos sensibles al aire se realizaron en una atmósfera de nitrógeno. Los reactivos se usaron como se recibieron de los proveedores comerciales a menos que se indique otra cosa. Los datos ^{1}H RMN se registraron usando el instrumento Bruker UltraShield 300 MHz/54 mm equipado con un Auto Muestreador Bruker B-ACS60 o el instrumento Varian 300 MHz. Los intermedios y compuestos finales se purificaron por cromatografía ultrarrápida usando uno de los siguientes instrumentos 1. Recolector Ultrarrápido Biotage de 4 canales Quad UV equipado con un Módulo de Bomba Quad 1 y el módulo de Cartucho Quad 12/25. 2 Recolector Ultrarrápido Biotage de 12 canales Quad UV equipado con un Módulo de Bomba Quad 3 y un módulo de Cartucho Quad 3. 3 Instrumento de cromatografía ultrarrápida ISCO combi-flash. Los espectros LC/ES se obtuvieron usando una MicroMass Platform LC (columna Phenomenex C18, 5 micras, 50 x 4,6 mm) equipado con un Manejador de Líquidos Gilson 215. Las condiciones de LC/MS convencionales son las siguientes:

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CONDICIONES PATRÓN-ÁCIDO FÓRMICO:

%A (Agua)	95,0
%D (Acetonitrilo)	5,0
% Ácido Fórmico	0,1
Flujo (ml/min)	3,500
Tiempo de detención (min)	4,4
Presión Mín (bar)	0
Presión Máx (bar)	400
Temperatura Izquierda del horno (°C)	25,0
Temperatura Derecha del horno (°C)	25,0

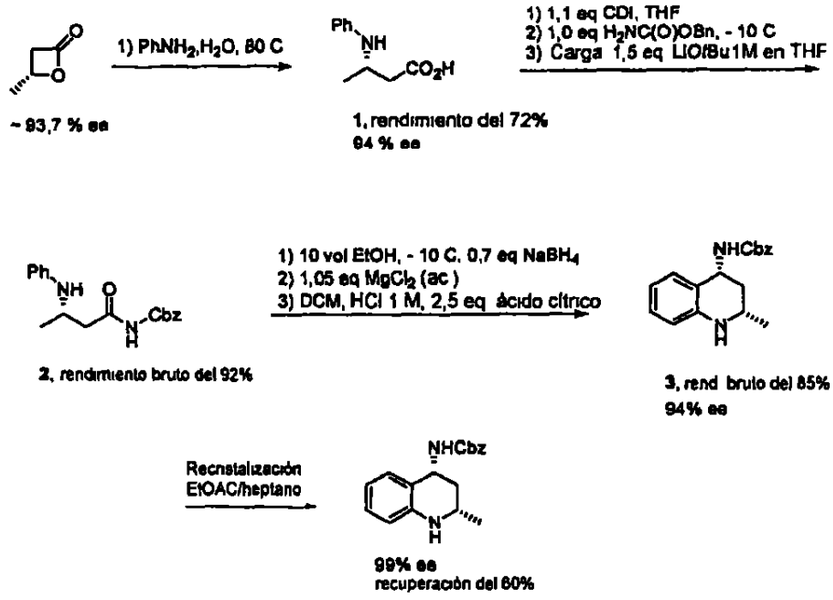
Tabla de tiempo del Gradiente de Bomba HP1100 LC

La tabla de tiempo del gradiente contiene 5 entradas que son

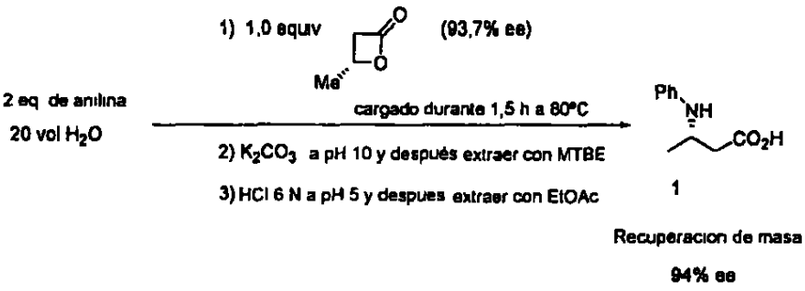
Tiempo	%A	%B	%C	%D	Flujo	Presión
0,00	0,0	0,0	95,0	5,0	3,500	400
3,50	0,0	0,0	0,0	100,0	3,500	400
4,30	0,0	0,0	0,0	100,0	3,500	400
4,40	0,0	0,0	95,0	5,0	4,000	400
5,00	0,0	0,0	95,0	5,0	4,000	400

LOS DATOS DE LC-MS SE ADQUIRIERON USANDO EL MÉTODO DEL "ÁCIDO FÓRMICO-PATRÓN" A MENOS QUE SE INDIQUE OTRA COSA.

Esquema 1



Esquema 2

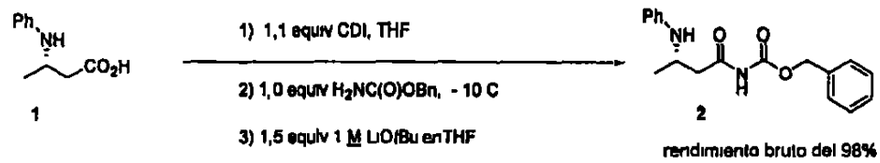


Ácido (S)-3-fenilamino-butírico (1)

Un reactor cilíndrico con camisa, válvula en el fondo, de 3 bocas y 30 l equipado con agitador en la parte superior, condensador de reflujo, embudo de adición y entrada de N_2 se lavó abundantemente con N_2 Se cargó agua (8,7 l) seguido de anilina (423 l, 4,9 mol). Se inició la agitación y la temperatura interna se estableció a 80°C. Después de que la temperatura interna alcanzara 77°C, se cargó (R)-β-butirolactona durante 1,5 h mediante un embudo de adición La temperatura interna se mantuvo entre 80-81,7°C durante el transcurso de la adición Cuando se completó la adición, la reacción se enfrió a 20°C durante 1 h. Se cargó K_2CO_3 (250 g, 1,8 mol, 0,75 equiv) en forma de un sólido y se determinó que el pH era de 10. La fase acuosa se extrajo con MTBE (3 x 2 l) y los extractos se desecharon. Después de ajustar el pH de la fase acuosa a 5 con HCl 6 N (225 ml), se extrajo con EtOAc (3 x 2 l). Después de cada extracción, el pH se comprobó y se ajustó de nuevo a 5 con HCl 6 N según fue necesario. Los extractos de EtOAc combinados se lavaron con salmuera saturada (2 l), se secaron con $MgSO_4$ y se concentraron por evaporación rotatoria para producir un aceite rosa. Recuperación: 300 g (72%). Se determinó que exceso enantiomérico por HPLC quiral era de 94%

^{1}H RMN ($CDCl_3$) δ. 7,24 (t, 2 H), 6,81 (t, 1 H), 6,73 (d, 2 H); 3,93 (m, 1 H); 2,68 (dd, 1 H), 2,51 (dd, 1 H); 1,30 (d, 3 H).

Esquema 3



Éster bencílico del ácido (S)-(fenilamino-butiril)-carbámico (2)

Un reactor de vidrio de 5 l recubierto con una camisa, equipado con agitador en la parte superior, embudo de adición y termopar se lavó abundantemente con N_2 Se cargó en el reactor una solución de ácido (S)-3-fenilaminobutírico (1, 100 g, 558 mmol) en 800 ml de THF (8 volúmenes en relación con el aminoácido). La temperatura interna de la mezcla de reacción se estableció a 20°C. Se cargó 1,1'-carbonildiimidazol (99,5 g, 614 mmol) en la solución agitada para producir una solución limpia junto con una exotermia media (5°C) y mucho desprendimiento de gas. Después de 1 h, se cargó carbamato de bencilo (84,3 g, 558 mmol) y la temperatura interna se estableció a -15°C. A -15°C, se cargó en la reacción una solución 1 M de LiOt-Bu en THF (837 ml, 837 mmol) mediante un embudo de adición en 30 min para mantener la temperatura interna entre -10 y -15°C. La solución se volvió de color pardo pálido opaco y fue más viscosa. La temperatura interna se mantiene a aproximadamente -10°C durante 15 min más y después se deja calentar a temperatura ambiente Después de 16 h, la reacción se interrumpió mediante la adición de 1000 ml de EtOAc (10 volúmenes) seguido de 280 ml de HCl 1 N y 1000 ml de H_2O (10 volúmenes) La fase acuosa resultante fue de pH 9 Las fases se separaron y la fase acuosa se extrajo con 600 ml más de EtOAc (6 volúmenes) Las fases orgánicas se combinaron y se lavaron con 1000 ml de salmuera al 10% (10 volúmenes) La solución orgánica resultante del producto bruto se destila hasta un volumen mínimo de 500 a 700 ml a de 170 a 200 torr (22,61 - 26,60 kPa) y a una temperatura del recipiente de 35 a 40°C. Este producto bruto se repartió entre 2,0 l de HCl 1 N (20 volúmenes) y 1,0 l de MTBE La fase oleosa ámbar formada que era la sal HCl del producto se mantuvo con la fase ácida acuosa. La fase de MTBE se extrajo con 1000 ml más de HCl 1 N (10 volúmenes) y las fases de HCl combinadas se lavaron de

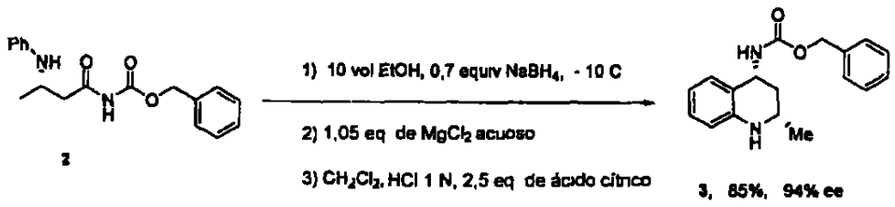
00432

440

nuevo con 500 ml más de MTBE El pH de la solución acuosa se ajustó a 9-10 mediante la adición de 495 ml de K_2CO_3 saturado acuoso. La solución básica acuosa se extrajo dos veces con 800 ml de EtOAc (8 volúmenes) y las fases orgánicas se combinaron, se lavaron con 500 ml de salmuera, se secaron sobre Na_2SO_4 y se evaporaron para producir 161 g (92%) de aceite ámbar bruto

^{1}H RMN ($CDCl_3$) δ. 7,35 (m, 5 H), 7,15 (t, 2 H); 6,72 (t, 1 H), 6,61 (d, 2 H), 5,15 (s, 2 H), 4,03 (m, 1 H), 3,02 (dd, 1 H); 2,84 (dd, 1 H); 1,28 (d, 3 H)

Esquema 4



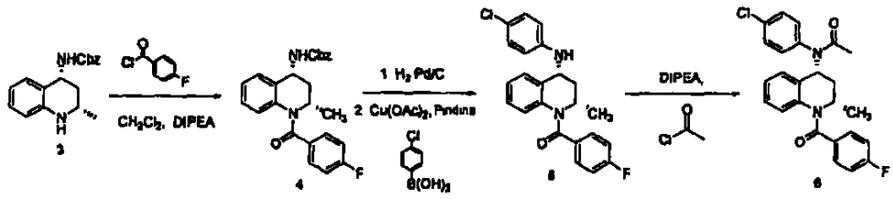
Éster bencílico del ácido (2S,4*R*)-(2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-carbámico (3)

Un reactor de vidrio de 5 l, recubierto con una camisa y equipado con agitador en la parte superior, embudo de adición y termopar se lavó abundantemente con N_2 Se cargó en el reactor una solución de éster bencílico del ácido (S)-(fenilamino-butiril)-carbámico (2) (160 g, 512 mmol) en EtOH (960 ml, 6 volúmenes) y la temperatura interna se estableció a -15°C. Se cargó el $NaBH_4$ (13,6 g, 359 mmol) en la solución agitada en 3 porciones Se cargó en el reactor una solución acuosa de $MgCl_2 \cdot 6H_2O$ (109 g, 538 mmol en 110 ml de agua) mediante un embudo de adición durante 1 h para mantener la temperatura interna entre -10 y -5°C Después de que se completara la adición, la temperatura interna se ajustó a 0°C y la mezcla se dejó en agitación durante 30 min más. El reactor se cargó con 960 ml de CH_2Cl_2 (6 volúmenes), ácido cítrico (246 g, 1280 mmol) y 960 ml de HCl 1 N (6 volúmenes). La temperatura interna se estableció a 20°C y la mezcla se dejó en agitación durante 16 h. La

mezcla de reacción se diluyó con 960 ml de EtOAc y el pH acuoso se ajustó a 9 mediante la adición de 470 ml de K_2CO_3 saturado acuoso. Las fases se separaron y la fase orgánica se lavó dos veces con 640 ml de agua y después con 640 ml de salmuera La fase orgánica se secó sobre Na_2SO_4 y se evaporó para proporcionar 130 g de un sólido (rendimiento del 86%) El producto bruto se recristalizó en 20 volúmenes de una mezcla 9/1 de heptano/EtOAc. El sólido se suspendió con 260 ml de EtOAc (2 volúmenes) y 780 ml de heptano (6 volúmenes) y se calentó a 75°C para proporcionar una solución transparente A 75°C, se añadieron lentamente 260 ml más de heptano (2 volúmenes) seguido de refrigeración gradual La cristalización comienza normalmente alrededor de 58 a 68°C. A temperatura ambiente, se añadieron lentamente 1300 ml más de heptano (10 volúmenes) Después de agitar a temperatura ambiente durante 2 h más, los sólidos se filtran y se lavan con 4 volúmenes de 9/1 de heptano/EtOAc. Los sólidos se secaron en un horno de vacío para proporcionar 90 g (recuperación del 60%). El producto tenía un exceso enantiomérico de 99,2% según se determinó por HPLC quiral

^{1}H RMN ($CDCl_3$) δ 7,38 (m, 5H); 7,22 (d, 1H); 7,07 (t, 1 H), 6,78 (t, 1 H), 6,69 (d, 1 H); 5,17 (s, 2 H); 5,07 (m, 1 H); 4,94 (d, 1 H), 3,58 (m, 1 H); 2,33 (m, 1 H), 1,60 (c, 1 H); 1,30 (d, 3 H)

Esquema 5



Procedimiento General A:

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-fluoro-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (6)

A una solución de éster bencílico del ácido (2*S*,4*R*)-(2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-carbámico (1,0 g, 3,38 mmol) en cloruro de metileno (50 ml) a temperatura ambiente se le añadió diisopropiletilamina (650 µl, 3,72 mmol) seguido de cloruro de 4-fluorobenzoílo. La reacción se agitó durante una noche a temperatura ambiente. La mezcla se vertió en agua y se extrajo con acetato de etilo Los extractos se lavaron con NaOH (ac.) 1 M y salmuera, se secaron sobre sulfato de magnesio, se filtraron, se secaron y se concentraron El residuo bruto se purificó por cromatografía sobre gel de sílice (hexanos al 75%/acetato de etilo al 25%) para producir la amida pura (720 mg, 51%).

Se disolvió éster bencílico del ácido (2*S*,4*R*)-[1-(4-fluorobenzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-carbámico (720 mg, 1,73 mmol) en etanol (30 ml) El recipiente en el que estaba la solución resultante se evacuó y se rellenó de nuevo con argón. Se añadió una cantidad catalítica de Paladio sobre Carbono (al 10%) El recipiente se evacuó de nuevo una vez más y en este momento se rellenó de nuevo con hidrógeno y se agitó en una botella Parr a 275,790 kPa de hidrógeno La reacción se completó después de 4 h. La mezcla se filtró cuidadosamente y se concentró al 10% del volumen La solución concentrada resultante se filtró a través de Celite® y se concentró para producir la amina bruta.

A una solución de (2*S*,4*R*)-(4-amino-2-metil-3,4-dihidro-2H-quinolin-1-il)-(4-fluoro-fenil)-metanona (1,0 g, 3,5 mmol) en DMF (20 ml, seca) se le añadieron ácido 4-clorofenilbórico (1,1 g, 7,0 mmol), piridina (850 µl, 10,5 mmol) y acetato de cobre (II) (1,27 g, 7,0 mmol) La mezcla verde heterogénea se agitó abierta al aire durante 1 h y después se calentó a 60°C y se agitó durante una noche (14 h). Después, la mezcla se enfrió a ta y se vertió en acetato de etilo agitado rápidamente (150 ml); los sólidos se retiraron por filtración a través de Celite®. Los extractos se lavaron varias veces con agua y después una vez con salmuera. Después, los extractos se secaron sobre sulfato de magnesio anhidro, se filtraron y se concentraron a presión reducida. El residuo bruto se purificó por cromatografía sobre gel de sílice (cloruro de

metileno al 95%/acetato de etilo al 5%) para producir el producto anilina (250 mg, 18%) en forma de un aceite amarillo.

A una solución de (2*S*,4*R*)-[4-(4-cloro-fenilamino)-2-metil-3,4-dihidro-2H-quinolin-1-il]-(4-fluoro-fenil)-metanona (250 mg, 0,636 mmol) en cloruro de metileno (5 ml) se le añadió diisopropiletilamina (120 µl, 0,70 mmol) seguido de cloruro de acetilo (90 µl, 1,27 mmol) La mezcla se agitó a ta durante 4 h La mezcla se concentró a presión reducida, se disolvió en acetato de etilo, se lavó con bicarbonato sódico sat. acuoso y salmuera y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 25/75 de hexanos/acetato de etilo) para producir *N*-(4-cloro-fenil)-*N*-[1-(4-fluoro-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida pura (200 mg, 71%).

^{1}H RMN ($CDCl_3$) δ. 1,1 (d, 3H), 1,1 (m, 1H), 2,0 (d, 3H), 2,3 (m, 1H), 4,7 (m, 1H), 5,6 (m, 1H), 6,5 (d, 1H),6,7-7,0 (m, 3H), 7,1-7,4 (m, 8H).

MS m/z· 436 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(2,3-dihidro-benzofuran-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (A-2)

Se obtuvo (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(2,3-dihidro-benzofuran-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida siguiendo el procedimiento general A, sustituyendo cloruro de de 4-fluorobenzoílo por cloruro de 2,3-dihidro-benzofuran-5-carbonilo cloruro. El resto del procedimiento se sigue como se indica en el procedimiento general A para producir (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(2,3-dihidro-benzofuran-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida

^{1}H RMN ($CDCl_3$) δ· 1,09 (d, 3H), 1,22 (t, 1H), 1,99 (s, 3H), 2,25 (s, 1H), 3,04 (m, 2H), 4,49 (t, 2H), 4,70 (m, 1H), 5,61 (s a, 1H), 6,50 (m, 2H), 6,88 (m, 2H), 7,10 (d, 2H), 7,18 (d, 2H), 7,26 (d, 1H), 7,34 (d, 2H).

MS m/z: 461,2 (M+1)

Éster etílico del ácido (2*S*,4*R*)-4-(4-(4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil)-fenil)-piperazin-1-carboxílico (A-4)

Se obtuvo éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico siguiendo el procedimiento general A, sustituyendo cloruro de 4-fluorobenzoílo por éster etílico del ácido 4-(4-clorocarbonil-fenil)-pierazin-1-carboxílico El resto del procedimiento se sigue como se indica en el procedimiento general A para producir éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico

Se preparó éster etílico del ácido 4-(4-clorocarbonil-fenil)-pierazin-1-carboxílico mediante el siguiente procedimiento. Se calentaron piperidina y éster metílico del ácido 4-fluoro-benzoico a 65°C en DMSO durante 48 h (Ref **Patente de Estados Unidos 6069143**). La reacción se interrumpió con $NaHCO_3$ y se extrajo 3 x acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El éster se usó directamente. Se acetiló éster metílico del ácido 4-piperazin-1-il-benzoico con cloroformiato de etilo y DIEA en CH_2Cl_2 para dar éster etílico del ácido 4-(4-metoxicarbonil-fenil)-pierazin-1-carboxílico. El éster metílico se hidrolizó con el ácido disolviendo en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente durante 2 horas. La mezcla se enfrió a 0°C y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido 4-(4-metoxicarbonil-fenil)-pierazin-1-carboxílico El ácido se convirtió en el cloruro de ácido por reacción con cloruro de oxalilo

^{1}H RMN ($CDCl_3$) δ: 1,10 (d, 3H), 1,24 (m, 4H), 2,00 (s, 3H), 2,27 (m, 1H), 3,13 (t, 4H), 3,55 (t, 4H), 4,12 (c, 2H), 4,70 (m, 1H), 5,56 (s a, 1H), 6,54 (d, 1H), 6,62 (d, 2H), 6,91 (t, 1H), 7,09 (d, 2H), 7,14 (d, 2H), 7,27 (m, 2H), 7,36 (d, 2H)

MS m/z 575,16 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[2-metil-1-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazina-7-carbonil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (A-6)

A una solución de éster bencílico del ácido (2*S*,4*R*)-(2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-carbámico (400 mg, 1,36 mmol) en cloruro de metileno (4 ml) a temperatura ambiente se le añadió trietilamina (0,320 ml, 2,3 mmol)

seguido de cloruro de 4-metil-3,4-dihidro-2H-benzo[1,4]oxazina-7-carbonilo (1,5 mmol) La reacción se agitó durante una noche a temperatura ambiente. La mezcla se vertió en agua y se extrajo con acetato de etilo Los extractos se lavaron con NaOH (ac.) 1 M y salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó por cromatografía sobre gel de sílice (hexanos al 75%/acetato de etilo al 25%) para producir la amida pura

Se disolvió éster bencílico del ácido (2*S*,4*R*)-[2-metil-1-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazina-7-carbonil)-1,2,3,4-tetrahidro-quinolin-4-il]-carbámico (300 mg) en etanol El recipiente en el que estaba la solución resultante se evacuó y se rellenó de nuevo con argón Se añadió una cantidad catalítica de Paladio sobre Carbono (al 10%). El recipiente se evacuó de nuevo una vez más y en este momento se rellenó de nuevo con hidrógeno y se agitó en una botella Parr a 275,790 kPa de hidrógeno (40 psi) La reacción se completó después de 4 horas La mezcla se filtró cuidadosamente y se concentró al 10% del volumen. La solución concentrada resultante se filtró a través de Celite® y se concentró para producir la amina bruta.

A una solución de (2*S*,4*R*)-(4-amino-2-metil-3,4-dihidro-2H-quinolin-1-il)-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-il)-metanona (662 mg, 1,87 mmol) en cloruro de metileno (8 ml) se le añadieron ácido 4-clorofenilbórico (583 mg, 3,74 mmol), trietilamina (1,81 ml, 13,09 mmol) y acetato de cobre (II) (681 mg, 3,74 mmol). La mezcla verde heterogénea se agitó abierta al aire durante 1 hora y después se calentó a 60°C y se agitó durante una noche (14 h) Después, la mezcla se enfrió a temperatura ambiente y se vertió en acetato de etilo agitado rápidamente (150 ml); los sólidos se retiraron por filtración a través de Celite®. Los extractos se lavaron varias veces con agua y después una vez con salmuera. Después, los extractos se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron a presión reducida El residuo bruto se purificó por cromatografía sobre gel de sílice (cloruro de metileno al 95%/acetato de etilo al 5%) para producir el producto anilina en forma de un aceite amarillo.

A una solución de (2*S*,4*R*)-[4-(4-Cloro-fenilamino)-2-metil-3,4-dihidro-2H-quinolin-1-il]-(4-metil-3,4-dihidro-2H-benzo[1,4]oxazin-7-il)-metanona (540 mg,

1,25 mmol) en cloruro de metileno (5 ml) se le añadió diisopropiletilamina (0,240 ml, 1,37 mmol) seguido de cloruro de acetilo (2 ml). La mezcla se agitó a temperatura ambiente 4 horas. La mezcla se concentró a presión reducida, se disolvió en acetato de etilo, se lavó con $NaHCO_3$ sat. ac y salmuera y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 25/75 de hexanos/acetato de etilo) para producir el producto final.

^{1}H RMN ($CDCl_3$) δ 1,1 (d, 3H), 1,1 (m, 1H), 2,0 (d, 3H), 2,3 (m, 1H), 2,8 (s, 3H), 3,2 (t, 2H), 4,2 (t, 2H), 4,7 (m, 1H), 5,6 (m, 1H), 6,3 (d, 1H), 6,5 (d, 1H), 6,6 (d, 1H), 6,8 (s, 1H), 6,9 (t, 1H), 7,2 (m, 5H), 7,4 (d, 2H).

MS m/z· 490 (M+1)

Éster etílico del ácido (2*S*,4*R*)-6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico (A-7)

A una solución de éster bencílico del ácido (2*S*,4*R*)-(2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-carbámico (990 mg, 3,49 mmol) en cloruro de metileno a temperatura ambiente se le añadió trietilamina (1,21 ml, 8,71 mmol) seguido de éster etílico del ácido 6-clorocarbonil-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico (3,49 mmol). La reacción se agitó durante una noche a temperatura ambiente. La mezcla se vertió en agua y se extrajo con acetato de etilo Los extractos se lavaron con NaOH (ac.) 1 M y salmuera, se secaron sobre $MgSO_4$, se filtraron, se secaron y se concentraron. El residuo bruto se purificó por cromatografía sobre gel de sílice (hexanos al 75%/acetato de etilo al 25%) para producir la amida pura.

Se disolvió éster etílico del ácido (2*S*,4*R*)-6-(4-benciloxicarbonilamino-2-metil-3,4-dihidro-2H-quinolin-1-carbonil)-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico (697 mmol) en etanol (30 ml). El recipiente en el que estaba la solución resultante se evacuó y se rellenó de nuevo con argón. Se añadió una cantidad catalítica de Paladio sobre Carbono (al 10%). El recipiente se evacuó de nuevo una vez más y en este momento se rellenó de nuevo con hidrógeno y se agitó en una botella Parr a 275,790 kPa de hidrógeno. La reacción se

completó después de 4 horas La mezcla se filtró cuidadosamente y se concentró al 10% del volumen La solución concentrada resultante se filtró a través de Celite® y se concentró para producir la amina bruta

A una solución de éster etílico del ácido (2*S*,4*R*)-6-(4-amino-2-metil-3,4-dihidro-2H-quinolin-1-carbonil)-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico (470 mg, 1,18 mmol) en cloruro de metileno se le añadieron ácido 4-clorofenilbónco (368 mg, 2,36 mmol), trietilamina (1,31 ml, 9,42 mmol) y acetato de cobre (II) (429 mg, 2,36 mmol) La mezcla verde heterogénea se agitó abierta al aire durante 1 hora y después se calentó a 60°C y se agitó durante una noche (14 horas) Después, la mezcla se enfrió a temperatura ambiente y se vertió en acetato de etilo agitado rápidamente (150 ml); los sólidos se retiraron por filtración a través de Celite®. Los extractos se lavaron varias veces con agua y después una vez con salmuera. Después, los extractos se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron a presión reducida El residuo bruto se purificó por cromatografía sobre gel de sílice (cloruro de metileno al 95%/acetato de etilo al 5%) para producir el producto anilina en forma de un aceite amarillo.

A una solución de éster etílico del ácido (2*S*,4*R*)-6-[4-(4-Cloro-fenilamino)-2-metil-3,4-dihidro-2H-quinolin-1-carbonil]-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico (343 mg, 0,673 mmol) en cloruro de metileno (2 ml) se le añadió diisopropiletilamina (0,129 ml, 0,739 mmol) seguido de cloruro de acetilo (2 ml). La mezcla se agitó a temperatura ambiente 4 horas La mezcla se concentró a presión reducida, se disolvió en acetato de etilo, se lavó con $NaHCO_3$ sódico sat. ac y salmuera y se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 25/75 de hexanos/acetato de etilo) para producir el producto puro.

^{1}H RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,2 (m, 1H), 1,3 (t, 3H), 2,0 (s, 3H), 2,3 (m, 1H), 3,3 (m, 2H), 4,0 (m, 2H), 4,3 (m, 2H), 4,7 (m, 1H), 5,5 (m, 1H), 6,4 (d, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,96 (t, 1H), 7,2 (m, 4H), 7,4 (d, 2H).

MS m/z 548 (M+1).

(2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(3,4-dihidro-2H-benzo[1,4]oxazina-6-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (A-8)

Se disolvió éster etílico del ácido 6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazina-4-carboxílico en cloruro de metileno (3 ml) y yodotrimetilsilano (1 ml). Después de 4 días, la reacción se interrumpió con $NaHCO_3$ sat ac El residuo se repartió entre cloruro de metileno y agua, después se extrajo tres veces con cloruro de metileno, se secó $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo) para producir el producto

^1H RMN ($CDCl_3$) δ 1,1 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 3,3 (m, 2H), 4,2 (m, 2H), 4,7 (m, 1H), 5,5 (m, 1H), 6,4 (d, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,96 (t, 1H), 7,2 (m, 5H), 7,4 (d, 2H)

MS m/z. 476 (M+1).

Éster metílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2-fluoro-fenoxi)-2,2-dimetil-butírico (A-9)

A una solución de éster bencílico del ácido (2*S*,4*R*)-(2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-carbámico en cloruro de metileno a temperatura ambiente se le añadió diisopropiletilamina seguido de cloruro de 3-fluoro-4-metoxi-benzoílo. La reacción se agitó durante una noche a temperatura ambiente. La mezcla se vertió en agua y se extrajo con acetato de etilo Los extractos se lavaron con NaOH (ac.) 1 M y salmuera, se secaron sobre $MgSO_4$, se filtraron, se secaron y se concentraron El residuo bruto se purificó por cromatografía sobre gel de sílice (hexanos al 75%/acetato de etilo al 25%) para producir la amida pura.

Se disolvió éster bencílico del ácido (2*S*,4*R*)-[1-(3-fluoro-4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-carbámico en etanol (30 ml) El recipiente en el que estaba la solución resultante se evacuó y se rellenó de nuevo con argón. Se añadió una cantidad catalítica de Paladio sobre Carbono (al 10%) El recipiente se evacuó de nuevo una vez más y en este momento se

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rellenó de nuevo con hidrógeno y se agitó en una botella Parr a 275,790 kPa de hidrógeno. La reacción se completó después de 4 horas La mezcla se filtró cuidadosamente y se concentró al 10% del volumen. La solución concentrada resultante se filtró a través de Celite® y se concentró para producir la amina bruta.

A una solución de (2*S*,4*R*)-(4-amino-2-metil-3,4-dihidro-2H-quinolin-1-il)-(3-fluoro-4-metoxi-fenil)-metanona en DMF (seca) se le añadieron ácido 4-clorofenilbórico, piridina y acetato de cobre (II). La mezcla verde heterogénea se agitó abierta al aire durante 1 hora y después se calentó a 60°C y se agitó durante una noche (14 h). Después, la mezcla se enfrió a temperatura ambiente y se vertió en acetato de etilo agitado rápidamente (150 ml), los sólidos se retiraron por filtración a través de Celite® Los extractos se lavaron varias veces con agua y después una vez con salmuera. Después, los extractos se secaron sobre $MgSO_4$ anhidro, se filtraron y se concentraron a presión reducida El residuo bruto se purificó por cromatografía sobre gel de sílice (cloruro de metileno al 95%/acetato de etilo al 5%) para producir el producto anilina en forma de un aceite amarillo.

A una solución de (2*S*,4*R*)-[4-(4-cloro-fenilamino)-2-metil-3,4-dihidro-2H-quinolin-1-il]-(3-fluoro-4-metoxi-fenil)-metanona en cloruro de metileno se le añadió diisopropiletilamina seguido de cloruro de acetilo La mezcla se agitó a ta durante 4 h. La mezcla se concentró a presión reducida, se disolvió en acetato de etilo, se lavó con $NaHCO_3$ sat. ac y salmuera y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 25/75 de hexanos/acetato de etilo) para producir el producto final puro

Se disolvió *N*-(4-cloro-fenil)-*N*-[1-(3-fluoro-4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (115 mg, 0,256 mmol) en DMF (5 ml) a temperatura ambiente. Se añadieron K_2CO_3 (175 mg, 1,28 mmol) y éster etílico del ácido 5-bromo-2,2-dimetil-pentanoico (100 mg, 0,511 mmol) y la mezcla de reacción se dejó en agitación durante una noche. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se

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secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente 2/1 de hexanos/acetato de etilo-acetato de etilo) para producir el producto.

^1H RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,2 (s, 6H), 1,2 (m, 1H), 2,0 (s, 3H), 2,0 (t, 1H), 2,3 (m, 1H), 3,8 (s, 3H), 4,0 (t, 2H), 4,7 (m, 2H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,6 (t, 1H), 6,7 (d, 1H), 6,9 (t, 1H), 7,2 (m, 5H), 7,4 (d, 2H)

MS m/z: 581 (M+1).

Ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2-fluoro-fenoxi)-2,2-dimetil-butírico (A-10)

Se disolvió éster metílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2-fluoro-fenoxi)-2,2-dimetil-butírico (100 mg) en metanol/THF (1:1, 5 ml) y se le añadió hidróxido de litio (1,0 N, 1 ml) Después de 1 hora, la reacción se acidificó (HCl) y se extrajo con cloruro de metileno La capa orgánica se secó, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de acetato de etilo-MeOH al 5%/acetato de etilo) para producir el producto

^1H RMN ($CDCl_3$) δ 1,1 (d, 3H), 1,2 (s, 6H), 1,2 (m, 1H), 2,0 (s, 3H), 2,0 (t, 1H), 2,3 (m, 1H), 4,0 (t, 2H), 4,7 (m, 2H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,6 (t, 1H), 6,7 (d, 1H), 6,9 (t, 1H), 7,2 (m, 5H), 7,4 (d, 2H), 11,1 (s a, 1H).

MS m/z: 567 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(1-isopropil-1*H*-indazol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (A-11)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(1-isopropil-1*H*-indazol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida siguiendo el procedimiento general A, sustituyendo cloruro de 4-fluorobenzoílo por cloruro de 1-isopropil-1*H*-indazol-5-carbonilo Se preparó cloruro de (1-isopropil-1*H*-indazol-5-carbonilo en tres etapas as partir de éster etílico del ácido 1*H*-indazol-5-carboxílico. Se alquiló éster etílico del ácido 1*H*-indazol-5-carboxílico usando 2-bromopropano en presencia de hidruro sódico en DMF a temperatura ambiente para producir el éster etílico del ácido 1-isopropil-1*H*-indazol-5-carboxílico deseado. La hidrólisis del éster usando hidróxido sódico 1 N en

etanol a 80°C dio ácido 1-isopropil-1*H*-indazol-5-carboxílico y el posterior tratamiento de este ácido carboxílico con cloruro de oxalilo y DMF catalítica produjo cloruro de 1-isopropil-1*H*-indazol-5-carbonilo con un rendimiento decente) El resto de los procedimientos se siguieron como se indica en el procedimiento general A para producir (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(1-isopropil-1*H*-indazol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida. (Estando la primera excepción en la desprotección del grupo benciloxicarbonilo por tratamiento con HBr al 30% en AcOH sustituyendo por paladio sobre carbono (al 10%) y la otra en la etapa de *N*-arilación de (2*S*,4*R*)-(4-amino-2-metil-3,4-dihidro-2H-quinolin-1-il)-(1-isopropil-1*H*-indazol-5-il)-metanona con ácido 4-clorofenilbórico, en presencia de acetato de cobre, se sustituyó piridina por trietilamina y la reacción se realizó en diclorometano a temperatura ambiente para producir la (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(1-isopropil-1*H*-indazol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida)

^{1}H RMN ($CDCl_3$) δ: 1,15 (3H, d; solapamiento 1H, t), 1,60 (2 x 3H, d), 2,02 (3H, s), 2,33 (1H, m), 4,78 (2 x 1H, m, solapamiento), 5,60 (1H, m), 6,44 (1H, d), 6,95 (1H, t), 7,00-7,40 (9H, complejo).

ESI-MS m/z: 501 (M + 1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(2,2-difluoro-benzo[1,3]dioxol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (A-12)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(2,2-difluoro-benzo[1,3]dioxol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida siguiendo el procedimiento general A, sustituyendo cloruro de 4-fluorobenzoílo por cloruro de 2,2-difluoro-1,3-benzodioxol-5-carbonilo. El resto de los procedimientos se siguieron como se indica en el procedimiento general A para producir (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(2,2-difluoro-benzo[1,3] dioxol-5-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida. (La única excepción estuvo en la etapa de N-arilación de (2*S*,4*R*)-4-amino-2-metil-3,4-dihidro-2H-quinolin-1-il)-(2,2-difluoro-benzo[1,3]dioxol-5-il)-metanona con ácido clorofenilborónico, en presencia de acetato de cobre, la piridina se sustituye por trietilamina y la

reacción se llevó a cabo con diclorometano a temperatura ambiente para obtener la (2S,4R)-N-(4-cloro-fenilamino)-2-metil-3,4-dihidro-2H-quinilin-1-il]-(2,2-difluoro-benzo[1,3]dioxol-5-il)-metanona con un rendimiento mayor del 70%)

^{1}H RMN ($CDCl_3$) δ. 1,15 (3H, d; solapamiento 1H, t), 2,02 (3H, s), 2,33 (1H, m), 4,78 (1H, m), 5,60 (1H, m), 6,44 (1H, d), 6,68 (1H, d), 6,95 (1H, t), 7,00-7,40 (8H, complejo).

MS m/z 499 (M + 1)

Ácido (2S,4R)-4-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazin-4-il)-2,2-dimetil-butírico (A-13)

El ácido (2S,4R)-4(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazin-4-il)-2,2-dimetil-butírico puede preparase a partir de (2S,4R)-N-(4-cloro-fenil)-N-[1-(3,4-dihidro-2H-benzo[1,4]oxazin-6-carbonil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]acetamida disuelta en DMF a temperatura ambiente Se añaden K_2CO_3 y éster metílico del ácido 4-bromo-2,2-dimetil-butírico (preparado de acuerdo con el procedimiento de *Tetrahedron* **1994**, 50(32), 9825-30) y la mezcla de reacción se permitió que se mantuviera en agitación durante una noche. La mezcla se repartió entre cloruro de metileno y agua, la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y concentró. El residuo bruto se purificó por cromatografía en sílica gel para obtener el producto.

Ácido (2S,4R)-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-3,4-dihidro-2H-quinolin-1-il)-2,2-dimetil-propiónico (A-14)

El ácido (2S,4R)-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-3,4-dihidro-2H-quinolinl-1-il)-2,2-dimetil-propiónico puede prepararse como se describió para el ácido (2S,4R)-4-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazin-4-il)-2,2-dimetil-butírico sustituyendo el éster metílico del

ácido 4-bromo-2,2-dimetil-burítico por éster metílico del ácido 3-bromo-2,3-dimetil-propiónico

Ácido (2S,4R)-3-(6-{4[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-3,4-dihidro-2H-quinolin-1-il)-2,2-dimetil-propiónico (A-15)

El ácido (2S,4R)-3-(6-{4[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-3,4-dihidro-2H-quinolin-1-il)-2,2-dimetil-propiónico puede preparase como se describió para el ácido (2S,4R)-4-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazin-4-il)-2,2-dimetil-butírico sustituyendo el éster metílico del ácido 4-bromo-2,2-metil-burítico por éster metílico del ácido 3-bromo-2,2-dimetil-propiónico.

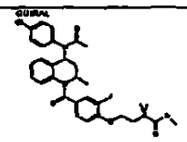
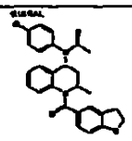
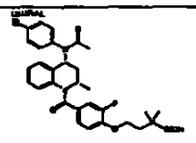
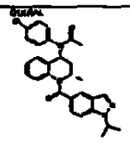
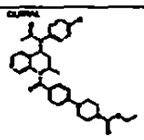
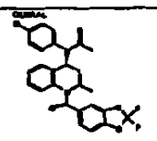
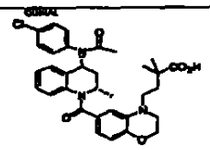
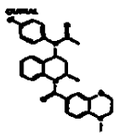
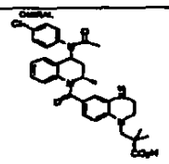
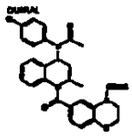
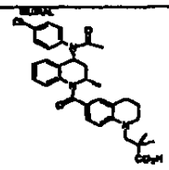
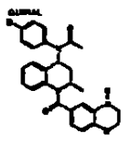
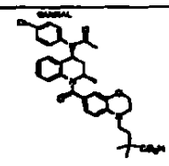
Ácido (2S,4R)-4-(7-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4,]oxazin-4-il)-2,2-dimetil-butírico (A-16)

El ácido (2S,4R)-4-(7-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4,]oxazin-4-il)-2,2-dimetil-butírico puede prepararse como se describió para el ácido (2S,4R)-4-(6-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-2,3-dihidro-benzo[1,4]oxazin-4-il)-2,2-dimetil-butírico

Los compuestos **A-13-A-16** pueden prepararse según los esquemas mostrados en el Esquema 2 y por los procedimientos generales A y otros descritos en este documento Los especialistas en la técnica serán capaces de reconocer, o de determinar, usando sólo la rutina experimental, muchos equivalentes de las realizaciones específicas de la invención descrita en éste documento.

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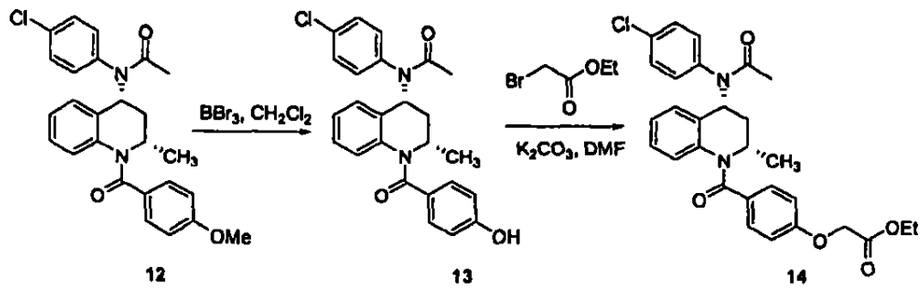
Tabla 1: Compuestos Derivados del Procedimiento General A.

Numero del compuesto	Estructura	Número de compuesto	Estructura
		A-9	
A-2		A-10	
		A-11	
A-4		A-12	
		A-13	
A-6		A-14	
A-7		A-15	
A-8		A-16	

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Esquema 6



12 13 14

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (8)

Se preparó (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida siguiendo el procedimiento general A, sustituyendo cloruro de 4-fluorobenzoílo por cloruro de 4-metoxibenzoílo Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-metoxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en diclorometano y se le añadió una solución de BBr_3 (1,0 M en diclorometano, 10 ml); la reacción se dejó en agitación a temperatura ambiente hasta que no quedó material de partida. La reacción se lavó cuidadosamente con $NaHCO_3$ sat. y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo se purificó por cromatografía ultrarrápida Biotage usando EtOAc al 100% para dar (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida.

Éster etílico del ácido (2*S*,4*R*)-(4-[4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil]-fenoxi)-acético (9)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,147 g) en DMF a temperatura ambiente y se e añadió K_2CO_3. Se añadió 4-bromoacetato de etilo (0,065 g) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se

filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 80/20 de hexanos/acetato de etilo-50/50 de hexanos acetato de etilo) para producir el producto en 130 mg, 73%.

(2*S*,4*R*)-2-{4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-(2-hidroxi-etil)-acetamida (B-1)

Se preparó (2*S*,4*R*)-2-(4-{4-[Acetil-(4-cloro-fenil)amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-(2-hidroxi-etil)-acetamida a partir del éster etílico del ácido (4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-acético (0,050 g, 0,096 mmol) por adición de 2-amino-etanol (0,145 ml, 2,4 mmol) con trazas de cianuro sódico en etanol (1 ml) a temperatura ambiente para dar un rendimiento del 50% de (2*S*,4*R*)-2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-(2-hidroxi-etil)-acetamida después de la purificación por HPLC.

^{1}H-RMN ($CDCl_3$) δ: 1,13 (m, 4H), 2,02 (s, 3H), 2,26 (m, 1H), 2,70 (a, 1H), 3,46 (t, 2H), 3,68 (t, 2H), 4,41 (t, 2H), 4,72 (m, 1H), 5,58 (sa, 1H), 6,50 (d, 1H), 6,67 (d, 2H), 6,90 (t, 1H), 7,02 (a, 1H), 7,13-7,28 (m, 6H), 7,36 (d, 2H).

MS m/z: 536,2 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(2-morfolin-4-il-2-oxo-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-2)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-{2-metil-1-[4-(2-morfolin-4-il-2-oxo-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida a partir de éster etílico del ácido (4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-acético (0,050 g, 0,096 mmol) por adición de morfolina (0,400 ml, 4,0 mmol) con trazas de cianuro sódico en etanol (1 ml) para dar un rendimiento del 63% de (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-{2-metil-1-[4-(2-morfolin-4-il-2-oxo-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida después de la purificación por HPLC.

^{1}H-RMN ($CDCl_3$) δ: 1,13 (m, 4H), 2,01 (s, 3H), 2,27 (m, 1H), 3,52-3,63 (m, 8H), 4,67 (s, 2H), 4,76 (m, 1H), 5,57 (sa, 1H), 6,49 (d, 1H), 6,70 (d, 2H), 6,90 (t, 1H), 7,13-7,28 (m, 6H), 7,36 (d, 2H).

MS m/z: 562 (M+1).

(2*S*,4*R*)-2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida (B-3)

Se obtuvo (2*S*,4*R*)-2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida a partir de éster etílico del ácido (4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-acético (0,050 g, 0,096 mmol) mediante la adición de isopropilamina (0,680 ml, 8 mmol) con resto de cianuro sódico en etanol (1 ml) para dar un rendimiento del 43% de (2*S*,4*R*)-2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida después de la purificación por HPLC

^{1}H RMN ($CDCl_3$) δ: 1,12-1,19 (m, 10H), 2,02 (s, 3H), 2,28 (m, 1H), 4,11 (m, 1H), 4,37 (s, 2H), 4,73 (m, 1H), 5,59 (s a, 1H), 6,24 (a, 1H), 6,48 (d, 1H), 6,70 (d, 2H), 6,90 (t, 1H), 7,12-7,30 (m, 6H), 7,37 (d, 2H).

MS m/z: 534 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-4)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 seguido de 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butil-éster del ácido tolueno-4-sulfónico y la reacción se dejó en agitación a 90°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC para producir el producto.

Se preparó 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butil-éster del ácido tolueno-4-sulfónico a partir de ácido 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butírico Se disolvió ácido 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butírico (1,74 g, 7,0 mmol) en THF (2 ml) a 0°C y se le añadió gota a gota BH_3SMe_3 (2,6 ml, 26 mmol) (Ref: Tetrahedron, **2002**, 9839) La reacción se dejó calentar a temperatura ambiente y se agitó durante 16 h. La reacción se interrumpió con

(2*S*,4*R*)-2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida (B-3)

Se obtuvo (2*S*,4*R*)-2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida a partir de éster etílico del ácido (4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-acético (0,050 g, 0,096 mmol) mediante la adición de isopropilamina (0,680 ml, 8 mmol) con resto de cianuro sódico en etanol (1 ml) para dar un rendimiento del 43% de (2*S*,4*R*)-2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-isopropil-acetamida después de la purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ. 1,12-1,19 (m, 10H), 2,02 (s, 3H), 2,28 (m, 1H), 4,11 (m, 1H), 4,37 (s, 2H), 4,73 (m, 1H), 5,59 (s a, 1H), 6,24 (a, 1H), 6,48 (d, 1H), 6,70 (d, 2H), 6,90 (t, 1H), 7,12-7,30 (m, 6H), 7,37 (d, 2H).

MS m/z: 534 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-4)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 seguido de 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butil-éster del ácido tolueno-4-sulfónico y la reacción se dejó en agitación a 90°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC para producir el producto.

Se preparó 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butil-éster del ácido tolueno-4-sulfónico a partir de ácido 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butírico Se disolvió ácido 4,4,4-trifluoro-3-hidroxi-3-trifluorometil-butírico (1,74 g, 7,0 mmol) en THF (2 ml) a 0°C y se le añadió gota a gota BH_3SMe_3 (2,6 ml, 26 mmol) (Ref. Tetrahedron, 2002, 9839). La reacción se dejó calentar a temperatura ambiente y se agitó durante 16 h. La reacción se interrumpió con

metanol y el disolvente se retiró para dar el 4,4,4-trifluoro-3-trifluorometil-butano-1,3-diol bruto. El alcohol se convirtió en el tosilato mediante la adición de 4,4,4-trifluoro-3-trifluorometil-butano-1,3-diol disuelto en piridina (2 ml) a cloruro de tosilo (1,39 ml) en 2 ml de CH_2Cl_2 y una cantidad catalítica de DMAP. La reacción se agitó a temperatura ambiente durante 2 h y se interrumpió.

^{1}H RMN ($CDCl_3$) δ. 1,12 (m, 4H), 2,01 (s, 3H), 2,24 (m, 1H), 2,25 (t, 2H), 3,94 (t, 2H), 4,70 (m, 1H), 5,53 (s a, 2H), 6,48 (d, 1H), 6,61 (d, 2H), 6,93 (t, 1H), 7,09-7,27 (m, 6H), 7,37 (d, 2H).

MS m/z. 629 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-[4-(3-piridin-3-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-5)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 seguido de 3-(3-bromo-propil)-piridina y la reacción se dejó en agitación a 90°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por HPLC para producir el producto.

^{1}H RMN ($CDCl_3$) δ: 1,12 (m, 4H), 1,83 (m, 2H), 2,01 (s, 3H), 2,24 (m, 1H), 2,76 (t, 2H), 3,89 (t, 2H), 4,73 (m, 1H), 5,60 (s a, 1H), 6,52 (d, 1H), 6,64 (d, 2H), 6,93 (t, 1H), 7,12-7,29 (m, 7H), 7,37 (d, 2H), 7,48 (d, 1H), 8,45 (m, 2H).

MS m/z: 554,36 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(1-[4-(3-hidroxi-3-metil-butoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-6)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 seguido de 4-bromo-2-metil-butan-2-ol y la reacción se dejó en agitación a 90°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre

$MgSO_4$, se filtró y se concentró El residuo bruto se purificó por HPLC para producir el producto

Se preparó 4-bromo-2-metil-butan-2-ol a partir de éster etílico del ácido 3-bromo-propiónico. Se disolvió éster etílico del ácido 3-bromo-propiónico (1,0 g, 5,5 mmol) en 10 ml de éter y se le añadieron 3,7 ml de bromuro de metilmagnesio (3,0 M en éter) a 0°C. La reacción se agitó a 0°C hasta que no quedó material de partida. La reacción se interrumpió con una solución saturada de cloruro amónico y se extrajo 3 x con éter. Los extractos orgánicos se recogieron juntos y se secaron sobre $MgSO_4$, se filtraron y se concentraron para dar 4-bromo-2-metil-butan-2-ol.

^{1}H RMN ($CDCl_3$) δ. 1,12 (d, 3H), 1,24 (s+m,7H), 1,90 (t, 2H), 2,01 (s, 3H), 2,22 (m, 2H), 4,07 (t, 2H), 4,72 (m, 1H), 5,60 (s a, 1H), 6,50 (d, 1H), 6,65 (d, 2H), 6,90 (t, 1H), 7,10-7,20 (m, 5H), 7,25 (t, 1H), 7,35 (d, 2H).

MS m/z. 521 (M+1).

Éster metílico del ácido (2*S*,4*R*)- 4-[4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-2,2-dimetil-butírico (B-7)

Se preparó éster metílico del ácido (2*S*,4*R*)- 4-[4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-2,2-dimetil-butírico a partir de éster etílico del ácido (2*S*,4*R*)- 4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico retirando el carbamato. El éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico se disolvió en acetonitrilo (2 ml). Se añadió yodotrimetilsilano y se permitió agitar la reacción a temperatura ambiente durante una noche. El exceso de reactivo se inactivó por adición de metanol (1 ml) y la mezcla se concentró a presión reducida. El residuo bruto se repartió entre acetato de etilo y bicarbonato sódico acuoso saturado. Los extractos se lavaron con hidróxido sódico 1 M, tiosulfato sódico acuoso saturado y salmuera, se secaron sobre sulfato sódico, se filtraron, se concentraron y se

purificaron por cromatografía en gel de sílice para producir *N*-(4-cloro-fenil)-*N*-[2-metil-1-(4-piperazin-1-il-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[2-metil-1-(4-piperazin-1-il-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF a temperatura ambiente. Se añadió K_2CO_3 seguido de éster metílico del ácido 4-bromo-2,2-dimetil-butírico y se permitió agitar la reacción a 90°C durante una noche La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por HPLC para dar el producto.

^{1}H-RMN ($CDCl_3$) δ: 1,12 (d, 3H), 1,18 (s+m,7H), 1,75 (m, 2H), 2,01 (s, 3H), 2,32 (m, 3H), 2,52 (m, 4H), 3,16 (m, 4H), 3,64 (s, 3H), 4,71 (m, 1H), 5,60 (sa, 1H), 6,56 (d, 1H), 6,62 (d, 2H), 6,93 (t, 1H), 7,08-7,29 (m, 6H), 7,36 (d, 2H).

MS m/z 631 (M+1).

Éster metílico del ácido (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butírico (B-8)

Se preparó éster metílico del ácido (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butírico a partir de éster etílico del ácido (2*S*,4*R*)-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-carbámico. Se disolvió éster etílico del ácido (2*S*,4*R*)-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-carbámico en acetonitrilo (2 ml). Se añadió yodotrimetilsilano y la reacción se dejó en agitación a temperatura ambiente durante una noche. El exceso de reactivo se inactivó mediante la adición de metanol (1 ml) y la mezcla se concentró a presión reducida El residuo bruto se repartió entre acetato de etilo y bicarbonato sódico saturado acuoso. Los extractos se lavaron con hidróxido sódico 1 M, tiosulfato sódico saturado acuoso y salmuera, se secaron sobre sulfato sódico, se filtraron, se concentraron y se purificaron por cromatografía sobre gel de sílice para producir *N*-(4-cloro-fenil)-*N*-[2-metil-1-(4-metilamino-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida .

Se disolvió (2*S*,4*R*)-(N-(4-cloro-fenil)-*N*-[2-metil-1-(4-metilamino-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,015 g, 0,033 mmol) en CH_2Cl_2 (0,5 ml) a temperatura ambiente. Se añadió borohidruro sódico (0,007 g, 1,5 equiv.) seguido de éster metílico del ácido 4-oxo-butírico (0,020 g, 4 equiv.) y la reacción se dejó en agitación durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de Hexano al 33%/EA) para producir el producto.

^{1}H RMN ($CDCl_3$) δ· 1,09-1,24 (m, 4H), 1,84 (m, 2H), 2,00 (s, 3H), 2,27 (m, 3H), 2,86 (s, 3H), 3,29 (t, 2H), 3,62 (s, 3H), 4,70 (m, 1H), 5,58 (s a, 1H), 6,39 (d, 2H), 6,59 (d, 1H), 6,96 (t, 1H), 7,05-7,21 (m, 5H), 7,25 (d, 1H), 7,36 (d, 2H).
MS m/z: 548 (M+1)

Ácido (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butírico (B-9)

Se preparó ácido (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butírico a partir de éster metílico del ácido (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butirico, se hidrolizó en el ácido disolviéndose en tetrahidrofurano y etanol, se le añadió hidróxido de litio (1 N) y se calentó 50°C durante 2 h. La mezcla se enfrió a temperatura ambiente y se acidificó para formar un precipitado blanco. El sólido se filtró para dar para producir el producto después de la punficación por HPLC.

^{1}H RMN ($CDCl_3$) δ: 1,10 (d, 3H), 1,18 (m, 1H), 1,81 (t, 2H), 2,02 (s, 3H), 2,28 (m, 3H), 2,86 (s, 3H), 3,28 (t, 2H), 4,70 (m, 1H), 5,58 (s a, 1H), 6,39 (d, 2H), 6,61 (d, 1H), 6,94 (t, 1H), 7,06-7,27 (m, 6H), 7,36 (d, 2H), 8,90 (a, 1H).
MS m/z: 534 (M+1).

(2*S*,4*R*)-4-[(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butiramida (B-10)

Se obtuvo (2*S*,4*R*)-4-[(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-metil-amino]-butiramida a partir de ácido

(2*S*,4*R*)-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico. El ácido (0,050 g, 0,096 mmol) se disolvió en DMF (1 ml) a temperatura ambiente y se le añadieron HOBt (0,020 g, 0,144 mmol), HATU (0,055 g, 0,144 mol) y diisopropiletilamina (0,067 ml, 0,384 mmol) seguido de cloruro amónico (0,011 g, 0,192 mmol) y se agitó a temperatura ambiente durante 16 h La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó mediante purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ· 1,10 (d, 3H), 1,18 (m, 1H), 1,80 (t, 2H), 2,00 (s, 3H), 2,13 (t, 2H), 2,27 (m, 1H), 2,85 (s, 3H), 3,27 (t, 2H), 4,70 (m, 1H), 5,65 (a, 2H), 5,85 (s a, 1H), 6,39 (d, 2H), 6,59 (d, 1H), 6,93 (t, 1H), 7,03-7,34 (m, 6H), 7,36 (d, 2H).

MS m/z· 533 (M+1)

Éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico (B-11)

Se preparó éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico a partir de 4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil-éster del ácido (2*S*,4*R*)-trifluoro-metanosulfónico añadiendo éster etílico del ácido piperidin-4-carboxílico (4 equiv.), Cs_2CO_3 (3 equiv.), $Pd_2(dba)_3$ al 10%, BINAP (0,20 equiv.) y 18-Corona-6 al 10% (0,10 equiv.) en tolueno a 110°C durante una noche La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC para producir el producto.

^{1}H RMN ($CDCl_3$) δ· 1,10 (d, 3H), 1,24 (m, 4H), 1,54-1,74 (mm, 4H), 2,00 (s, 3H), 2,27 (m, 1H), 2,57 (m, 1H), 2,80 (m, 1H), 3,01 (m, 1H), 3,48 (m, 1H), 3,71 (m, 1H), 4,10 (c, 2H), 4,70 (m, 1H), 5,56 (s a, 1H), 6,56 (d, 1H), 6,64 (d, 2H), 6,92 (t, 1H), 7,07-7,28 (m, 6H), 7,35 (d, 2H).

MS m/z. 574,31 (M+1).

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464

Éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico (B-12)

El éster etílico del ácido (2*S*,4*R*)- 1-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico se preparó siguiendo el mismo procedimiento que para el éster etílico del ácido (2*S*,4*R*)- 1-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico, sustituyendo el éster etílico del ácido pipendin-3-carboxílico por éster etílico del ácido piperidin-4-carboxílico para producir el producto

^{1}H-RMN ($CDCl_3$) δ: 1,10 (d, 3H), 1,23 (t, 3H), 1,23 (m, 1H), 1,77 (m, 2H), 1,94 (m, 2H), 2,01 (s, 3H), 2,28 (m, 1H), 2,40 (m, 1H), 2,77 (t, 2H), 3,62 (m, 2H), 4,11 (c, 2H), 4,70 (m, 1H), 5,58 (sa, 1H), 6,56 (d, 1H), 6,64 (d, 2H), 6,92 (t, 1H), 7,07-7,28 (m, 6H), 7,35 (d, 2H)

MS m/z: 574,4 (M+1).

Éster *terc*-butílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico (B-13)

Se preparó éster *terc*-butílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-pierazin-1-carboxílico siguiendo el procedimiento para éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico, sustituyendo éster etílico del ácido piperidin-4-carboxílico por éster *terc*-butílico del ácido pierazin-1-carboxílico para producir el producto.

^{1}H RMN ($CDCl_3$) δ 1,10 (d, 3H), 1,24 (m, 1H), 1,45 (s, 9H), 2,00 (s, 3H), 2,27 (m, 1H), 3,12 (t, 4H), 3,52 (t, 4H), 4,71 (m, 1H), 5,56 (s a, 1H), 6,54 (d, 1H), 6,62 (d, 2H), 6,92 (t, 1H), 7,09-7,28 (m, 6H), 7,36 (d, 2H).

MS m/z: 603,4 (M+1)

Ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico (B-14)

Se preparó ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico a partir de éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico. Se hidrolizó al ácido disolviéndolo en tetrahidrofurano y etanol y se añadió hidróxido de litio (1 N) y se calentó a 50°C durante 2 h. La mezcla se enfrió a temperatura ambiente, se acidificó para formar un precipitado blanco El sólido se filtró para dar para dar el producto después de la purificación por HPLC.

^{1}H-RMN ($CDCl_3$) δ· 1,10 (d, 3H), 1,23 (m, 1H), 1,64 (m, 2H), 2,00 (m, 5H), 2,34 (m, 1H), 2,59 (m, 1H), 2,84 (m, 1H), 3,08 (m, 1H), 3,40 (m, 1H), 3,67 (m, 1H), 4,71 (m, 1H), 5,58 (sa, 1H), 6,57 (d, 1H), 6,66 (d, 2H), 6,93 (t, 1H), 7,07-7,28 (m, 6H), 7,37 (d, 2H), 9,30 (a, 1H)

MS m/z: 546,3 (M+1).

Amida del ácido (2*S*,4*R*)-1-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico (B-15)

Se preparó amida del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico a partir de ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico. El ácido (0,120 g, 0,22 mmol) se disolvió en DMF (2,5 ml) a temperatura ambiente y se le añadieron HOBt (0,044 g, 0,33 mmol), HATU (0,125 g, 0,33 mol) y diisopropiletilamina (0,15 ml, 0,88 mmol) seguido de cloruro amónico (0,024 g, 0,44 mmol) y se agitó a temperatura ambiente durante 16 h. La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo bruto se purificó mediante purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ. 1,10 (d, 3H), 1,23 (m, 1H), 1,79 (m, 4H), 2,01 (m, 3H), 2,27 (m, 1H), 2,48 (m, 1H), 2,96 (m, 1H), 3,13 (m, 1H), 3,35 (m, 1H), 3,52 (m, 1H), 4,70 (m, 1H), 5,50 (a, 2H), 6,24 (a, 1H), 6,56 (d, 1H), 6,67 (d, 2H), 6,92 (t, 1H), 7,08-7,28 (m, 6H), 7,37 (d, 2H).

MS m/z: 545,4 (M+1)

Ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico (B-16)

Se preparó ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico a partir de éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico (0,300 g, 0,522 mol), se hidrolizó en el ácido disolviéndose en tetrahidrofurano y etanol, se le añadió hidróxido de litio (1 N) y se calentó 50°C durante 2 h. La mezcla se enfrió a temperatura ambiente y se acidificó para formar un precipitado blanco El sólido se filtró para dar para producir el producto después de la purificación por HPLC ^{1}H RMN ($CDCl_3$) δ 1,11 (d, 3H), 1,23 (m, 1H), 1,77 (m, 2H), 1,94 (m, 2H), 2,02 (s, 3H), 2,27 (m, 1H), 2,43 (m, 1H), 2,78 (t, 2H), 3,60 (m, 2H), 4,71 (m, 1H), 5,58 (s a, 1H), 6,57 (d, 1H), 6,63 (d, 2H), 6,93 (t, 1H), 7,07-7,28 (m, 6H), 7,37 (d, 2H), 9,30 (a, 1H).

MS m/z: 546,3 (M+1).

Amida del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico (B-17)

Se preparó amida del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico a partir de ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-3-carboxílico. El ácido (0,2 g, 0,366 mmol) se disolvió en DMF (3 ml) a temperatura ambiente y se le añadieron HOBt (0,74 g, 0,55 mmol), HATU (0,209 g, 0,55 mol) y diisopropiletilamina (0,25 ml) seguido de cloruro amónico (0,040 g, 0,74 mmol) y se agitó a temperatura ambiente durante 16 h La reacción se diluyó con acetato de etilo y se lavó con NaOH 1 N, HCl 1 N y salmuera Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó mediante purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ. 1,10 (d, 3H), 1,20 (m, 1H), 1,73 (m, 2H), 1,84 (m, 2H), 2,01 (s, 3H), 2,24 (m, 2H), 2,65 (m, 2H), 3,66 (m, 2H), 4,70 (m, 1H), 5,62 (a, 2H),

6,93 (a, 1H), 6,56 (d, 1H), 6,60 (d, 2H), 6,92 (t, 1H), 7,05-7,27 (m, 6H), 7,37 (d, 2H)

MS m/z· 545,3 (M+1)

Ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propiónico (B-18)

Se preparó ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propiónico siguiendo el procedimiento para éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico, sustituyendo éster etílico del ácido piperidin-4-carboxílico por éster metílico del ácido 3-amino-propiónico para producir el éster metílico del ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propiónico El éster se hidrolizó en el ácido disolviéndose en tetrahidrofurano y etanol, se le añadió hidróxido de litio (1 N) y se calentó 50°C durante 2 h La mezcla se enfrió a temperatura ambiente y se acidificó para formar un precipitado blanco El sólido se filtró para dar para producir el producto después de la purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ. 1,10 (d, 3H), 1,23 (m, 1H), 2,03 (s, 3H), 2,27 (m, 1H), 2,51 (s, 2H), 3,30 (t, 2H), 4,71 (m, 1H), 5,61 (s a, 1H), 6,27 (d, 2H), 6,59 (d, 1H), 6,93 (t, 1H), 7,01 (d, 2H), 7,02-7,27 (m, 4H), 7,37 (d, 2H), 8,90 (a, 1H)

MS m/z· 506,3 (M+1).

(2*S*,4*R*)-3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propionamida (B-19)

Se preparó (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propionamida a partir de ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenilamino)-propiónico. El ácido (0,060 g, 0,118 mmol) se disolvió en DMF (1,5 ml) a temperatura ambiente y se le añadieron HOBt (0,024 g, 0,177 mmol), HATU (0,068 g, 0,177 mol) y diisopropiletilamina (0,082 ml, 0,472 mmol) seguido de cloruro amónico (0,014 g, 0,236 mmol) y se agitó a temperatura ambiente durante 18 h La reacción se diluyó con acetato de etilo, se lavó con

NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó mediante purificación por HPLC.

^{1}H RMN ($CDCl_3$) δ· 1,10 (d, 3H), 1,23 (m, 1H), 1,64 (a, 1H), 2,01 (s, 3H), 2,27 (m, 1H), 2,44 (t, 2H), 3,37 (t, 2H), 4,69 (m, 1H), 5,40 (a, 1H), 5,61 (s a, 1H), 5,80 (a, 1H), 6,31 (d, 2H), 6,59 (d, 1H), 6,94 (t, 1H), 7,02 (d, 2H), 7,10-7,23 (m, 4H), 7,36 (d, 2H).

MS m/z. 505,3 (M+1).

Ácido (2*S*,4*R*)-[4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-acético (B-20)

Se preparó ácido (2*S*,4*R*)- [4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-acético siguiendo el mismo procedimiento que para el éster etílico del ácido (2*S*,4*R*)-1-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperidin-4-carboxílico, sustituyendo éster etílico del ácido piperazin-1-il-acético por éster etílico del ácido pipendin-4-carboxílico para producir el éster etílico del ácido (2*S*,4*R*)- [4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-acético. El éster se hidrolizó al ácido disolviéndolo en tetrahidrofurano y etanol y se añadió hidróxido de litio (1 N) y se calentó a 50°C durante 2 h. La mezcla se enfrió a temperatura ambiente, se acidificó para formar un precipitado blanco. El sólido se filtró para dar el producto después de la purificación por HPLC.

^{1}H-RMN ($CDCl_3$) δ· 1,10 (d, 3H), 1,20 (m, 1H), 2,00 (s, 3H), 2,24 (m, 1H), 3,04 (t, 4H), 3,50 (m, 6H), 4,70 (m, 1H), 5,56 (sa, 1H), 6,51 (d, 1H), 6,63 (d, 2H), 6,89 (t, 1H), 7,07-7,25 (m, 6H), 7,35 (d, 2H).

MS m/z: 561 (M+1).

(2*S*,4*R*)-2-[4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-acetamida (B-21)

Se obtuvo (2*S*,4*R*)-2-[4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-piperazin-1-il]-acetamida a partir de ácido (2*S*,4*R*)-[4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-

carbonil)-fenil)-piperazin-1-il]-acético. El ácido (0,120 g, 0,21 mmol) se disolvió en DMF (2 ml) a temperatura ambiente y se le añadieron HOBt (0,043 g, 0,32 mmol), HATU (0,122 g, 0,32 mol) y diisopropiletilamina (0,15 ml, 0,64 mmol) seguido de cloruro amónico (0,023 g, 0,42 mmol) y se agitó a temperatura ambiente durante 18 h. La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó mediante purificación por HPLC

^{1}H RMN ($CDCl_3$) δ: 1,10 (d, 3H), 1,20 (m, 1H), 2,00 (s, 3H), 2,24 (m, 1H), 3,04 (t, 4H), 3,50 (m, 6H), 4,70 (m, 1H), 5,40 (a, 1H), 5,56 (s a, 1H), 5,80 (a, 1H), 6,51 (d, 1H), 6,63 (d, 2H), 6,89 (t, 1H), 7,07-7,25 (m, 6H), 7,35 (d, 2H).

MS m/z: 560 (M+1)

(2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[2-metil-1-[4-(2-oxo-imidazolidin-1-il)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (B-22)

Se disolvió *N*-[1-(4-amino-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-*N*-(4-cloro-fenil)-acetamida (156 mg, 0,373 mmol) en cloruro de metileno (3 ml) y se le añadieron trietilamina (0,078 ml, 0,559 mmol) y 1-cloro-2-isocianato-etano 0,038 ml, 0,448 mmol). La reacción se agitó a temperatura ambiente durante una noche y la reacción se interrumpió con $NaHCO_3$ sat. ac El residuo se repartió entre cloruro de metileno y agua, después se extrajo tres veces con cloruro de metileno, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ. 1,2 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 4,0 (t, 2H), 4,4 (t, 2H), 4,8 (m, 1H), 5,6 (m, 1H), 6,5 (d, 1H), 6,9 (t, 1H), 7,2 (m, 9H), 7,4 (d, 2H)

MS m/z: 503 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[2-metil-1-[4-(2-oxo-oxazolidin-3-il)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (B-23)

Se disolvió *N*-[1-(4-amino-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-*N*-(4-cloro-fenil)-acetamida (61 mg, 0,142 mmol) en cloruro de metileno (2 ml) y

se le añadió trietilamina (0,100 ml, 0,700 mmol). Se añadió 2-bromoetilcloroformiato (0,023 ml, 0,213 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de 1 hora a temperatura ambiente, se añadieron DMF (2 ml) y Cs_2CO_3 (100 mg, 0,307 mmol) y la mezcla se agitó durante una noche. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 1/1 de hexanos/acetato de etilo a acetato de etilo al 100%) para producir el producto.

^{1}H RMN ($CDCl_3$) δ. 1,2 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 3,8 (t, 2H), 4,4 (t, 2H), 4,8 (m, 1H), 5,6 (m, 1H), 6,5 (d, 1H), 6,9 (t, 1H), 7,2 (m, 8H), 7,4 (d, 2H)

MS m/z 504 (M+1)

(2*S*,4*R*)-N-(4-Cloro-fenil)-N-{1-[4-(1,1,-dioxo-1l6-isotioazolidin-2-il)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-24)

La N-[1-(4-Amino-benzoil)-2-metil-1,2,3,4,-tetrahidro-quinolin-4-il]-N-(4-cloro-fenol)-acetamida (98 mg, 0,228 mmol) se disolvió en cloruro de metileno (2 ml) y se añadió trietilamina (0,050 ml, 0,337 mmol). Se añadió cloruro de 3-cloro-propano-1-sulfonilo (0,033 ml, 0,274 mmol) y se permitió que la reacción se calentara a temperatura ambiente. Tras 1 h a temperatura ambiente, se añadieron DMF (2 ml) y Cs_2CO_3 (100 mg, 0,307 mmol) y la mezcla se agitó durante una noche. La mezcla se repartió entre cloruro de metileno y agua, la capa del cloruro de metileno se secó sobre $MgSO_4$, se filtró y concentró El residuo bruto se purificó por HPLC preparatoria.

1H-RMN (CDCl3) δ: 1,2 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 2,5 (quin., 2H), 3,3 (t, 2H), 3,6 (t, 2H), 4,8 (m, 1H), 5,6 (m, 1H), 6,5 (d, 1H), 6,9 (t, 1H), 7,0 (d, 1H), 7,2 (m, 7H), 7,4 (d, 2H)

MS m/z: 538 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-ciano-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-26)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF a temperatura ambiente y se añadió K_2CO_3. Se añadió 4-bromobutilnitrilo y se permitió que la reacción se calentara a 80°C durante una noche. La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 50%/Hexano al 50%) para dar el producto.

^{1}H-RMN ($CDCl_3$) δ. 1,13 (d, 3H), 1,15 (m, 1H), 1,90 (m, 1H), 2,02 (s, 3H), 2,09 (m, 1H), 2,30 (m, 1H), 2,54 (t, 2H), 3,99 (t, 2H), 4,72 (sexteto, 1H), 5,6 (sa, 1H), 6,52 (d, 1H), 6,65 (d, 2H), 6,93 (t, 1H), 7,15 (m, 5H), 7,27 (t, 1H), 7,37 (d, 2H).
MS m/z: 502 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-{4-[3-(1*H*-tetrazol-5-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-27)

El nitrilo se preparó a partir de (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-{1-[4-(3-ciano-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida disolviéndose en tolueno, se le añadieron azida sódica y clorhidrato de trietilamonio y la mezcla se calentó a 80°C durante una noche La reacción se enfrió a temperatura ambiente y se le añadió agua, seguido de ácido clorhídrico (1 N) hasta que se hizo ácida La solución acuosa se extrajo tres veces con diclorometano Los extractos combinados se secaron sobre sulfato de magnesio, se filtraron, se secaron y se concentraron. El producto bruto se trituró con éter etílico/hexanos para producir un sólido blanco con un rendimiento del 63%

^{1}H RMN ($CDCl_3$) δ. 1,02 (d, 3H), 1,19 (m, 1H), 1,89 (s, 3H), 1,96 (m, 2H), 2,11 (m, 1H), 2,79 (m, 2H), 3,63 (m, 2H), 4,59 (sextuplete, 1H), 5,42 (s a, 1H), 6,35 (m, 3H), 6,77 (t, 1H), 6,91-7,08 (m, 7H), 7,22 (d, 1H).
MS m/z: 545 (M+1).

Éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butírico (B-28)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxl-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF a temperatura ambiente y se le añadió K_2CO_3. Se añadló 4-bromobutirato de etilo y la reacción se dejó calentar a 80°C durante una noche La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 50%/Hexano al 50%) para producir el producto.

^{1}H RMN ($CDCl_3$) δ 1,10 (d, 3H), 1,11 (m, 1H), 1,20 (t, 3H), 2,43 (t, 2H), 1,99 (s, 3H), 2,24 (m, 1H), 3,90 (t, 2H), 4,09 (c, 2H), 4,72 (sextuplete, 1H), 5,55 (s a, 1H), 6,49 (d, 1H)< 6,62 (d, 2H), 6,90 (t, 1H), 7,11 (d, 2H), 7,16 (m, 1H), 7,18 (d, 2H), 7,26 (d, 1H), 7,34 (d, 2H)

MS m/z: 549 (M+1).

(2*S*,4*R*)-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*,*N*-dietil-butiramida (B-29)

Se preparó (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-N,N-dietil-butiramida a partir de éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butírico. Se hidrolizó éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butírico (0,511 g, 0,93 mmol) en el ácido disolviéndose en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente 4 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco El sólido se filtró para dar ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-1-etildieno-penta-2,4-dieniloxi)-butírico con un rendimiento del 74% El ácido (0,050 g, 0,09 mmol) se convirtió en la amida disolviéndose en THF (2 ml) a temperatura ambiente. Se añadieron HOBt (0,019 g), EDCI (0,022 g) y dietilamina (0,010 ml) junto con 2 gotas de DMF y se agitó a temperatura ambiente durante 11 h La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre

$MgSO_4$, se filtraron y se concentraron. El residuo bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo al 50%/50% hexano a acetato de etilo al 100%) para producir el producto (0,023 mg, 54%).

^1H RMN ($CDCl_3$) δ. 0,91 (d, 3H), 0,96 (t, 6H), 1,06 (m, 1H), 1,58 (m, 2H), 1,86 (s, 3H), 2,11 (m, 1H), 2,29 (m, 2H), 3,11-3,17 (m, 4H), 3,78 (m, 2H), 4,56 (sextuplete, 1H), 5,43 (s a, 1H), 6,34 (d, 1H), 6,48 (d, 2H), 6,76 (t, 1H), 6,59-7,19 (m, 8H)

MS m/z: 576 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-{4-[3-(2-oxo-pirrolidin-1-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-30)

Se disolvió *N*-(3-hidroxipropil)-2-pirrolidona en benceno a temperatura ambiente añadiendo PPh_3 (0,044 g, 0,16 mmol), (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,100 g, 0,22 mmol) y se agitó durante 5 min Se añadió DEAD (0,029 g, 0,16 mmol) y la reacción se agitó durante 18 h a temperatura ambiente. La reacción se concentró y purificó por cromatografía en gel de sílice (MeOH al 4%/CH_2Cl_2 al 96% a MeOH al 5%/CH_2Cl_2 al 95% a MeOH al 6%/CH_2Cl_2 al 94%) para dar el producto con un rendimiento del 45%.

^1H-RMN ($CDCl_3$) δ: 1,13 (d, 3H), 1,14 (m, 1H), 1,96 (m, 4H), 2,02 (s, 3H), 2,34 (t, 3H), 3,39 (c, 4H), 3,90 (m, 2H), 4,72 (sexteto, 1H), 5,59 (sa, 1H), 6,52 (d, 1H), 6,63 (d, 2H), 7,18 (m, 6H), 7,37 (d, 2H).

MS m/z: 560 (M+1).

Éster etílico del ácido (2*S*,4*R*)-1-[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-1*H*-imidazol-2-carboxílico (B-31)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF a temperatura ambiente y se le añadió K_2CO_3. Se añadió éster etílico del ácido 1-(3-bromo-propil)-1*H*-imidazol-2-carboxílico (preparado a partir del dibromuro y el imidazol correspondiente con NaH en THF) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío El residuo se

repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (MeOH al 5%/CH_2Cl_2 al 95%/NH_4OH a MeOH al 10%/CH_2Cl_2 al 90%/NH_4OH) para producir el producto. ^1H RMN ($CDCl_3$) δ 1,10 (d, 3H), 1,11 (m, 1H), 1,38 (t, 3H), 2,01 (s, 3H), 2,22 (m, 2H), 3,83 (m, 2H), 4,35 (c, 2H), 4,55 (m, 2H), 4,71 (sextuplete, 1H), 5,58 (s a, 1H), 6,49 (d, 1H), 6,63 (d, 2H), 6,90 (t, 1H), 7,08-7,28 (m, 9H), 7,36 (d, 1H).

Amida del ácido (2*S*,4*R*)-1-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-1*H*-imidazol-2-carboxílico (B-32)

Se preparó amida del ácido (2*S*,4*R*)-1-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-1*H*-imidazol-2-carboxílico a partir de éster etílico del ácido (2*S*,4*R*)-1-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-1*H*-imidazol-2-carboxílico El éster (0,100 g, 0,16 mmol) se hidrolizó en el ácido disolviéndose en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente durante 4 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido (2*S*,4*R*)-1-[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-1*H*-imidazol-2-carboxílico con un rendimiento del 65%. El ácido (0,066 g, 0,09 mmol) se convirtió en la amida disolviéndose en DMF (2 ml) a temperatura ambiente. Se añadieron HATU (0,061 g, 0,16 mmol), HOBt (0,021 g, 0,15 mmol) y diisopropiletilamina (0,074 ml, 0,43 mmol) y se agitó durante 5 min seguido de cloruro amónico (0,011 g, 0,20 mmol). La reacción se agitó a temperatura ambiente durante 12 h y se concentró. El residuo se diluyó con acetato de etilo y se lavó con HCl 1 N y se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (de MeOH al 5%/CH_2Cl_2 al 95%/NH_4OH a MeOH al 10%/CH_2Cl_2 al 90%/NH_4OH a MeOH al 15%/CH_2Cl_2 al 85%/NH_4OH) para producir el producto (0,050 mg, 81%)

^{1}H RMN ($CDCl_3$) δ: 1,11 (d, 3H), 1,37 (m, 1H), 2,00 (s, 3H), 2,22 (m, 3H), 3,82 (t, 2H), 4,57 (t, 2H), 4,72 (sextuplete, 1H), 5,56 (s a, 1H), 6,49 (d, 1H), 6,60 (d, 2H), 6,90 (t, 1H), 6,89 (t, 1H), 6,93 (d, 2H), 7,11 (d, 2H), 7,15-7,27 (m, 5H), 7,34 (d, 1H)

MS m/z: 586 (M+1)

Ácido (2*S*,4*R*)-3-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-5-metil-3H-imidazol-4-carboxílico (B-33)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida en DMF a temperatura ambiente y se le añadió K_2CO_3. Se añadió éster etílico del ácido 3-(3-bromo-propil)-5-metil-3H-imidazol-4-carboxílico (preparado a partir del dibromuro y el imidazol correspondiente con NaH en THF) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por cromatografía sobre gel de sílice (MeOH al 2%/CH_2Cl_2 al 98% a MeOH al 10%/CH_2Cl_2 al 90%) para producir éster etílico del ácido (2*S*,4*R*)-3-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-5-metil-3H-imidazol-4-carboxílico. El éster (0,080 g, 0,12 mmol) se hidrolizó en el ácido disolviéndose en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente 16 horas. La mezcla se enfrió a temperatura ambiente y se acidificó para formar un precipitado blanco El sólido se filtró para dar ácido (2*S*,4*R*)-3-[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-5-metil-3H-imidazol-4-carboxílico con un rendimiento del 61%.

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 3H), 1,29 (m, 1H), 2,05 (s, 3H), 2,34 (m, 2H), 2,45 (m, 1H), 2,61 (s, 3H), 4,08 (m, 2H), 4,43 (m, 2H), 4,73 (sextuplete, 1H), 5,53 (s a, 1H), 6,55 (d, 1H), 6,73 (d, 2H), 6,96 (t, 1H), 7,18 (m, 3H), 7,41 (m, 5H), 9,08 (s, 1H)

MS m/z: 601 (M+1)

10469
476

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-imidazol-1-il-3-metil-butoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-34)

Se disolvió 3-imidazol-1-il-3-metil-butan-1-ol en benceno a temperatura ambiente con PPh_3 (0,088 g, 0,33 mmol), se le añadió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,133 g, 0,30 mmol) y se agitó durante 5 min. Se añadió DEAD (0,058 g, 0,33 mmol) y la reacción se agitó durante 18 h a temperatura ambiente. La reacción se concentró y se purificó por cromatografía sobre gel de sílice (de MeOH al 4%/ CH_2Cl_2 al 96% a MeOH al 5%/ CH_2Cl_2 al 95% a MeOH al 6%/CH_2Cl_2 al 94%) para producir el producto con un rendimiento del 46%

Preparación de 3-imidazol-1-il-3-metil-butan-1-ol

Se preparó 3-imidazol-1-il-3-metil-butan-1-ol a partir de 2,2-dimetilacrilato de etilo. Se mezclaron 2,2-dimetilacrilato de etilo (2,04 ml, 14,7 mmol) e imidazol (0,500 g, 7,34 mmol) y se calentaron a 90°C durante 48 h y se enfriaron a temperatura ambiente. La mezcla de reacción se diluyó con CH_2Cl_2 y agua La fase acuosa se extrajo 3 x CH_2Cl_2 y se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (MeOH al 10%/CH_2Cl_2 al 90%) para dar un rendimiento del 35% de éster etílico del ácido 3-imidazol-1-il-3-metil-butírico. El éster se redujo en el alcohol (solicitud de Patente de Estados Unidos WO03047586). Se disolvió éster etílico del ácido 3-imidazol-1-il-3-metil-butírico (0,500 g, 2,5 mmol) en THF (40 ml) y se enfrió a 0°C y se le añadieron gota a gota 2,55 ml de $LiAlH_4$ (1,0 M en éter) durante 15 min. La reacción se dejó calentar a temperatura ambiente durante 1 h y se interrumpió con la adición gota a gota de una solución sat. de Na_2SO_4. La suspensión resultante se secó sobre Na_2SO_4 sólido y se diluyó con acetato de etilo, se filtró a través de un lecho de Celite y se concentró.

^1H RMN ($CDCl_3$) δ: 1,09 (d, 3H), 1,11 (m, 1H), 1,56 (s, 6H), 1,97 (s, 3H), 2,08 (m, 1H), 2,16 (t, 2H), 3,67 (m, 2H), 4,67 (sextuplete, 1H), 5,51 (s a, 1H), 6,49 (m, 3H), 6,87 (t, 1H), 6,96-7,61 (m, 10 H), 7,64 (m, 1H)

MS m/z: 568 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[2-metil-1-{4-[3-(3-metil-[1,2,4]oxadiazol-5-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-35)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-(2-metil-1-{4-[3-(3-metil-[1,2,4]oxadiazol-5-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida a partir de éster metílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butírico Se suspendió acetamida oxima (0,043 g, 0,58 mmol) en THF en atmósfera de N_2 y se añadió NaH (dispersión en aceite al 60%) (0,025 g, 1,0 mmol) seguido de tamices moleculares de 4 Å y se calentó a 60°C durante 1 h. Se añadió éster metílico del ácido (2*S*,4*R*)- 4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butírico y se calentó a reflujo durante 4,5 h La reacción se filtró y se concentró y repartió entre CH_2Cl_2 y agua. La capa acuosa se extrajo 3x con CH_2Cl_2 y se secó sobre $MgSO_4$, se filtró, se concentró y se purificó por cromatografía en gel de sílice (100% EtOAc) para dar (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-{4-[3-(3-metil-[1,2,4]oxadiazol-5-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida con un rendimiento del 44%.

^{1}H-RMN ($CDCl_3$) δ: 1,12 (d, 3H), 1,13 (m, 1H), 2,00 (s, 3H), 2,23 (m, 2H), 2,38 (s, 3H), 3,00 (m, 2H), 3,96 (m, 2H), 4,72 (sexteto, 1H), 5,58 (sa, 1H), 6,49 (d, 1H), 6,62 (d, 2H), 6,91 (t, 1H), 7,31-7,25 (m, 7 H), 7,34 (d, 1H).

MS m/z: 559 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-[4-(3-pirazol-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-37)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (75 mg, 0,17 mmol) en DMF (1 ml) a temperatura ambiente. Se añadió K_2CO_3 (47 mg, 0,34 mmol) seguido de 1-(3-bromopropil)-pirazol (64 mg, 0,34 mmol) (preparado a partir de la reacción de 1,3-dibromopropano y pirazol con hidruro sódico en tetrahidrofurano). La reacción se dejó en agitación a 70°C durante 3 h. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua y después se extrajo tres veces con acetato de etilo. Las capas orgánicas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron.

El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 1/99 de metanol/diclorometano-3/97 de metanol/diclorometano) para producir el producto

^{1}H RMN ($CDCl_3$) δ. 1,1 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 2,3 (m, 2H), 3,8 (t, 2H), 4,3 (t, 2H), 4,7 (m, 1H), 5,6 (m, 1H), 6,2 (t, 1H), 6,5 (d, 1H), 6,65 (d, 2H), 6,9 (t, 1H), 7,1-7,4 (m, 9H), 7,5 (s, 1H).

MS m/z 443/445 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(3-pirrol-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-38)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (75 mg, 0,17 mmol) en DMF (1 ml) a temperatura ambiente Se añadió K_2CO_3 (47 mg, 0,34 mmol) seguido de 1-(3-bromopropil)-pirrol y la reacción se dejó en agitación a 70°C durante 3 h La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua y después se extrajo tres veces con acetato de etilo Las capas orgánicas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo bruto se purificó por cromatografía sobre gel de sílice (1/1 de acetato de etilo/hexanos) para producir el producto

^{1}H RMN ($CDCl_3$) δ· 1,1 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,1 (m, 2H), 2,3 (m, 1H), 3,8 (t, 2H), 4,1 (t, 2H), 4,8 (m, 1H), 5,6 (m, 1H), 6,1 (d, 2H), 6,5 (d, 1H), 6,6 (d, 2H), 6,65 (d, 2H), 6,9 (t, 1H), 7,1-7,3 (m, 6H), 7,4 (d, 2H).

MS m/z. 442/444 (M+1).

Ácido (2*S*,4*R*)-5-{4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil}-furan-2-carboxílico (B-39)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,28 g, 0,64 mmol) en DMF a temperatura ambiente y se le añadió K_2CO_3 (0,125 g, 0,89 mmol). Se añadió éster metílico del ácido 5-clorometil-furan-2-carboxílico (0,130 g, 0,64 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se

filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice para producir el producto en forma de un aceite incoloro con un rendimiento del 53%

Se hidrolizó éster metílico del ácido (2*S*,4*R*)-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-furan-2-carboxílico (0,145 g, 0,25 mmol) en el ácido disolviéndose en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente 4 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido (2*S*,4*R*)-5-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-furan-2-carboxílico en forma de un sólido blanco.

^{1}H RMN ($CDCl_3$) δ· 1,12-1,19 (m, 4H), 2,03 (s, 3H), 2,23-2,29 (m, 1H), 4,73-4,75 (m, 1H), 4,95 (s, 2H), 5,59 (s a, 1H) 6,48-6,51 (m, 2H), 6,69 (d, 2H), 6,91 (t, 1H), 7,12-7,37 (m, 9H).

MS m/z: 559 (M+1).

Amida del ácido (2*S*,4*R*)-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-furan-2-carboxílico (B-40)

Se convirtió ácido (2*S*,4*R*)-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-furan-2-carboxílico (0,065 g, 0,12 mmol) en la amida disolviéndose en THF (1 ml) a temperatura ambiente. Se añadieron HOBt (0,024 g), EDCI (0,033 g) y cloruro amónico (0,013 g, 0,232 mmol) junto con 2 gotas de DMF y se agitó a temperatura ambiente durante 11 h. La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron. El residuo bruto se purificó por cromatografía sobre gel de sílice (10 acetato de etilo·1 metanol) para producir el producto en forma de un sólido blanco con un rendimiento del 61%.

^{1}H RMN ($CDCl_3$) δ. 1,13-1,20 (m, 4H), 2,01 (s, 3H), 2,23-2,29 (m, 1H), 4,72-4,74 (m, 1H), 4,99 (s, 2H), 5,59 (s a, 1H) 6,47-6,51 (m, 2H), 6,71 (d, 2H), 6,91 (t, 1H), 7,09-7,38 (m, 9H).

MS m/z: 558 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[2-metil-1-[4-(3-piperazin-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (B-41)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-(2-metil-1-[4-(3-piperazin-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida a partir de éster *terc*-butílico del ácido (2*S*,4*R*)-4-[3-(4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-pierazin-1-carboxílico. Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,40 g, 0,92 mmol) en DMF a temperatura ambiente y se le añadió K_2CO_3 (0,127 g, 0,921 mmol). Se añadió éster *terc*-butílico del ácido 4-(3-cloro-propil)-pierazin-1-carboxílico (0,242 g, 0,921 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice para producir el producto en forma de un aceite incoloro con un rendimiento del 50%.

Se disolvió éster *terc*-butílico del ácido (2*S*,4*R*)-4-[3-(4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-pierazin-1-carboxílico (246 mg) en HCl 4 M en dioxano (2 ml). La mezcla se agitó durante 2 h a temperatura ambiente. Después de la concentración, el sólido blanco se lavó con EtOAc para proporcionar el compuesto del título con un rendimiento del 100%

^{1}H RMN (DMSO, sal 2HCl) δ: 1,00-1,02 (m, 4H), 1,88-1,94 (m, 3H), 2,10-2,15 (m, 1H), 3,15-3,80 (m, 12H), 4,02 (t, 2H), 4,56-4,59 (m, 1H), 5,49 (s a, 1H), 6,50 (d, 1H), 6,76 (d, 2H), 6,96 (t, 1H), 7,04 (d, 2H), 7,16 (t, 1H), 7,39-7,53 (m, 5H).
MS m/z: 561 (M+1)

(2*S*,4*R*)-*N*-(1-{4-[3-(4-Acetil-piperazin-1-il)-propoxi]-benzoil}-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (B-42)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-(2-metil-1-[4-(3-piperazin-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (168 mg) en CH_2Cl_2 (2 ml) Se añadieron cloruro acético (47 mg) y DIEA (52 µl). La mezcla de

reacción se agitó a temperatura ambiente durante una noche. La fase orgánica se lavó con $NaHCO_3$ sat (2 x 5 ml), se secó sobre Na_2SO_4 y se concentró El residuo se purificó por cromatografía en gel de sílice (EtOAc) para dar (2*S*,4*R*)-*N*-(1-{4-[3-(4-acetil-piperazin-1-il)-propoxi]-benzoil}-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida pura (100 mg, 57%).

^{1}H-RMN ($CDCl_3$) δ 1,13 (d, 4H), 1,88-1,94 (m, 2H), 2,02 (s, 3H), 2,06 (s, 3H), 2,20-2,48 (m, 7H), 3,43 (sa, 2H), 3,59 (sa, 2H), 3,94 (t, 2H), 4,74 (sexteto, 1H), 5,60 (sa, 1H), 6,53 (d, 1H), 6,66 (d, 2H), 6,91 (t, 1H) 7,11-7,38 (m, 8H).

MS m/z. 603 (M+1).

Éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico (B-43)

A una solución de dietilazodicarboxilato (120 mg) en 5 ml de THF a 0°C se le añadió PPh_3 (181 mg). La mezcla se agitó durante 10 min a 0°C Después, se añadió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (200 mg). La mezcla se agitó durante 20 min a 0°C. Se añadió éster etílico del ácido 4-hidroxi-ciclohexanocarboxílico (80 mg). La mezcla de reacción final se agitó durante una noche a TA. La mezcla se concentró a presión reducida, se disolvió en acetato de etilo, se lavó con bicarbonato sódico sat. acuoso y salmuera y se secó sobre sulfato de magnesio, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 30/70 de hexanos/acetato de etilo) para producir éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico puro (100 mg, 37%).

^{1}H RMN ($CDCl_3$) δ. 1,13 (d, 4H), 1,22 (t, 3H), 1,26-1,60 (m, 5H), 2,00-2,18 (m, 5H), 2,20-2,39 (m, 3H), 4,11 (c, 2H), 4,72 (sextuplete, 1H), 5,60 (s a, 1H), 6,53 (d, 1H), 6,64 (d, 2H), 6,91 (t, 1H) 7,11-7,38 (m, 8H).

MS m/z: 589 (M+1)

Ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico (B-44)

Se hidrolizó éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico (0,060, 0,10 mmol) en el ácido disolviéndose en tetrahidrofurano y etanol y se le añadió hidróxido sódico (1 N) La mezcla se agitó a temperatura ambiente 10 horas. La mezcla se enfrió a temperatura ambiente y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico en forma de un polvo blanco con un rendimiento del 62%.

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 4H), 1,24-1,60 (m, 5H), 2,01 (s, 6H), 2,20-2,39 (m, 2H), 4,72 (sextuplete, 1H), 5,60 (s a, 1H), 6,53 (d, 1H), 6,64 (d, 2H), 6,91 (t, 1H) 7,11-7,38 (m, 8H).

MS m/z. 561 (M+1).

Amida del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico (B-45)

Se convirtió ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-ciclohexanocarboxílico (0,070 g, 0,125 mmol) en la amida disolviéndose en THF (1 ml) a temperatura ambiente Se añadieron HOBt (0,025 g), EDCI (0,035 g) y cloruro amónico (0,014 g, 0,25 mmol) junto con 2 gotas de DMF y se agitó a temperatura ambiente durante 11 h. La reacción se diluyó con acetato de etilo y se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo al 50%/metanol al 50%) para producir el producto en forma de un polvo blanco con un rendimiento del 71%.

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 4H), 1,19-1,60 (m, 7H), 2,01 (s, 4H), 2,20-2,39 (m, 2H), 4,72 (sextuplete, 1H), 5,60 (s a, 1H), 6,54 (d, 1H), 6,63 (d, 2H), 6,91 (t, 1H) 7,11-7,38 (m, 8H).

MS m/z: 560 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(2-oxo-oxazolidin-5-ilmetoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-46)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,5 g, 1,14 mmol) en DMF a temperatura ambiente y se le añadió K_2CO_3 (1,26 g, 9,13 mmol). Se añadió 2-clorometil-oxirano (0,42 g, 4,57 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 50%/Hexano al 50%) para producir (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[2-metil-1-(4-oxiranilmetoxi-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,55 g, 77%), que se elaboró además en el producto siguiendo la ref (*Tetrahedron Lett* **2002**, 43(46), 8327).

^{1}H RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 2,03 (s, 3H), 2,27 (m, 1H), 3,57 (m, 1H), 3,68 (m, 1H), 4,05 (m, 2H), 4,73 (m, 1H), 4,86 (m, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)

MS m/z: 535 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-etil-2-oxo-oxazolidin-5-ilmetoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-47)

Se preparó (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-{1-[4-(3-etil-2-oxo-oxazolidin-5-ilmetoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida a partir de (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-{2-metil-1-[4-(2-oxo-oxazolidin-5-ilmetoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida siguiendo la referencia (*Tetrahedron Lett* **2002**, 43(46), 8327)

^{1}H-RMN ($CDCl_3$) d. 1,15 (m, 7H), 2,03 (s, 3H), 2,27 (m, 1H), 3,28 (c, 2H), 3,47 (m, 1H), 3,63 (t, 1H), 4,05 (d, 2H), 4,73 (m, 2H), 5,58 (sa, 1H), 6,47 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 563 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-dietilamino-2-hidroxi-propoxi)-benzoil] -2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-48)

La (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[2-metil-1-(4-oxiranilmetoxi-benzoil)-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida se elaboró adicionalmente hasta (2*S*,4*R*)-*N*-{1-[4-(3-amino-2-hidroxi-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-

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quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida siguiendo la referencia (*Tetrahedron Lett* **2002**, 43(46), 8327). La amina se hizo reaccionar con acetaldehído, $Na(OAc)_3BH$ en diclorometano a temperatura ambiente durante una noche Después se lavó con NaOH 1 N, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC para dar el producto con un rendimiento del 38%

^{1}H-RMN ($CDCl_3$) d· 1,05-1,23 (m, 10H), 2,03 (s, 3H), 2,27 (m, 1H), 2,69-2,95 (m, 6H), 3,85 (m, 1H), 3,98 (m, 1H), 4,18 (m, 1H), 4,72 (sexteto, 1H), 5,58 (sa, 1H), 6,58 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)

MS m/z. 564 (M+1)

(2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida (B-49)

Se preparó (2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida a partir de ácido (2*S*,4*R*)- 4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-1-etiliden-penta-2,4-dieniloxi)-butírico por acoplamiento de NH_4Cl, HATU, DIEA, HOBt en DMF a temperatura ambiente para producir (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida La mezcla de reacción se concentró y repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró El residuo se purificó por cromatografía en gel de sílice (metanol al 10%/diclorometano al 90%) para dar (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida pura con un rendimiento del 46%.

^{1}H-RMN ($CDCl_3$) d. 1,13 (d, 3H), 1,15 (t, 1H), 1,68 (sa, 2H), 2,04 (s, 3H), 2,08 (m, 2H), 2,27 (m, 1H), 2,38 (t, 2H), 3,97 (t, 2H), 4,72 (sexteto, 1H), 5,48 (sa, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 520 (M+1)

(2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-*N*-etil-butiramida (B-50)

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Se convirtió ácido (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-1-etilideno-penta-2,4-dieniloxi)-butírico (0,064 g, 0,123 mmol) en la amida disolviéndose en THF (2 ml) a temperatura ambiente. Se añadieron HOBt (0,025 g), EDCI (0,028 g) y etilamina (0,36 mmol) junto con 2 gotas de DMF y se agitó a temperatura ambiente durante 11 h La reacción se diluyó con acetato de etilo, se lavó con NaOH 1 N, HCl 1 N y salmuera. Los extractos orgánicos se secaron sobre $MgSO_4$, se filtraron y se concentraron El residuo bruto se purificó por cromatografía sobre gel de sílice (acetato de etilo al 50%/50% hexano a acetato de etilo al 100%) para producir el producto (0,050 g, 74%).

^{1}H RMN ($CDCl_3$) δ. 1,06 (t, 3H), 1,13 (d, 3H), 1,15 (t, 1H), 1,81 (s, 1H), 2,04 (s, 3H), 2,06 (m, 2H), 2,27 (m, 1H), 2,32 (t, 2H), 3,28 (c, 2H), 3,91 (t, 2H), 4,72 (sextuplete, 1H), 5,66 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,88 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 548 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(4-hidroxi-4-metil-pentiloxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-51)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,1 g, 0,23 mmol) en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 (0,317 g, 2,3 mmol). Se añadió 5-bromo-2-metil-pentan-2-ol (0,092 g, 0,51 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 70%/Hexano al 30%) para producir el producto (0,097 g, 79%)

^{1}H RMN ($CDCl_3$) δ 1,13 (d, 3H), 1,15 (t, 1H), 1,26 (s, 6H), 1,52-1,90 (m, 5H), 2,04 (s, 3H), 2,27 (m, 1H), 3,91 (t, 2H), 4,72 (sextuplete, 1H), 5,48 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 535 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-imidazol-1-il-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-52)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,1 g, 0,23 mmol) en DMF (5 ml) a temperatura ambiente Se añadió K_2CO_3 (0,317 g, 2,3 mmol). Se añadió 1-(3-bromo-propil)-1*H*-imidazol (0,174 g, 0,92 mmol) y se permitió que la reacción se calentara a 80°C durante una noche La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 60%/Hexano al 40%) para dar el producto (0,020 g, 16%)

^{1}H-RMN ($CDCl_3$) d: 1,16 (d, 3H), 1,15 (t, 1H), 2,02 (s, 3H), 2,18 (m, 2H), 2,28 (m, 1H), 3,85 (t, 2H), 4,17 (t, 2H), 4,72 (sexteto, 1H), 5,58 (sa, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,84 (s, 1H), 6,88 (t, 1H), 7,03 (s, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H), 7,43 (s, 1H)

MS m/z: 543 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(3-pirrolidin-1-il-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-53)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,1 g, 0,23 mmol) en DMF (5 ml) a temperatura ambiente. Se añadió K_2CO_3 (0,317 g, 2,3 mmol). Se añadió 1-(3-Bromo-propil)-pirrolidina (0,177 g, 0,92 mmol) y se permitió que la reacción se calentara a 80°C durante una noche. La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (metanol al 10%/diclorometano al 90%) para dar el producto (0,01 g, 8%).

^{1}H-RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,58-1,76 (m, 2H), 2,04 (s, 3H), 2,05-2,18 (m, 2H), 2,27 (m, 1H), 2,38 (m, 2H), 3,28 (t, 2H), 3,33 (m, 4H), 3,96 (t, 2H), 4,72 (sexteto, 1H), 5,54 (sa, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,88 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 546 (M+1)

Ácido (2*S*,4*R*)-*N*-4-{4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butírico (B-54)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,126 g, 0,242 mmol) en 3 ml de DMF a temperatura ambiente y se le añadió K_2CO_3 (0,267 g, 1,94 mmol) Se añadió éster metílico del ácido 4-bromo-2,2-dimetil-butírico (0,202 g, 0,969 mmol, preparado de acuerdo con el procedimiento de *Tetrahedron* 1994, 50 (32), 9825-30) y la reacción se dejó calentar a 80°C durante una noche La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 50%/Hexano al 50%) para producir el éster metílico del ácido (2*S*,4*R*)-4-{4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butírico (0,105 g, 77%).

El éster se hidrolizó en el ácido disolviéndose en 6 ml de tetrahidrofurano/metanol (1/1) y se le añadió hidróxido potásico (0,042 g en 2 ml de agua). La mezcla se calentó a 40°C durante 3 horas La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido (2*S*,4*R*)-*N*-4-{4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butírico (0,085 g, 83%).

^{1}H RMN ($CDCl_3$) δ: 1,14 (d, 3H), 1,15 (t, 1H), 1,25 (s, 6H), 2,02 (t, 2H), 2,05 (m, 2H), 2,27 (m, 1H), 3,96 (t, 2H), 4,72 (sextupiete, 1H), 5,52 (a, 2H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 549 (M+1)

Ácido (2*S*,4*R*)-4-{4-[4-(acetil-fenil-amino)-2-metil-3,4-dihidro-2H-quinolin-1-carbonil]-fenoxi}-2,2-dimetil-butírico (B-55)

Se disolvió ácido 4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butírico (300 mg, 0,545 mmol) en etanol Se añadió Pd/C (Paladio al 10%), seguido de gas H_2 (1 atm-globo) Después de 3 horas, la mezcla de reacción se filtró y se concentró. El residuo

bruto se purificó por cromatografía sobre gel de sílice (gradiente de acetato de etilo - metanol al 5%/acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ· 1,1 (d, 3H), 1,2 (m, 1H), 1,2 (s, 3H), 1,3 (s, 3H), 2,0 (s, 3H), 2,1 (t, 1H), 2,3 (m, 1H), 3,9 (m, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 5,9 (d, 1H), 6,5 (d, 1H), 6,4 (d, 2H), 6,9 (t, 1H), 7,2 (m, 7H), 7,4 (d, 2H), 10,8 (s a, 1H).

MS m/z: 515 (M+1).

(2*S*,4*R*)-*N*-4-(4-[4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butiramida (B-56)

Se preparó (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butiramida a partir de ácido (2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-butírico acoplando NH_4Cl, HATU, DIEA, HOBt en DMF a temperatura ambiente para producir (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida. La mezcla de reacción se concentró y se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida pura (63%).

^{1}H RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,25 (s, 6H), 1,98 (t, 2H), 2,04 (s, 3H), 2,27 (m, 1H), 3,96 (t, 2H), 4,72 (sextuplete, 1H), 5,52 (a, 2H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 548 (M+1)

Éster bencílico del ácido (2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-piperidin-1-carboxílico (B-57)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,31 g, 0,71 mmol) en DMF a temperatura ambiente y se añadió K_2CO_3 (0,392 g, 2,84 mmol). Se añadió éster bencílico del ácido 4-bromometil-piperidin-1-carboxílico (0,668 g, 2,14 mmol) y

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se permitió que la reacción se calentara a 80°C durante una noche La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 60%/Hexano al 40%) para dar el producto (0,25 g, 53%).

^{1}H-RMN ($CDCl_3$) d 1,13 (d, 3H), 1,15 (t, 1H), 1,24 (m, 2H), 1,76 (m, 2H), 1,88 (m, 1H), 2,04 (s, 3H), 2,27 (m, 1H), 2,75 (m, 2H), 3,68 (d, 2H), 4,17 (sa, 2H), 4,72 (sexteto, 1H), 5,12 (s, 2H), 5,58 (sa, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,38 (m, 13H).

MS m/z: 666 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(1-etil-piperidin-4-ilmetoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-58)

Se convirtió éster bencílico del ácido (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-piperidin-1-carboxílico (0,25 g) en la pipendina por hidrogenación con Pd/C (0,075 g) en una atmósfera de hidrógeno en etanol (17 ml) La mezcla de reacción se filtró a través de celite y se concentró para dar (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(piperidin-4-ilmetoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (0,17 g, 85%)

La piperidina se hizo reaccionar con acetaldehído y $Na(OAc)_3BH$ en diclorometano a temperatura ambiente durante una noche. Después, se lavó con NaOH 1 N, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto (55%).

^{1}H RMN ($CDCl_3$) d: 0,98-1,18 (m, 7H), 1,37 (m, 2H), 1,72-1,93 (m, 5H), 2,04 (s, 3H), 2,27 (m, 1H), 2,37 (c, 2H), 2,95 (m, 2H), 3,73 (d, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 560 (M+1)

(2*S*,4*R*)-*N*-(1-[4-(1-Acetil-piperidin-4-ilmetoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (B-59)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-(2-metil-1-[4-(piperidin-4-ilmetoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (0,075 g, 0,14 mmol) en diclorometano a temperatura ambiente Se añadieron DIEA (0,1 ml, 0,56 mmol) y cloruro de acetilo (0,2 ml, 2,8 mmol). La reacción se agitó a temperatura ambiente durante una noche La mezcla de reacción se concentró al vacío. El residuo bruto se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto (0,049 g, 49%).

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 3H), 1,15 (t, 1H), 1,24 (m, 2H), 1,81 (m, 2H), 1,93 (m, 1H), 2,04 (s, 3H), 2,09 (s, 3H), 2,27 (m, 1H), 2,55 (t, 1H), 3,09 (t, 1H), 3,73 (m, 2H), 3,85 (m, 1H), 4,63 (m, 1H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).
MS m/z: 574 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-[4-(2-pirrol-1-il-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-60)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,11 g, 0,25 mmol) en DMF a temperatura ambiente y se añadió K_2CO_3 (0,207 g, 1,5 mmol). Se añadió 1-(2-Bromo-etil)-1*H*-pirrol (0,088 g, 0,5 mmol) y se permitió que la reacción se calentara a 80°C durante una noche. La mezcla de reacción se concentró *al vacío*. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 70%/Hexano al 30%) para dar el producto (0,114 g, 85%).
^{1}H-RMN ($CDCl_3$) d· 1,13 (d, 3H), 1,15 (t, 1H), 1,98 (s, 3H), 2,27 (m, 1H), 4,11 (t, 2H), 4,17 (t, 2H), 4,72 (sexteto, 1H), 5,58 (sa, 1H), 6,12 (t, 2H), 6,48 (d, 1H), 6,57 (d, 2H), 6,68 (t, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)
MS m/z: 528 (M+1)

Ácido (2*S*,4*R*)-*N*-3-(4-[4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil]-fenoxi)-2,2-dimetil-propiónico (B-61)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,32 g, 0,74 mmol) en 10 ml de DMF a temperatura ambiente y se le añadió K_2CO_3 (0,51 g, 3,7 mmol). Se añadió éster etílico del ácido 3-cloro-2,2-dimetil-propiónico (0,25 g, 1,52 mmol) y la reacción se dejó calentar a 90°C durante 6 días La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 60%/Hexano al 40%) para producir el éster etílico del ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-propiónico (0,13 g, 32%)

El éster se hidrolizó en el ácido disolviéndose en 8 ml de tetrahidrofurano/metanol (1/1) y se le añadió hidróxido potásico (0,052 g en 2,5 ml de agua) La mezcla se calentó a 40°C durante 3 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar el producto (0,098 g, 79%).

^{1}H RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,31 (s, 6H), 2,03 (s, 3H), 2,27 (m, 1H), 3,88 (c, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,69 (d, 2H), 6,83 (t, 2H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 535 (M+1)

(2*S*,4*R*)-*N*-3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-propionamida (B-63)

Se preparó (2*S*,4*R*)-*N*-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-propionamida a partir de ácido (2*S*,4*R*)-*N*-3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-propiónico acoplando NH_4Cl, HATU, DIEA, HOBt en DMF a temperatura ambiente para producir (2*S*,4*R*)-*N*-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-butiramida. La mezcla de reacción se concentró y se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó por

cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto con un rendimiento del 88%

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 3H), 1,15 (t, 1H), 1,31 (s, 6H), 1,71 (s a, 1H), 2,03 (s, 3H), 2,27 (m, 1H), 3,83 (c, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,17(a, 1H), 6,52 (d, 1H), 6,69 (d, 2H), 6,83 (t, 2H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)

MS m/z 534 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-[2-(1-metanosulfonil-piperidin-4-il)-etoxi]-benzoil}-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-64)

Se disolvió éster *terc*-butílico del ácido 4-(2-Hidroxi-etil)-piperidin-1-carboxílico (0,119 g, 0,52 mmol) en tolueno a temperatura ambiente con PPh_3 (0,136 g, 0,52 mmol), después se le añadió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,150 g, 0,35 mmol) y se agitó durante 5 min. Se añadió DEAD (0,090 g, 0,52 mmol) y la reacción se agitó durante 18 h a temperatura ambiente. La reacción se concentró y se purificó por cromatografía sobre gel de sílice (CH_2Cl_2 al 45%/EtOAc al 55%) para producir éster *terc*-butílico del ácido (2*S*,4*R*)-4-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-piperidin-1-carboxílico (0,2 g, 90%)

El éster se convirtió en (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[2-metil-1-[4-(2-piperidin-4-il-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida haciéndose reaccionar con HCl (4 M en dioxano) en diclorometano a temperatura ambiente durante 3 horas. La piperidina se disolvió en diclorometano a temperatura ambiente y se le añadió DIEA. Se añadió cloruro de metanosulfonilo y la reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró al vacío. El residuo bruto se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto con un rendimiento del 76%.

^{1}H RMN ($CDCl_3$) δ. 1,13 (d, 3H), 1,15 (t, 1H), 1,22-1,38 (m, 2H), 1,68-1,87 (m, 5H), 2,04 (s, 3H), 2,27 (m, 1H), 2,67 (t, 2H), 2,76 (s, 3H), 3,77 (m, 2H), 3,94 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,69 (d, 2H), 6,83 (t, 2H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 624 (M+1)

(2*S*,4*R*)-*N*-(1-{4-[2-(1-Acetil-piperidin-4-il)-etoxi]-benzoil}-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (B-65)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-(2-metil-1-[4-(2-piperidin-4-il-etoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (0,085 g, 0,15 mmol) en diclorometano a temperatura ambiente y se le añadió DIEA (0,1 g, 0,56 mmol). Se añadió cloruro de acetilo (0,2 ml, 2,8 mmol) y la reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se concentró al vacío El residuo bruto se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto (0,068 g, 75%).

^{1}H RMN ($CDCl_3$) δ. 1,15 (d, 3H), 1,15 (t, 1H), 1,21 (m, 2H), 1,58-1,77 (m, 5H), 1,98 (s, 3H), 2,04 (s, 3H), 2,27 (m, 1H), 2,51 (t, 1H), 2,98 (t, 1H), 3,72 (m, 1H), 3,93 (t, 2H), 4,51 (m, 1H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,69 (d, 2H), 6,83 (t, 2H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS *m/z*: 588 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(2-imidazol-1-il-etoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-66)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,065 g, 0,15 mmol) en DMF a temperatura ambiente y se le añadió K_2CO_3 (0,12 g, 0,87 mmol). Se añadió 1-(2-bromo-etil)-1*H*-imidazol (0,08 g, 0,45 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto (0,06 g, 76%).

^{1}H RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,98 (s, 3H), 2,27 (m, 1H), 4,13 (t, 2H), 4,28 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,48 (d, 1H), 6,64 (d, 2H), 6,91 (t, 1H), 6,98 (s, 1H), 7,03 (s, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H), 7,55 (s, 1H)

MS m/z: 529 (M+1)

Ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico (B-67)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,17 g, 0,39 mmol) en 5 ml de DMF a temperatura ambiente y se añadió K_2CO_3 (0,323 g, 2,34 mmol). Se añadió éster etílico del ácido 1-(2-bromo-etil)-ciclobutanocarboxílico (0,184 g, 0,78 mmol) preparado de acuerdo con el procedimiento de *Tetrahedron* **1994**, 50(32), 9825-30 y se permitió que la reacción se calentara a 80°C durante una noche. La mezcla de reacción se concentró *al vacío*. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 50%/Hexano al 50%) para dar el éster etílico del ácido 1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico (0,155 g, 67%)

El éster se hidrolizó al ácido disolviéndolo en 8 ml de tetrahidrofurano/metanol (1/1) y se añadió hidróxido potásico (0,08 g en 3 ml de agua). La mezcla se calentó a 40°C durante 3 horas. La mezcla se enfrió a ta, se acidificó para formar un precipitado blanco. El sólido se filtró para dar el producto (0,145 g, 98%).

^{1}H-RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,96 (m, 4H), 2,04 (s, 3H), 2,27 (m, 1H), 2,29 (t, 2H), 2,49 (m, 2H), 3,96 (t, 2H), 4,72 (sexteto, 1H), 5,58 (sa, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 561 (M+1)

Amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico (B-68)

Se preparó amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico a partir de ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-

ciclobutanocarboxílico mediante el acoplamiento de NH_4Cl, HATU, DIEA y HOBt en DMF a temperatura ambiente para producir amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico. La mezcla de reacción se concentró y se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto puro (63%)

^{1}H RMN ($CDCl_3$) δ: 1,16 (d, 3H), 1,15 (t, 1H), 1,77-1,96 (m, 4H), 2,04 (s, 3H), 2,16-2,48 (m, 5H), 3,96 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z: 560 (M+1)

Ácido (2*S*,4*R*)-*N*-4-{4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-difluoro-butírico (B-69)

Se disolvió éster metílico del ácido 2,2-difluoro-4-hidroxi-butírico (0,27 g, 3,21 mmol, preparado de acuerdo con el procedimiento de la Patente de Estados Unidos 4421690) en tolueno a temperatura ambiente con PPh_3 (0,421 g, 3,21 mmol), después se le añadió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,20 g, 0,46 mmol) y se agitó durante 5 min. Se añadió DEAD (0,028 g, 3,21 mmol) y la reacción se agitó durante 18 h a temperatura ambiente. La reacción se concentró y se purificó por cromatografía sobre gel de sílice (CH_2Cl_2 al 45%/EtOAc al 55%) para producir éster metílico del ácido (2*S*,4*R*)-*N*-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-difluoro-butírico (0,23 g, 87%)

El éster se hidrolizó en el ácido disolviéndose en 8 ml de tetrahidrofurano/metanol (1/1) y se le añadió hidróxido potásico (0,1 g en 4 ml de agua). La mezcla se calentó a 40°C durante una noche. La mezcla se enfnó a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar el producto (0,038 g, 97%).

^{1}H RMN ($CDCl_3$) δ· 1,13 (d, 3H), 1,15 (t, 1H), 2,04 (s, 3H), 2,18-2,44 (s a, 4H),

3,95 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)

MS m/z: 557 (M+1).

Amida del ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-pentanoico (B-70)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,146 g, 0,34 mmol) en 5 ml de DMF a temperatura ambiente y se le añadió K_2CO_3 (0,186 g, 1,35 mmol). Se añadió éster etílico del ácido 5-bromo-pentanoico (0,14 g, 0,67 mmol) y la reacción se dejó calentar a 80°C durante una noche. La mezcla de reacción se concentró al vacío El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 50%/Hexano al 50%) para producir el éster etílico del ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-pentanoico (0,148 g, 78%).

El éster se hidrolizó en el ácido disolviéndose en 10 ml de tetrahidrofurano/metanol (1/1) y se le añadió hidróxido potásico (0,182 g en 5 ml de agua). La mezcla se calentó a 40°C durante 3 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-pentanoico (0,128 g, 91%).

Se preparó amida del ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-pentanoico a partir del ácido por acoplamiento de NH_4Cl, HATU, DIEA, HOBt en DMF a temperatura ambiente para producir amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-ciclobutanocarboxílico. La mezcla de reacción se concentró y se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó

por cromatografía sobre gel de sílice (metanol al 10%/diclorometano al 90%) para producir el producto puro con un rendimiento del 69%

^{1}H RMN ($CDCl_3$) δ· 1,13 (d, 3H), 1,15 (t, 1H), 1,68 (m, 4H), 1,95 (s, 3H), 2,16-2,37 (m, 3H), 3,86 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 5,79 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H)

MS m/z. 534 (M+1)

Ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-pentanoico (B-71)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,12 g, 0,28 mmol) en 5 ml de DMF a temperatura ambiente y se le añadió K_2CO_3 (0,155 g, 1,12 mmol). Se añadió éster etílico del ácido 5-bromo-2,2-dimetil-pentanoico (0,123 g, 0,56 mmol, preparado de acuerdo con el procedimiento de *Tetrahedron* **1994**, 50(32), 9825-30) y la reacción se dejó calentar a 80°C durante una noche La mezcla de reacción se concentró al vacío. El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (EtOAc al 50%/Hexano al 50%) para producir éster metílico del ácido (2*S*,4*R*)-*N*-5-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2,2-dimetil-pentanoico (0,076 g, 48%).

El éster se hidrolizó en el ácido disolviéndose en 8 ml de tetrahidrofurano/metanol (1/1) y se le añadió hidróxido potásico (0,03 g en 2 ml de agua) La mezcla se calentó a 40°C durante 3 horas. La mezcla se enfrió a ta y se acidificó para formar un precipitado blanco. El sólido se filtró para dar el producto (0,057 g, 79%).

^{1}H RMN ($CDCl_3$) δ: 1,13 (d, 3H), 1,15 (t, 1H), 1,27 (s, 6H), 1,70 (m, 4H), 1,1,98 (s, 3H), 2,28 (m, 1H), 3,89 (t, 2H), 4,72 (sextuplete, 1H), 5,58 (s a, 1H), 6,52 (d, 1H), 6,67 (d, 2H), 6,86 (t, 1H), 7,08-7,35 (m, 6H), 7,38 (d, 2H).

MS m/z. 535 (M+1)

Ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-imidazol-2-carboxílico (B-72)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (0,165 g, 0,38 mmol) en DMF a temperatura ambiente y se añadió K_2CO_3 (0,315 g, 2,28 mmol) Se añadió éster metílico del ácido 1-(2-bromo-etil)-1*H*-imidazol-2-carboxílico (0,304 g, 1,14 mmol) y se permitió que la reacción se calentara a 80°C durante una noche La mezcla de reacción se concentró *al vacío* El residuo se repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (EtOAc al 50%/Hexano al 50%) para dar éster metílico del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-imidazol-2-carboxílico (0,176 g, 83%)

El éster se hidrolizó al ácido disolviéndolo en tetrahidrofurano y etanol y se añadió hidróxido sódico (1 N). La mezcla se agitó a temperatura ambiente 4 horas La mezcla se enfrió a temperatura ambiente, se acidificó para formar un precipitado blanco El sólido se filtró para dar el producto con un rendimiento del 74%

^{1}H-RMN ($CDCl_3$) d: 1,13 (d, 3H), 1,15 (t, 1H), 1,98 (s, 3H), 2,27 (m, 1H), 4,29 (sa, 2H), 4,72 (sexteto, 1H), 5,09 (sa, 2H), 5,58 (sa, 1H), 6,48 (d, 1H), 6,64 (d, 2H), 6,91 (t, 1H), 6,98 (s, 1H), 7,03 (s, 1H), 7,08-7,40 (m, 10H), 8,65 (sa, 1H)
MS m/z: 573 (M+1)

Amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-imidazol-2-carboxílico (B-73)

Se preparó la amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-imidazol-2-carboxílico a partir de ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-imidazol-2-carboxílico por acoplamiento de NH_4Cl, HATU, DIEA, HOBt en DMF a temperatura ambiente para producir la amida del ácido (2*S*,4*R*)-*N*-1-[2-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-etil]-1*H*-

imidazol-2-carboxílico. La mezcla de reacción se concentró y repartió entre acetato de etilo y agua, después se extrajo tres veces con acetato de etilo, se secó sobre sulfato de magnesio, se filtró y se concentró. El residuo se purificó por cromatografía en gel de sílice (metanol al 10%/diclorometano al 90%) para dar el producto puro con un rendimiento del 67%.

^{1}H-RMN ($CDCl_3$) d: 1,15 (d, 3H), 1,17 (t, 1H), 2,03 (s, 3H), 2,27 (m, 1H), 4,26 (sa, 2H), 4,72 (sexteto, 1H), 4,78 (sa, 2H), 5,58 (sa, 1H), 6,48 (d, 1H), 6,64 (d, 2H), 6,91 (t, 1H), 6,98 (s, 1H), 7,03 (s, 1H), 7,08-7,40 (m, 10H).

MS m/z: 572 (M+1)

(2*S*,4*R*)-*N*-[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-2,2-dimetil-propionamida (B-74)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (60 mg, 0,122 mmol) en cloruro de metileno (2 ml) y trietilamina (0,034 ml, 0,243 mmol) y se enfrió a -40°C. Se añadió cloruro de pivaloílo (10 gotas mediante una pipeta) y la mezcla se calentó a 0°C durante 30 minutos. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente 1/1 de hexanos/acetato de etilo-acetato de etilo) para producir el producto

^{1}H RMN ($CDCl_3$) δ 1,1 (s, 3H), 1,1 (s, 9H), 1,2 (m, 1H), 2,0 (m, 2H), 2,0 (s, 3H), 2,3 (m, 1H), 3,4 (c, 2H), 4,0 (t, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 6,0 (s, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H)

MS m/z: 576 (M+1).

(2*S*,4*R*)-*N*-{1-[4-(3-Acetilamino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (B-75)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (99 mg, 0,202 mmol) en cloruro de metileno (2 ml) y trietilamina (0,056 ml, 0,404 mmol) y se enfrió a -40°C. Se añadió cloruro de acetilo (15 gotas mediante una pipeta) y la mezcla se calentó a 0°C durante 30 minutos. La mezcla se repartió entre cloruro de

metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 1/1 de hexanos/acetato de etilo a acetato de etilo) para producir el producto.

^1H RMN ($CDCl_3$) δ. 1,1 (s, 3H), 1,2 (m, 1H), 1,9 (s, 3H), 2,0 (m, 2H), 2,0 (s, 3H), 2,3 (m, 1H), 3,4 (c, 2H), 4,0 (t, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 5,7 (s a, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H)

MS m/z· 534 (M+1)

(2*S*,4*R*)-*N*-(1-{4-[3-(Acetil-etil-amino)-propoxi]-benzoil}-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (B-76)

Se disolvió (2*S*,4*R*)-*N*-(1-[4-(3-acetilamino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (30 mg, 0,056 mmol) en DMF (1 ml). Se añadieron hidruro sódico (20 mg, 0,833 mmol) y yodoetano (10 gotas mediante una pipeta) y la reacción se agitó a temperatura ambiente durante una noche La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa.

^1H RMN ($CDCl_3$) δ· 1,1 (m, 7H), 2,0 (m, 8H), 2,3 (m, 1H), 3,3 (c, 1H), 3,4 (c, 1H), 3,4 (t, 2H), 3,9 (t, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,7 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H).

MS m/z: 562 (M+1).

[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carboxil}-fenoxi)-propil]-amida del ácido (2*S*,4*H*)-1-metil-pirrolidin-2-carboxílico (B-77)

Se disolvió (2*S*,4*R*)-*N*-(1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il)-*N*-(4-cloro-fenil)-acetamida (100 mg, 0,204 mmol) en cloruro de metileno (2 ml) y piridina (2ml). Se añadieron N-metil prolina (33 mg, 0,255 mmol) y EDC (63 mg, 0,255 mmol) y la reacción se agitó durante 1 hora La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se seco sobre $MgSO_4$, se filtró y concentró. El residuo bruto se purificó por cromatografía en sílica gel (acetato de etilo) para producir el producto

^{1}H RMN ($CDCl_3$) δ: 1,1 (s, 3H), 1,2 (m, 1H), 1,8 (m, 2H), 2,0 (m, 2H), 2,0 (s, 3H), 2,2 (m, 2H), 2,3 (m, 1H), 2,4 (s, 3H), 2,6 (m, 1H), 3,2 (m, 2H), 3,4 (c, 2H), 4,0 (t, 2H), 4,1 (m, 1H), 4,8 (m, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H)

MS m/z: 603 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(3-trifluorometano-sulfonilamino-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-78)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (34 mg, 0,069 mmol) en cloruro de metileno (0,5 ml) y trietilamina (0,019 ml, 0,138 mmol) y se enfrió a -40°C. Se añadió anhídrido trifluorometanosulfónico (0,015 ml, 0,086 mmol) y la mezcla se calentó a 0°C durante 30 minutos. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 1/1 de hexanos/acetato de etilo-acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ· 1,1 (s, 3H), 1,2 (m, 1H), 1,9 (m, 2H), 2,0 (s, 3H), 2,3 (m, 1H), 3,6 (m, 2H), 4,0 (t, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,6 (t, 1H), 6,7 (d, 1H), 6,9 (t, 1H), 7,2 (m, 7H), 7,4 (d, 2H).

MS m/z 624 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-metanosulfonilamino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-79)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-Amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (29 mg, 0,059 mmol) en cloruro de metileno (0,5 ml) y trietilamina (10 gotas mediante pipeta) y se enfrió a -40°C. Se añadió cloruro de metanosulfonilo (5 gotas mediante pipeta) y la mezcla se calentó a 0°C durante 30 minutos. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró El residuo bruto se purificó por cromatografía en gel de sílice (gradiente de 1/1 de hexanos/acetato de etilo-acetato de etilo) para dar el producto.

^{1}H-RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,2 (m, 1H), 1,9 (m, 2H), 2,0 (s, 3H), 2,3 (m, 1H), 2,9 (s, 3H), 3,3 (c, 2H), 3,9 (t, 2H), 4,6 (t, 1H), 4,7 (m, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,7 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H).

MS m/z: 570 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-{4-[3-(2-oxo-oxazolidin-3-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-80)

Se disolvió (2*S*,4*R*)-*N*-(1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (50 mg, 0,102 mmol) en cloruro de metileno (3 ml) y trietilamina (0,150 ml, 1,08 mmol) y se enfrió a -40°C Se añadió 2-bromoetilcloroformiato (0,016 ml, 0,153 mmol) y la reacción se dejó calentar a temperatura ambiente. Después de 1 hora a temperatura ambiente, se añadieron DMF (2 ml) y Cs_2CO_3 (100 mg, 0,307 mmol) y la mezcla se agitó durante una noche. La mezcla se repartió entre cloruro de metileno y agua; la capa de cloruro de metileno se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 1/1 de hexanos/acetato de etilo-acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ. 1,1 (s, 3H), 1,2 (m, 1H), 1,9 (m, 2H), 2,0 (s, 3H), 2,3 (m, 1H), 3,4 (t, 2H), 3,5 (t, 2H), 3,9 (t, 2H), 4,3 (t, 2H), 4,7 (m, 1H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H)

MS m/z: 562 (M+1)

Ácido (2*S*,4*R*)-3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propano-1-sulfónico (B-82)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (207 mg, 0,481 mmol) en DMF (5 ml) a temperatura ambiente Se añadió NaH (58 mg, 2,40 mmol) seguido de ácido 3-cloro-propano-1-sulfónico (sal sódica, 135 mg, 0,60 mmol) y la reacción se dejó en agitación durante una noche. La mezcla se repartió entre cloruro de metileno y HCl (1,0 N/agua), después se extrajo tres veces con cloruro de metileno, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa para producir el producto.

^{1}H RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,1 (m, 1H), 2,0 (s, 3H), 2,2 (m, 3H), 3,2 (t, 2H), 3,9 (t, 2H), 4,8 (d, 1H), 5,6 (s a, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H), 10,6 (s a, 1H).

MS m/z 557 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{2-metil-1-[4-(3-sulfamoil-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-83)

Se disolvió ácido (2*S*,4*R*)-3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propano-1-sulfónico (175 mg, 0,315 mmol) en cloruro de metileno (3 ml) y se enfrió a 0°C Se añadió PCl_5 (78 mg, 0,378 mmol) y la reacción se agitó a temperatura ambiente durante una noche La mezcla se repartió entre cloruro de metileno y agua; la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El cloruro de sulfonilo bruto se disolvió en acetona (5 ml); se añadió hidróxido de amonio concentrado (3,5 ml) Después de 15 minutos, la mezcla se repartió entre cloruro de metileno y agua; la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa para dar el producto

^{1}H-RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,1 (m, 1H), 2,0 (s, 3H), 2,2 (m, 3H), 3,2 (t, 2H), 3,9 (t, 2H), 4,8 (d, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 8H), 7,4 (d, 2H).

MS m/z: 556 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-{1-[4-(3-dibenzilsulfamoil-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-84)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (300 mg, 0,693 mmol) en DMF (10 ml) a temperatura ambiente Se añadió Cs_2CO_3 (1,12 g, 3,46 mmol) seguido de dibencilamida del ácido 3-cloro-propano-1-sulfónico (350 mg, 1,03 mmol) y se permitió agitar la reacción durante una noche. La mezcla se repartió entre cloruro de metileno y agua; la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (2/1 hexanos/ acetato de etilo) para dar el producto.

^{1}H-RMN ($CDCl_3$) δ: 1,1 (d, 3H), 1,1 (m, 1H), 2,0 (s, 3H), 2,2 (m, 3H), 3,0 (t, 2H), 3,9 (t, 2H), 4,3 (s, 4H), 4,7 (d, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 18H).

MS m/z: 736 (M+1).

Éster metílico del ácido (2*S*,4*R*)-4-{4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2-metil-butírico (B-85)

Se disolvió (2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (230 mg, 0,531 mmol) en DMF (5 ml) a temperatura ambiente. Se añadió Cs_2CO_3 (433 mg, 1,33 mmol) seguido de éster metílico del ácido 4-cloro-2-metil-butírico (120 mg, 0,796 mmol) y se permitió agitar la reacción durante una noche. La mezcla se repartió entre cloruro de metileno y agua; la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por cromatografía en gel de sílice (gradiente de 1/1 hexanos/acetato de etilo - acetato de etilo) para dar el producto

^{1}H-RMN ($CDCl_3$) δ 1,1 (d, 3H), 1,2 (d, 3H), 1,2 (m, 1H), 1,8 (m, 1H), 2,0 (s, 3H), 2,1 (m, 1H), 2,2 (m, 1H), 2,7 (m, 1H), 3,7 (s, 3H), 3,9 (t, 2H), 4,7 (m, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H).

MS m/z: 549 (M+1).

Ácido (2*S*,4*R*)-4-{4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2-metil-butírico (B-86)

Se disolvió el éster metílico del ácido (2*S*,4*R*)-4-{4-[4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-2-metil-butírico (100 mg) en metanol/THF, y se añadió hidróxido de litio (1,0 N, 2 ml). Después de 1 hora, la reacción se acidificó y se extrajo con cloruro de metileno. La capa orgánica se secó, se filtró y se concentró El residuo bruto se purificó por cromatografía en gel de sílice (gradiente de acetato de etilo-MeOH al 5%/acetato de etilo) para dar el producto.

^{1}H-RMN ($CDCl_3$) δ. 1,1 (d, 3H), 1,2 (d, 3H), 1,2 (m, 1H), 1,8 (m, 1H), 2,0 (s, 3H), 2,1 (m, 1H), 2,2 (m, 1H), 2,7 (m, 1H), 3,9 (t, 2H), 4,7 (m, 1H), 5,6 (sa, 1H), 6,5 (d, 1H), 6,6 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H), 10,6 (sa, 1H).

MS m/z: 535 (M+1).

Éster etílico del ácido (2*S*,4*R*)-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-fluoro-acético (B-87)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (202 mg, 0,46 mmol) en DMF (2 ml) a temperatura ambiente. Se añadió Cs_2CO_3 (760 mg, 2,33 mmol) seguido de éster etílico del ácido bromo-fluoro-acético (0,070 ml, 0,583 mmol) y la reacción se dejó en agitación durante una noche La mezcla se repartió entre cloruro de metileno y agua; la capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (2/1 de hexanos/acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ. 1,1 (d, 3H), 1,2 (m, 1H), 1,3 (t, 3H), 2,0 (s, 3H), 2,3 (m, 1H), 4,3 (c, 2H), 4,8 (m, 1H), 5,6 (s a, 1H), 5,9 (d, 1H), 6,5 (d, 1H), 6,9 (m, 3H), 7,2 (m, 6H), 7,4 (d, 2H).

MS m/z: 539 (M+1).

Ácido (2*S*,4*R*)-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-fluoro-acético (B-88)

Se disolvió éster etílico del ácido (2*S*,4*R*)-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-fluoro-acético (100 mg) en metanol/THF (1 1, 5 ml) y se le añadió hidróxido potásico (1,0 N, 1 ml). Después de 1 hora, la reacción se acidificó y se extrajo con cloruro de metileno La capa orgánica se secó, se filtró y se concentró. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de acetato de etilo-MeOH al 5%/acetato de etilo) para producir el producto.

^{1}H RMN ($CDCl_3$) δ. 1,1 (d, 3H), 1,2 (m, 1H), 2,0 (s, 3H), 2,3 (m, 1H), 4,8 (m, 1H), 5,6 (s a, 1H), 5,9 (d, 1H), 6,5 (d, 1H), 6,9 (m, 3H), 7,2 (m, 6H), 7,4 (d, 2H), 11,1 (s a, 1H).

MS m/z: 511 (M+1)

(2*S*,4*R*)-N-(4-Cloro-fenil)-N-{1-[4-(4-metanosulfonilamino-3,3-dimetil-4-oxo-butoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-89)

La (2*S*,4*R*)-N-(4-cloro-fenil)-N-{1-[4-(4-metanosulfonilamino-3,3-dimetil-4-oxo-butoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida se disolvió en cloruro de metileno (5 ml) y en oxalil cloruro (2 ml) Se añadió una única gota de DMF, y la mezcla se agitó a temperatura ambiente hasta que cesó la evolución del gas. Se retiraron todos los volátiles. La suspensión se disolvió en cloruro de metileno (10 ml) y trietilamina (2 ml). Se añadió metanosulfonamida (200 mg, 2,10 mmol) y la mezcla de reacción se agitó durante 3 horas. La mezcla se repartió entre cloruro de metileno y agua, la capa orgánica se secó sobre Na_2SO_4, se filtró y concentró El residuo bruto se purificó por HPLC preparatoria

^{1}H-RMN ($CDCl_3$) δ 1,1 (d, 3H), 1,2 (m, 1H), 1,2 (s, 3H), 1,3 (s, 3H), 2,0 (s, 3H), 2,1 (t, 1H), 2,3 (m, 1H), 3,4 (m, 4H), 3,9 (m, 2H), 4,7 (m, 1H), 5,6 (sa, 1H), 5,9 (d, 1H), 6,5 (d, 1H), 6,4 (d, 2H), 6,9 (t, 1H), 7,2 (m, 6H), 7,4 (d, 2H).

MS m/z: 626 (M+1).

Ácido (2*S*,4*R*)-4-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-3-(*S*)-hidroxi-butírico (B-90)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (200 mg, 0,46 mmol) en DMF (5 ml) a temperatura ambiente Se añadió Cs_2CO_3 (374 mg, 1,15 mmol) seguido de éster metílico del ácido 4-bromo-3-(*S*)-(*terc*-butil-dimetil-silaniloxi)-butírico (214 mg, 0,69 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas La mezcla se concentró a presión reducida y se disolvió en acetato de etilo (15 ml). La mezcla de reacción se lavó con $NaHCO_3$ sat. ac. (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente 5/95 de acetato de etilo/hexano-50/50 de acetato de etilo/hexano) para producir el producto sólido ligeramente amarillo (74 mg, 37%).

Se disolvió éster etílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-3-(*S*)-(*terc*-butil-dimetil-silaniloxi)-butírico (99 mg, 0,148 mmol) en THF (4 ml). A esta solución

se le añadió fluoruro de tetrabutilamonio (1,0 M en THF, 1 ml). La mezcla de reacción se agitó a temperatura ambiente durante 3 horas. La mezcla se concentró a presión reducida y se disolvió en DCM (15 ml). La mezcla de reacción se lavó con $NaHCO_3$ sat. ac. (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 2/98 de metanol/diclorometano-10/90 de metanol/diclorometano) para producir el producto sólido blanco (41 mg, 51%)

Se disolvió éster metílico del ácido (2*S*,4*R*)-4-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-3-(*S*)-hidroxi-butírico (41,2 mg, 0,075 mmol) en MeOH/THF (2:1, 3 ml). A esta solución se le añadió LiOH 2 N (2 ml). La reacción se agitó a temperatura ambiente durante 18 horas La mezcla de reacción se concentró al vacío para retirar el MeOH y el THF Después, se añadió una solución acuosa 6 N de HCl para acidificar la mezcla de reacción a pH 2-3. La mezcla de reacción se extrajo con DCM (5 ml x 3) El extracto se lavó con salmuera (15 ml) y se secó sobre $MgSO_4$, se filtró y se concentró. El residuo bruto se purificó por HPLC preparativa para producir el producto (35 mg, 87%)

^{1}H RMN ($CDCl_3$, 300 MHz) δ: 1,05-1,14 (m, 4H), 2,0 (s, 3H), 2,25-2,27 (m, 1H), 2,60-2,62 (m, 2H), 3,87-3,88 (m, 2H), 4,28-4,34 (m, 1H), 4,70-4,77 (m, 1H), 5,58-5,62 (ancho, 1H), 6,49-6,93 (m, 4H), 7,12-7,39 (m, 8H)

MS m/z: 538 (M+1).

Éster metílico del ácido (2*S*,4*R*)-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-carbámico (B-91)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (150 mg, 0,30 mmol) en DCM (1 ml) A esta solución se le añadió TEA (36,4 mg, 0,36 mmol) seguido de cloroformiato de metilo (34 mg, 0,36 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas La mezcla se concentró a presión reducida y se disolvió en DCM (15 ml) La mezcla de reacción se lavó con $NaHCO_3$ sat ac. (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se

secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía sobre gel de sílice (gradiente de 5/95 de acetato de etilo/hexano-50/50 de acetato de etilo/hexano) para producir un producto sólido blanco (71 mg, 52%)

^1H RMN ($CDCl_3$, 300 MHz) δ: 0,68-0,88 (m, 2H), 1,00-1,05 (m, 4H), 1,23 (s, 3H), 1,61-1,64 (ancho, 1H) 2,02 (s, 3H), 2,22-2,33 (m, 1H), 3,31-3,37 (m, 1H), 3,62 (s, 3H), 3,93-3,97 (m, 1H), 4,73-4,75 (m, 1H) 5,28-5,31 (ancho, 1H), 6,50-6,93 (m, 4H), 7,12-7,39 (m, 8H)

MS m/z: 551 (M+1).

Éster metílico del ácido (2*S*,4*R*)-[3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-etil-carbámico (B-92)

El éster metílico del ácido (2*S*,4*R*)-[3-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoxi)-propil]-carbámico (41 mg, 0,074 mmol) se disolvió en THF/DMF (10:1, 3 ml) A esta solución se le añadió Hidruro Sódico (2 mg, 0,089 mmol), seguido de yoduro de etilo (14 mg, 0,089 mmol). La reacción se agitó a temperatura ambiente durante 7 horas y se interrumpió añadiendo 1 ml de agua. La mezcla se concentró a presión reducida y se disolvió en DCM (15 ml). La mezcla de reacción se lavó con $NaHCO_3$ ac. sat. (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo se purificó por cromatografía en gel de sílice (gradiente de 5/95 acetato de etilo/hexano-50/50 acetato de etilo/hexano) para dar un producto sólido amarillo claro (15 mg, 35%).

^1H-RMN ($CDCl_3$, 300 MHz) δ: 0,68-0,83 (m, 2H), 1,00-1,14 (m, 2H), 1,18-1,26 (m, 3H), 1,23 (t, 3H), 1,59-1,67 (ancho, 1H), 1,61-1,64 (ancho, 1H), 1,96-2,02 (m, 5H) 2,26-2,31 (m, 1H), 3,25-3,37 (m, 4H), 3,62-3,64 (m, 3H), 3,89-3,91 (m, 2H), 4,73-4,77 (m, 1H) 5,5-5,65 (ancho, 1H), 6,50-6,93 (m, 4H), 7,12-7,39 (m, 8H)

MS m/z: 579 (M+1).

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-[4-(3-ureido-propoxi)-benzoil]-1,2,3,4-tetrahidro-quinolin-4-il}-acetamida (B-93)

A una solución de (2*S*,4*R*)-*N*-{1-[4-(3-Amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (50 mg, 0,10 mmol) en DCM (1 ml) se le añadió isocianato de trimetilsililo (23 mg, 0,20 mmol) La mezcla de reacción se agitó a temperatura ambiente durante 18 horas La reacción se interrumpió mediante la adición de 0,2 ml de agua y se concentró a presión reducida. El residuo bruto se purificó por HPLC preparativa para producir el producto (9 mg, 17%)

MS m/z: 536 (M+1)

Éster metílico del ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-benzoico (B-94)

Se disolvió (2*S*,4*R*)-*N*-(4-cloro-fenil)-*N*-[1-(4-hidroxi-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-acetamida (150 mg, 0,35 mmol) en DMF (5 ml) a temperatura ambiente Se añadió Cs_2CO_3 (283 mg, 0,87 mmol) seguido de 3-(bromometil)benzoato de metilo (119 mg, 0,52 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró a presión reducida y se disolvió en acetato de etilo (15 ml) La mezcla de reacción se lavó con $NaHCO_3$ sat. ac. (15 ml), agua (15 ml) y salmuera (15 ml) La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo bruto se purificó por cromatografía sobre gel de sílice (gradiente de 5/95 de acetato de etilo/hexano-50/50 acetato de etilo/hexano) para producir el producto sólido ligeramente amarillo (111 mg, 54%).

^{1}H RMN ($CDCl_3$, 300 MHz) δ: 1,02-1,08 (d, 3H), 1,55 (s, 1H), 2,02 (s, 3H), 2,24-2,32 (m, 1H), 3,88-3,91 (s, 3H), 4,70-4,78 (m, 1H), 5,02-5,05 (s, 2H), 5,58-5,61 (a, 1H), 6,51-6,53 (m, 3H), 6,89-7,29 (m, 8H), 7,36-7,46 (m, 2H), 7,56-7,58 (m, 1H), 7,97-8,04 (m, 2H).

MS m/z: 584 (M+1).

Ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-benzoico (B-95)

Se disolvió éster metílico del ácido (2*S*,4*R*)-3-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenoximetil)-benzoico (93 mg, 0,16 mmol) en MeOH/THF (2.1, 3 ml) A esta solución se le añadió LiOH (2 M en H_2O, 2 ml) La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró al vacío para retirar el MeOH y el THF. Después, se añadió una solución acuosa 6 N de HCl para acidificar la mezcla de reacción a pH 2-3. La mezcla de reacción se extrajo con DCM (5 ml x 3) El extracto se lavó con agua (15 ml) y salmuera (15 ml) y se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida El residuo bruto se purificó por HPLC preparativa para producir el producto (90 mg, 100%).

^{1}H RMN ($CDCl_3$, 300 MHz) δ: 1,08-1,09 (d, 3H), 1,21-1,26 (s, 1H), 2,03 (s, 3H), 2,24-2,32 (m, 1H), 4,70-4,78 (m, 1H), 5,02-5,05 (s, 2H), 5,58-5,61 (a, 1H), 6,51-6,53 (m, 3H), 6,89-7,29 (m, 8H), 7,36-7,46 (m, 2H), 7,56-7,58 (m, 1H), 7,97-8,04 (m, 2H).

MS m/z 570 (M+1)

(2*S*,4*R*)-*N*-(4-Cloro-fenil)-*N*-(2-metil-1-{4-[3-(2-oxo-imidazolidin-1-il)-propoxi]-benzoil}-1,2,3,4-tetrahidro-quinolin-4-il)-acetamida (B-96)

Se disolvió (2*S*,4*R*)-*N*-{1-[4-(3-amino-propoxi)-benzoil]-2-metil-1,2,3,4-tetrahidro-quinolin-4-il}-*N*-(4-cloro-fenil)-acetamida (120 mg, 0,24 mmol) en DCM (3 ml) a temperatura ambiente. Se añadió TEA (48 mg, 0,48 mmol) seguido de isocianato de 2-cloroetilo (51 mg, 0,48 mmol) y la reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró a presión reducida y se disolvió en acetato de etilo (15 ml). La mezcla de reacción se lavó con $NaHCO_3$ ac sat (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida El residuo bruto se purificó por cromatografía en gel de sílice (gradiente de 5/95 acetato de etilo/hexano-50/50 acetato de etilo/hexano) para dar un producto sólido amarillo claro (163 mg, 100%).

Se disolvió (2*S*,4*R*)-*N*-[1-(4-{3-[3-(2-Cloro-etil)-ureido]-propoxi}-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-*N*-(4-cloro-fenil)-acetamida (151 mg, 0,25 mmol) en DMF (3 ml) a temperatura ambiente. Se añadió Cs_2CO_3 (98 mg, 0,30

mmol) La reacción se agitó a temperatura ambiente durante 18 horas. La mezcla se concentró a presión reducida y se disolvió en acetato de etilo (15 ml). La mezcla de reacción se lavó con $NaHCO_3$ ac. sat. (15 ml), agua (15 ml) y salmuera (15 ml). La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró a presión reducida. El residuo bruto se purificó por HPLC preparativa para dar el producto (9 mg, 6,4%).

^{1}H-RMN ($CDCl_3$, 300 MHz) δ 1,11-1,14 (d, 3H), 1,88-1,93 (m, 1H), 1,98-2,01 (m, 5H), 2,26-2,27 (m, 1H), 3,27-3,29 (m, 1H), 3,43-3,47 (1, 2H), 3,77-3,83 (m, 1H) 3,93-3,96 (m, 1H), 4,17-4,20 (m, 1H), 4,51-4,57 (m, 1H), 4,72-4,74 (m, 1H), 4,97-4,10 (ancho,1H), 5,52-5,65 (a, 1H), 6,50-6,93 (m, 4H), 7,12-7,39 (m, 8H)
MS m/z: 562 (M+1).

Éster metílico del ácido (2*S*,4*R*)-*N*-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-*N*-metil-succinámico

Se preparó éster metílico del ácido (2*S*,4*R*)-*N*-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-*N*-metil-succinámico a partir de (2*S*,4*R*)-*N*-[1-(4-Amino-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-*N*-(4-cloro-fenil)-acetamida A una solución de (2*S*,4*R*)-*N*-[1-(4-Amino-benzoil)-2-metil-1,2,3,4-tetrahidro-quinolin-4-il]-*N*-(4-cloro-fenil)-acetamida (115 mg, 0,265 mmol) en diclorometano (5,0 ml) se le añadió diisopropiletilamina (50 µl, 0,265 mmol) seguido de la adición de cloruro de metilsuccinilo (44 mg, 0,291 mmol) y se agitó a temperatura ambiente durante una noche. La mezcla de reacción se diluyó con diclorometano y se extrajo con bicarbonato sódico saturado acuoso y salmuera, se secó sobre sulfato sódico, se filtró y se concentró a presión reducida. El producto se purificó sobre gel de sílice por cromatografía ultrarrápida usando hexano/acetato de etilo (1:1), acetato de etilo (100%) y acetato de etilo/metanol (10%) para producir éster metílico del ácido (2*S*,4*R*)-*N*-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-succinámico (55 mg, 35%).

^{1}H RMN ($CDCl_3$) δ 1,11 (3H, s; solapamiento 1H, t), 2,00 (3H, s), 2,30 (1H, m), 2,60-2,80 (2 x 2H, m), 3,70 (3H, s), 4,70 (1H, m), 5,55 (1H, m), 6,55 (1H, d), 6,90(1H, dd), 7,10-7,40 (9H, complejo), 7,80 (1H, s a)

ESI-MS m/z. 548 (M + 1).

A una solución de éster metílico del ácido (2*S*,4*R*)-*N*-(4-{4-[Acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-succinámico (55 mg, 0,100 mmol) en DMF se le añadió hidruro sódico (dispersión al 60% en aceite). Después de 30 minutos, a la mezcla de reacción se le añadió yodometano (16 µl, 0,11 mmol) y se agitó a temperatura ambiente durante una noche. La reacción se interrumpió con agua y se extrajo con acetato de etilo Los extractos orgánicos combinados se lavaron con bicarbonato sódico saturado acuoso y salmuera, se secaron sobre sulfato sódico, se filtraron y se concentraron a presión reducida. El producto se purificó sobre gel de sílice por cromatografía ultrarrápida usando acetato de etilo y acetato de etilo/metanol (10%) para producir éster metílico del ácido (2*S*,4*R*)-*N*-(4-{4-[acetil-(4-cloro-fenil)-amino]-2-metil-3,4-dihidro-2H-quinolin-1-carbonil}-fenil)-*N*-metil-succinámico (16 mg, 26%).

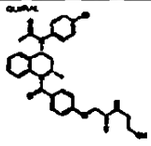
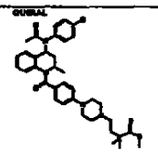
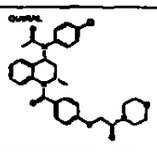
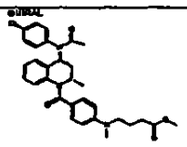
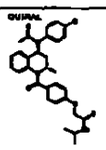
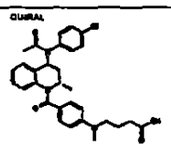
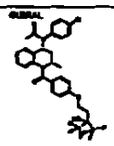
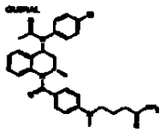
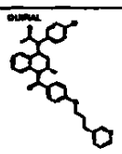
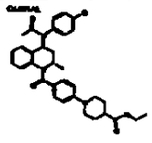
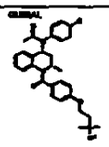
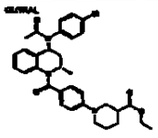
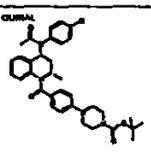
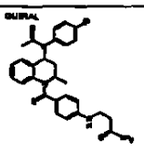
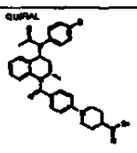
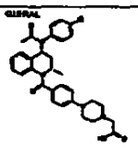
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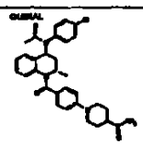
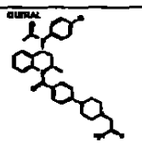
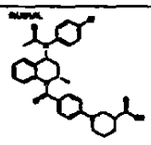
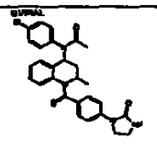
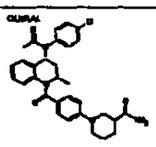
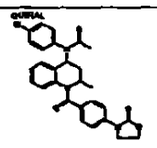
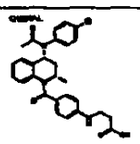
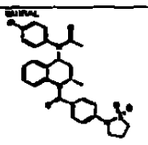
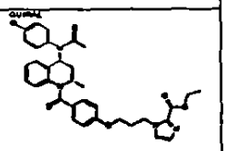
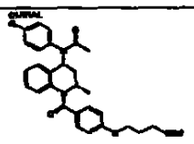
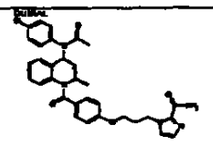
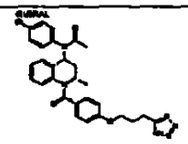
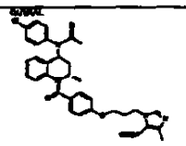
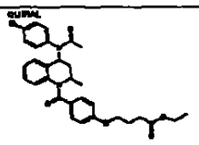
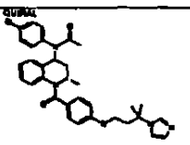
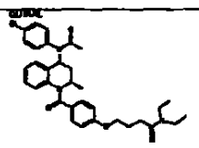
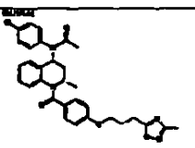
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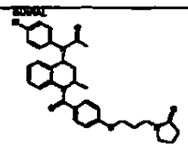
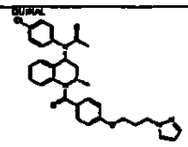
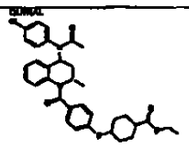
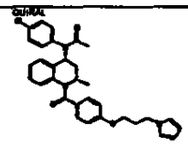
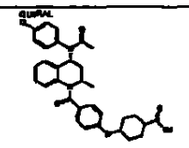
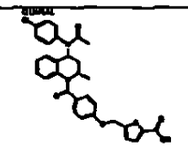
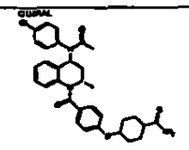
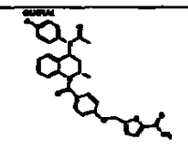
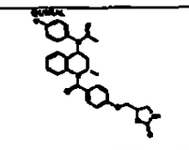
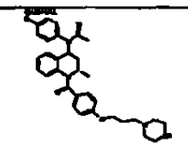
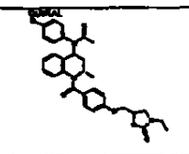
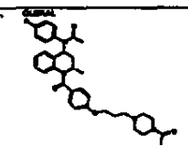
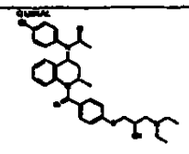
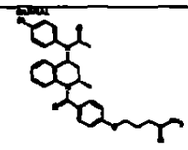
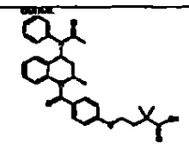
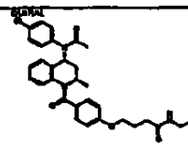
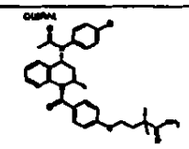
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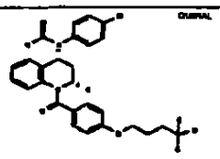
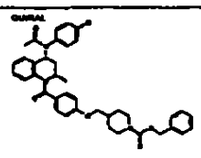
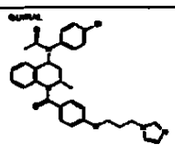
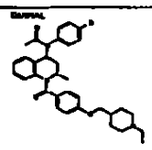
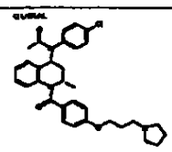
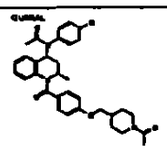
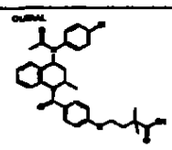
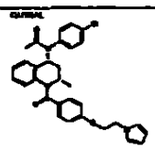
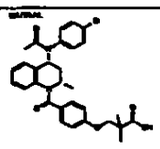
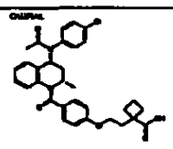
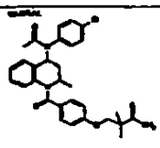
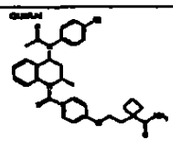
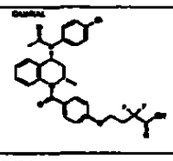
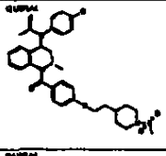
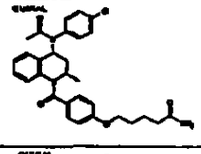
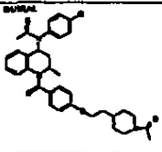
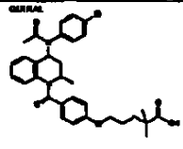
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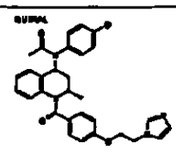
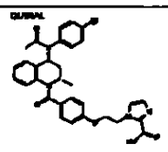
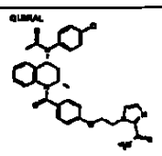
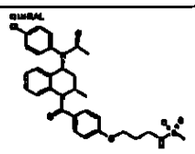
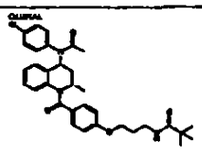
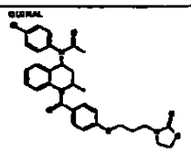
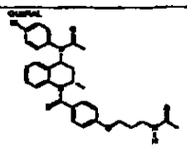
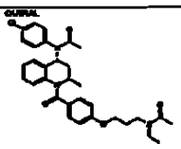
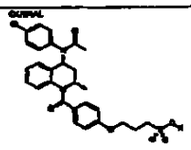
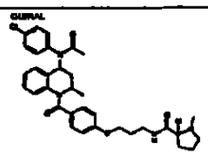
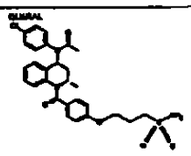
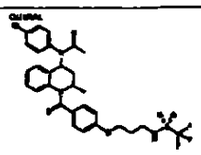
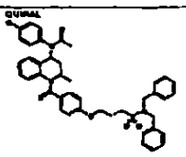
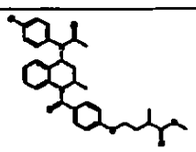
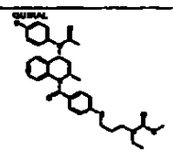
Tabla 2

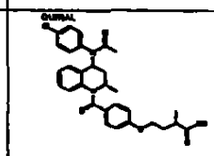
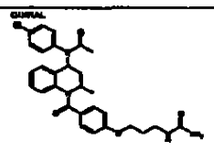
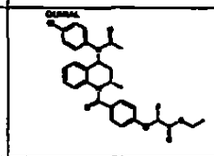
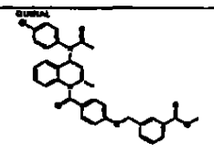
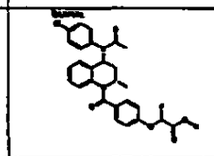
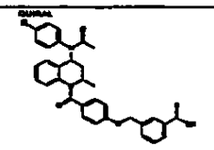
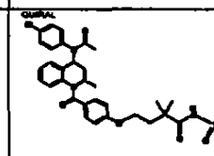
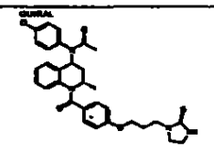
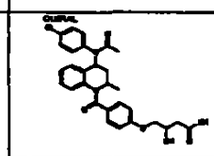
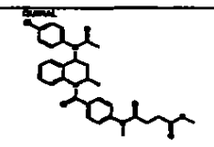
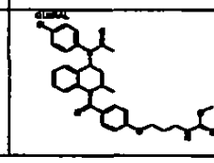
Numero de compuesto	Estructura	Número del compuesto	Estructura
B-1		B-7	
B-2		B-8	
B-3		B-9	
B-4		B-10	
B-5		B-11	
B-6		B-12	
B-13		B-19	
B-14		B-20	

Número de compuesto	Estructura	Número del compuesto	Estructura
B-15		B-21	
B-16		B-22	
B-17		B-23	
B-18		B-24	
		B-31	
B-26		B-32	
B-27		B-33	
B-28		B-34	
B-29		B-35	

Numero de compuesto	Estructura	Número del compuesto	Estructura
B-30			
B-37		B-43	
B-38		B-44	
B-39		B-45	
B-40		B-46	
B-41		B-47	
B-42		B-48	
B-49		B-55	
B-50		B-56	

Numero de compuesto	Estructura	Número del compuesto	Estructura
B-51		B-57	
B-52		B-58	
B-53		B-59	
B-54		B-60	
B-61		B-67	
B-62		B-68	
		B-69	
B-64		B-70	
B-65		B-71	

Número de compuesto	Estructura	Número del compuesto	Estructura
B-66		B-72	
B-73		B-79	
B-74		B-80	
B-75			
B-76		B-82	
B-77		B-83	
B-78		B-84	
B-85		B-92	

Número de compuesto	Estructura	Número del compuesto	Estructura
B-86		B-93	
B-87		B-94	
B-88		B-95	
B-89		B-96	
B-90		B-97	
B-91			

Los Compuestos Descritos Inhiben la Unión de PGD_2 a CRTH2

Este ensayo de unión de radioligando a membrana evalúa la capacidad de los compuestos para inhibir la unión de [^{3}H] Prostaglandina D_2 (PGD_2) al receptor CRTH2 humano clonado expresado de manera estable en células HEK-293 (que expresan el receptor CRTH2 humano y la subunidad α o la proteína G heterotriménca 16 se preparó por Biosignal Company) usando Ensayo de Centelleo de Proximidad

Se preparó un tampón de unión que contenía Tris-HCl 50 mM (pH 7,5), $MgCl_2$ 5 mM y EDTA 1 mM inmediatamente antes de realizar el ensayo. Se

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preparó una solución de lecho/membrana al doble de la concentración final del ensayo que comprende membranas (membranas compradas en Biosignal) de las células HEK-293 clonadas para expresar el receptor CRTH2 unido y [^{3}H] PGD_2 al doble de la concentración final del ensayo y se guardaron en hielo antes de añadirlas a los pocillos. Se preparó PGD_2 fría a veinte veces la concentración final del ensayo y se guardó en hielo antes de añadirla a los pocillos Se usaron para este ensayo placas de Corning Nº 3653 de determinación de unión no específica (NSB).

Se prepararon concentraciones de soluciones madre 10 mM de compuestos en DMSO al 100% y se guardaron a temperatura ambiente. Después se construyó una curva de respuesta a la concentración de 10 puntos para cada compuesto, comenzando a 10 μM (concentración final del ensayo). Los compuestos se prepararon a 40 veces la concentración final del ensayo con nueve diluciones consiguientes de 3 veces

Se añadieron 0,1 μl de cada concentración del compuesto al pocillo apropiado de la placa 384 y se añadieron 2 μl de PGD_2 fría en los pocillos para determinar NSB Después se añadieron 20 μl de [^{3}H] PGD_2 y después 20 μl de solución de lecho/membrana 2x a cada pocillo.

Las placas se dejaron incubar a temperatura ambiente durante aproximadamente 2 horas y después se contaron en Packard Topcount usando el protocolo de tritio SPA para 1 minuto/pocillo

Se determinó el porcentaje de inhibición de la unión de PGD_2 (PGD_2 usada al valor K_D o inferior) a las membranas de células HEK-293, el ensayo siempre se realizó como duplicado para n=1 para un total de n=2

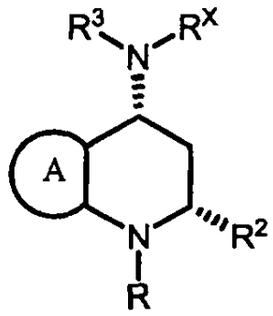
Los compuestos A-1 a A-12, B-1 a B-97 tienen una K_i menor de 1 μM.

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REIVINDICACIONES

1. Un compuesto representado por la siguiente fórmula estructural.



o una sal farmacéuticamente aceptable del mismo, en la que.

El anillo A es un aromático monocíclico opcionalmente sustituido;

R es $-X_1-R^1$;

R^X es $-X_2-R^4$;

cada uno de X_1 y X_2 son independientemente $-S(O)_2-$, -C(O)-, o -C(O)NH-,

R^1 es: A) un grupo aromático o heteroaromático que tiene 5-6 átomos en el anillo, sustituido con·

i) T^1-V-T-R^Y,

ii)T^1-V-T-M-R^Y; o

iii) V-R^9 en el que R^9 es un grupo carbocíclico o heterocíclico no aromático opcionalmente sustituido;

y en el que el grupo aromático o heteroaromático representado por R1 está opcionalmente sustituido también con 1-2 grupos seleccionados independientemente representados por R^Z; o

B) un grupo aromático o un grupo heteroaromático que tiene 5-6 átomos en el anillo, condensado con un anillo heterocíclico no aromático monocíclico o con un anillo monocíclico aromático en el que el anillo heterocíclico no aromático monocíclico o el anillo aromático está opcionalmente sustituido;

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-SR^o$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, -

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$NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$;

cada R' es independientemente hidrógeno, alquilo, $-C(O)OR^o$, $S(O)_2R^o$ o $-C(O)R^o$,

cada R^o es independientemente hidrógeno o un grupo alquilo, grupo heterocíclico no aromático o grupo aromático y el alquilo, el grupo heterocíclico no aromático y el grupo aromático representados por R^o están opcionalmente sustituidos con uno o más grupos seleccionados independientemente representados por $R^{\#}$;

$R^{\#}$ es R^+, $-OR^+$, -O(haloalquilo), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$ o $-C(=NH)-N(R^+)_2$,

R^+ es -H, un grupo alquilo C_1-C_3, un grupo heteroarilo monocíclico, un grupo heterocíclico no aromático o un grupo fenilo opcionalmente sustituido con alquilo, haloalquilo, alcoxi, haloalcoxi, halo, -CN, $-NO_2$, amina, alquilamina o dialquilamina, o $-N(R^+)_2$ es un grupo heterocíclico no aromático, con la condición de que los grupos heterocíclicos no aromáticos representados por R^+ y $-N(R^+)_2$ que comprenden una amina de anillo secundario están opcionalmente acilados o alquilados,

R^Y es $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-S(O)R^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)NR^5_2$, $-OC(O)NR^5_2$, $-NR^5_2$, $-OR^5$, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido;

V es un enlace covalente, -O-, -C(O)-, -N(R')-, -S-, -S(O)-, $-C(O)NR^5$-, $-NR^5C(O)$-, $-S(O)_2NR^5$-, $-NR^5S(O)_2$- o $-S(O)_2$-;

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T es alquileno C_{1-10} de cadena lineal; con la condición de que T sea C_{2-10} cuando V es un enlace covalente, y T sea C_{2-10} cuando V es -O-, -S- o –H(R')- y R^Y es –CN, -OH, -SH, $-N(R^5)_2$,

T^1 es un enlace covalente o un alquileno C_{1-10} de cadena lineal, donde T y T^1 juntos no contienen más de 10 átomos de carbono y donde T y T^1 están opcional e independientemente sustituidos en cualquiera de uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, nitrógeno opcionalmente *N*-sustituido que contiene un grupo heterocíclico no aromático espiro, amina, alquilamina, dialquilamina, alcoxi o hidroxilo;

cada R^5 es independientemente -H, alquilo, haloalquilo, hidroxialquilo, carboxialquilo, $-C(O)OCH_2C_6H_5$, $S(O)_2CH_3$, -C(O)OH, -C(O)OMe, -C(O)OEt, $C(O)NH_2$, bencilo, pirrolidinilo, morfolinilo o $-N(R^5)_2$ es un grupo heterocíclico no aromático que contiene nitrógeno,

M es un grupo aromático monocíclico sustituido, heteroaromático o un o carbocíclico o heterocíclico no aromático monocíclico opcionalmente sustituido;

R^2 es alquilo C_{1-3},

R^3 es un grupo aromático opcionalmente sustituido que tiene 5-6 átomos en el anillo.,

R^4 es alquilo C_{1-3} o hidroxialquilo C_{1-3};

con la condición de que cuando R^1 sea fenilo *para* sustituido con V-T-R^Y, R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es –C(O) y V es –O- cuando.

1) T es un alquileno C1-C10 sustituido con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, alcoxi, haloalcoxi, espiro cicloalquilo, nitrógeno opcionalmente *N*-sustituido que contiene un grupo heterocíclico no aromático espiro, amina, alquilamina, dialquilamina, alcoxi o hidroxilo; y

2) T-R^Y no es $-CH_2-CH_2-C(CH_3)_2-CONH_2$, $-CH_2-CH_2-C(CH_3)_2-OH$, $-CH_2-CH_2-CH_2-C(CH_3)_2-OH$, $-CH_2-CH_2-C(CH_3)_2-COOH$, $-CH_2-C$ (espiro ciclopropil)-CH_2-COOH o $-CH_2-C(CH_3)_2-COOH$);

con la condición de que cuando R^1 sea fenilo *para* sustituido con V-T-R^Y, R^2 es metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es –C(O) y V es un enlace covalente entonces, T-R^Y no es $–CH_2-CH_2-COOH$,

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es fenilo *para* sustituido con V-R^9 en el que R^9 es un grupo heterocíclico no aromático opcionalmente sustituido, V es un enlace covalente entonces, el heterocíclico no aromático sustituido en el fenilo representado por R^1 es distinto de.

N-morfolinilo, *N*-etoxicarbonil-4-piperidinilo, *N*-acetil-4-piperdinilo, *N*-etoxicarbonil-4-piperidi-3-enilo, *N*-pirrolidinilo, *N*-etil-*N'*-piperazinilo, *N*-acetil-*N'*-pierazinilo o N-($CH_2C(O)NH_2$)-*N'*-piperazinilo;

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 fenilo *para* sustituido con V-R^9 en el que R^9 es un grupo heterocíclico no aromático opcionalmente sustituido, V es –O- entonces el heterocíclico no aromático sustituido en el fenilo representado por R1 es distinto de.

N-etoxicarbonil-4-piperdinilo o *N*-acetil-4-piperdinilo,

con la condición de que cuando R^2 sea metilo, R^3 es fenilo, R^x es $C(O)CH_2CH_3$, X^1 es C(O) y R1 es fenilo *para* sustituido con un grupo heterocíclico no aromático, entonces el heterocíclico no aromático sustituido en le fenilo representado por R^1 es distinto de .

N-acetil-4-piperdinilo o *N*-morfolinilo;

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es fenilo condensado con un grupo heterocíclico no aromático opcionalmente sustituido, el grupo heterocíclico no aromático condensado con el fenilo representado por R1 es distinto de tetrahidrofuranilo o N'-metil morfolinilo,

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es piridinilo *para* sustituido con un grupo heterocíclico aromático, entonces el heterocíclico no aromático sustituido en el pindinilo representado por R^1 es distinto de *N*-morfolinilo; y

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es fenilo condensado con un grupo aromático opcionalmente sustituido, el grupo aromático condensado con el fenilo representado por R^1 es distinto de *N*-isopropil triazolilo, *N*-metil triazolilo, *N*-isopropil imidazolilo, 2, metil *N* hidroxietil imidazolilo, 2, metil *N* carboximetil imidazolilo, *N* carboxietil triazolil *N*-isopropil pirazolilo, y

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es imidazolilo condensado con un grupo aromático opcionalmente sustituido, el grupo aromático condensado con el imidazolilo representado por R^1 es distinto de fenilo.

con la condición de que cuando R^2 sea metilo, R^3 es *para* clorofenilo, R^x es $C(O)CH_3$, X_1 es C(O) y R^1 es tiazolilo condensado con un grupo aromático opcionalmente sustituido, el grupo aromático condensado con el tiazolilo representado por R^1 es distinto de fenilo.

2 El compuesto de la Reivindicación 1, en el que:

El anillo A es un grupo fenilo opcionalmente sustituido,

R^2 es metilo o etilo,

R^3 es un grupo fenilo opcionalmente sustituido;

R^4 es metilo, etilo, hidroximetilo, ciclopropilo, hidroxietilo, y

X_1 y X_2 son -C(O)-.

3. El compuesto de la Reivindicación 2, en el que:

R^1 es un anillo fenilo sustituido con V-T-R^Y, y opcionalmente también está sustituido con 1-2 grupos seleccionados independientemente representados por R^Z,

V es un enlace covalente, -O- o -N(R')-; y

T es alquileno C_{1-6} de cadena lineal opcionalmente sustituido en cualquiera de uno o más de los átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, nitrógeno

opcionalmente *N*-sustituido que contiene un grupo espiro heterocíclico no aromático, amina, alquilamina, dialquilamina, alcoxi, o hidroxilo.

4 El compuesto de la Reivindicación 3, en el que:

R^Y es $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)N(R^5)_2$, $-NR^5{}_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7, o un grupo heteroarilo opcionalmente sustituido representado por R^8,

R^7 es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo opcionalmente sustituido, y

R^8 es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido.

5 El compuesto de la Reivindicación 4, en el que:

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} se selecciona independientemente entre halógeno, haloalquilo, R°, -OR°, -O(haloalquilo), -SR°, 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R°$, $-NR'C(O)R°$, $-NR'NR'C(O)R°$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R°$, $-C(O)C(O)R°$, $-C(O)CH_2C(O)R°$, $-CO_2R°$, $-C(O)R°$, $-C(O)N(R°)_2$, $-OC(O)R°$, $-OC(O)N(R°)_2$, $-S(O)_2R°$, $-SO_2N(R')_2$, $-S(O)R°$, $-NR'SO_2N(R')_2$, $-NR'SO_2R°$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$

6 El compuesto de la Reivindicación 5, donde:

R^Y es $-C(O)OR^5$, $-C(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8;

cada R^5 es independientemente -H, alquilo, o $-NR^5_2$ es un grupo heterocíclico no aromático que contiene nitrógeno;

R^7 es piperidinonilo, morfolinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo;

R^8 es tetrazolilo, oxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo o imidazolilo,

V es un enlace covalente, o -O-; y

T es un alquileno C_{1-5} de cadena lineal opcionalmente sustituido en el átomo de carbono adyacente a R^Y con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, dialquilamina, alcoxi, o hidroxilo

7 El compuesto de la Reivindicación 2, en el que:

R^1 es un anillo fenilo sustituido con V-T-R^Y, y además opcionalmente sustituido con 1-2 grupos seleccionados de forma independiente, representados por R^Z;

V es un enlace covalente, -N(R')- o –O-; y

T es un alquileno C_{1-10} de cadena lineal opcionalmente monosustituido en cualquier átomo de carbono sustituible con haluro, alquilo, haloalquilo, amino, dialquilamina o hidroxilo.

8. El compuesto de la Reivindicación 6, en el que:

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14},

cada R^{14} es independientemente halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-SR^o$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, -

$C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)NR^o_2$, o $-O(CH_2)_nC(O)NR^o_2$;

n es un número entero de 1-4;

R^1 es un anillo fenilo sustituido en las posiciones *para* o *meta* con V-T-R^Y, y opcionalmente también está sustituido con 1-2 grupos seleccionados independientemente representados por R^Z;

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-CO_2R^o$, $-NR'SO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, y $-OC(O)N(R^o)_2$;

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-CO_2R^o$,, $-C(O)R^o$, $-N(R')_2$, $-NR'SO_2R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, y $-OC(O)N(R^o)_2$;

cada R' es independientemente H o alquilo, y

cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo.

9. El compuesto de la Reivindicación 8, en el que:

R^Y es $-C(O)OR^5$, $-C(O)N(R^5)_2$, -OH, *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, 2-morfolinilo *N*-sustituido, 3-morfolinilo *N*-sustituido, *N*-imidazolidinilo, 2-imidazolidinilo, 4-imidazolidinilo, 5-imidazolidinilo, 2-imidazolidinilo *N*-sustituido, *N*-imidazolidinilo *N'*-sustituido, 4-imidazolidinilo *N*-sustituido, 5-imidazolidinilo *N*-sustituido, *N*-imidazolidinonilo, 4-imidazolidinonilo, 5-imidazolidinonilo, 4-imidazolidinonilo *N*-sustituido, 5-imidazolidinonilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-pirrolidin-2-onilo, 3-pirrolidin-2-onilo, 4-pirrolidin-2-onilo, 5-pirrolidin-2-onilo, 3-pirrolidin-2-onilo *N*-sustituido, 4-pirrolidin-2-onilo *N*-sustituido, 5-pirrolidin-2-onilo *N*-sustituido, *N*-pirrolidin-3-onilo, 2-pirrolidin-3-onilo, 4-pirrolidin-3-onilo, 5-pirrolidin-3-onilo, 2-pirrolidin-3-onilo *N*-sustituido, 4-pirrolidin-3-onilo *N*-sustituido, 5-pirrolidin-3-onilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-

piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperidin-2-onilo, 3-piperidin-2-onilo, 4-piperidin-2-onilo, 5-piperidin-2-onilo, 6-piperidin-2-onilo, 3-piperidin-2-onilo *N*-sustituido, 4-piperidin-2-onilo *N*-sustituido, 5-piperidin-2-onilo *N*-sustituido, 6-piperidin-2-onilo *N*-sustituido, *N*-piperidin-3-onilo, 2-piperidin-3-onilo, 4-piperidin-3-onilo, 5-piperidin-3-onilo, 6-piperidin-3-onilo, 2-piperidin-3-onilo *N*-sustituido, 4-piperidin-3-onilo *N*-sustituido, 5-piperidin-3-onilo *N*-sustituido, 6-piperidin-3-onilo *N*-sustituido, *N*-piperidin-4-onilo, 2-piperidin-4-onilo, 3-piperidin-4-onilo, 5-piperidin-4-onilo, 6-piperidin-4-onilo, 2-piperidin-4-onilo *N*-sustituido, 3-piperidin-4-onilo *N*-sustituido, 5-piperidin-4-onilo *N*-sustituido, 6-piperidin-4-onilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, 2-piperazinilo *N*-sustituido, furanilo, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, 4-(1,2,3)oxadiazolilo, 5-(1,2,3)oxadiazolilo, 3-(1,2,4)oxadiazolilo, 5-(1,2,4)oxadiazolilo, 3-(1,2,5)oxadiazolilo, 4-(1,2,5)oxadiazolilo, 2-(1,3,4)oxadiazolilo, 5-(1,3,4)oxadiazolilo, *N*-pirrolilo, 2-pirrolilo, 3-pirrolilo, 2-pirrolilo *N*-sustituido, 3-pirrolilo *N*-sustituido, *N*-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 3-pirazolilo *N*-sustituido, 4-pirazolilo *N*-sustituido, 5-pirazolilo *N*-sustituido, 2-piridinilo, 3-piridinilo, 4-piridinilo, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido, o 5-imidazolilo *N*-sustituido;

V es -O-, y

T es un alquileno C_{1-3} de cadena lineal sustituido en el átomo de carbono adyacente a R^Y con flúor, metilo, gem dimetilo, gem difluorofluorometilo, espiro ciclopropilo, espiro ciclobutilo, espiro azetidinilo opcionalmente *N*-sustituido, espiro aziridinilo opcionalmente *N*-sustituido, espiro pirrolidinilo opcionalmente *N*-sustituido, espiro piperidinilo opcionalmente *N*-sustituido, amina, metilamina, dimetilamina, o hidroxilo.

10 El compuesto de la Reivindicación 9, en el que:

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, R°, $-OR^\circ$, -O(haloalquilo);

R^3 es un grupo fenilo opcionalmente sustituido en la posición *meta* o *para* por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, R^o, $-OR^o$, $-N(R')_2$, $-NR'SO_2R^o$ y -O(haloalquilo)

11 El compuesto de la Reivindicación 10, donde:

R^Y es $-C(O)OR^5$, $-C(O)NR^5{}_2$, -OH, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido, o 5-imidazolilo *N*-sustituido; y

R^5 es -H, metilo, o etilo.

12. El compuesto de la Reivindicación 11, en el que·

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14},

cada R^{14} es independientemente halógeno, R^o, $-OR^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, -CN, $NHC(O)N(R^o)_2$, $(CH_2)_nOH$, $O(CH_2)_nOH$, $(CH_2)_nC(O)NR^o{}_2$, o $O(CH_2)_nC(O)NR^o{}_2$;

R^1 es un anillo fenilo sustituido en las posición *para* por V-T-R^Y y opcionalmente está también sustituido en la posición *meta* por R^Z,

R^Z es cloruro, fluoruro, bromuro, $-OR^o$,o $-R^o$

R^3 es un grupo fenilo opcionalmente sustituido en la posición para por R^{11},

R^{11} es cloruro, fluoruro, bromuro, $-OR^o$ $-N(R')_2$, $-NR'SO_2R^o$ o $-R^o$;

R' es independientemente hidrógeno o un grupo alquilo C_{1-3}; y

R^o es independientemente hidrógeno, haloalquilo, o un grupo alquilo C_{1-3}.

13. El compuesto de la Reivindicación 2, en el que:

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R^1 es un anillo fenilo sustituido por V-R^9 donde R^9 es un grupo carbocíclico o heterocíclico no aromático opcionalmente sustituido y opcionalmente está también sustituido por 1-2 grupos independientemente seleccionados representados por R^Z.

14 El compuesto de la Reivindicación 13, en el que

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11}, y

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-SR^o$, 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$.

15 El compuesto de la Reivindicación 14, en el que:

R^9 es un ciclohexanilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo, S,S-dióxido de isotiazolidinilo, o piperidinilo opcionalmente sustituido.

16 El compuesto de la Reivindicación 15, en el que.

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14};

cada R^{14} es independientemente halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-SR^o$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, -

$C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)NR^o_2$, o $-O(CH_2)_nC(O)NR^o_2$;

n es un número entero de 1-4;

R^1 es un anillo fenilo sustituido en la posición *para* o *meta* por un grupo carbocíclico o heterocíclico no aromático representado por $V-R^9$, y opcionalmente también está sustituido con 1-2 grupos seleccionados independientemente representados por R^Z;

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-CO_2R^o$, $-NR'SO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, y $-OC(O)N(R^o)_2$;

V es un enlace covalente o -O-,

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} se selecciona independientemente entre halógeno, haloalquilo, $-R^o$, $-OR^o$, -O(haloalquilo), 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-CO_2R^o$, $-N(R')_2$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-NR'SO_2R^o$, $-OC(O)R^o$, y $-OC(O)N(R^o)_2$;

cada R' es independientemente H o alquilo, y

cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo.

17 El compuesto de la Reivindicación 16, en el que

R^9 es oxazolidinilo, tiazolidinilo, tetrahidrofuranilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o piperidinilo, cada uno opcionalmente sustituido con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-C(O)NR^{12}_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2NR^{12}_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)NR^{12}_2$, $-OC(O)NR^{12}_2$, $-(CH_2)_nCO_2H$, $-(CH_2)_nC(O)NR^o$, $-(CH_2)_nC(CH_3)_2CO_2H$, $-(CH_2)_nC(CH_3)_2C(O)NR^o$ o $-NR^{12}_2$,

n es un número entero de 1 a 4; y

cada R^{12} es independientemente -H, alquilo, haloalquilo o hidroxialquilo

18 El compuesto de la Reivindicación 17, en el que:

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, -R^o, -OR^o, y -O(haloalquilo);

R^3 es un grupo fenilo opcionalmente sustituido en la posición *para* o *meta* por uno o más grupos seleccionados independientemente representados por R^{11}, y

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, -R^o, -OR^o, -$N(R')_2$, -$NR'SO_2R^o$ y -O(haloalquilo)

19. El compuesto de la reivindicación 18, en el que:

R^9 es *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, 2-morfolinilo *N*-sustituido, 3-morfolinilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, 2-piperazinilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, cada uno opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$ o -$C(O)N(R^{12})_2$, y donde los sustituyentes *N* son alquilo, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR^o$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR^o$ o -$C(O)NR^{12}{}_2$; y

n es un número entero de 1-4

20 El compuesto de la Reivindicación 19, en el que:

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14},

cada R^{14} es independientemente halógeno, R^o, -OR^o, -CO_2R^o, -$C(O)R^o$, -$C(O)NR^o{}_2$, -$OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, -CN, $NHC(O)NR^o{}_2$, -$(CH_2)_nOH$, -$O(CH_2)_nOH$, -$(CH_2)_nC(O)NR^o{}_2$, o -$O(CH_2)_nC(O)NR^o{}_2$;

n es un número entero de 1-4,

R^1 es un anillo fenilo sustituido en la posición *para* por un grupo carbocíclico o heterocíclico no aromático representado por V-R^9, y opcionalmente está también sustituido en la posición *meta* por R^Z;

R^Z es cloruro, fluoruro, bromuro, -OR^o, o -R^o;

R^3 es un grupo fenilo opcionalmente sustituido en la posición *para* por R^{11};

R^{11} es cloruro, fluoruro, bromuro, -OR^o, -$N(R')_2$, -$NR'SO_2R^o$ o R^o,

R' es independientemente hidrógeno o un grupo alquilo C_{1-3}, y

R^o es independientemente hidrógeno, haloalquilo, o un grupo alquilo C_{1-3}.

21 El compuesto de la Reivindicación 20, en el que

R^9 es *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, o 2-piperazinilo *N*-sustituido, y está opcionalmente sustituido en cualquier átomo de carbono sustituible con cloruro, fluoruro, bromuro, metilo, etilo, -$C(O)OR^{12}$, -$OC(O)R^{12}$, -$C(O)R^{12}$ o $C(O)NH_2$, y donde los sustituyentes *N* son metilo, etilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$(CH_2)_nCO_2H$, -$(CH_2)_nC(O)NR^o$, -$(CH_2)_nC(CH_3)_2CO_2H$, -$(CH_2)_nC(CH_3)_2C(O)NR^o$, o -$C(O)NH_2$,

N es un número entero de 1-4; y

cada R^{12} es independientemente -H, metilo o etilo.

22 El compuesto de la Reivindicación 2, en el que

R^1 es un grupo fenilo condensado a un anillo heterocíclico no aromático monocíclico opcionalmente sustituido representado por R^{10}, o un anillo aromático monocíclico representado por R^{13}

23 El compuesto de la Reivindicación 22, en el que

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14};

cada R^{14} es independientemente halógeno, haloalquilo, R^o, $-OR^o$, $-O(haloalquilo)$, $-SR^o$, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)NR^o_2$, $-O(CH_2)_nC(O)NR^o_2$,

n es un número entero de 1-4,

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} se selecciona independientemente entre halógeno, haloalquilo, $-R^o$, $-OR^o$, $-O(haloalquilo)$, $-SR^o$, 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-NO_2$, $-CN$, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$.

24 El compuesto de la Reivindicación 23, en el que:

R^{10} es oxazolidinilo, oxazolidinonilo, dioxolanilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrotienilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, ditiolanilo, pirrolidinilo, piperazinilo, piperidinilo, piperidinilo, S,S-dióxido de tetrahidrotienilo, S,S-dióxido de tiomorfolinilo, o S,S-dióxido de tetrahidrotiopiranilo, cada uno de los cuales está opcionalmente sustituido; y

R^{13} es pirazolilo, triazolilo, imidazolilo, furanilo, pirrolilo, tienilo, ciclopentadienilo y S,S-dióxido de tienilo, cada uno de los cuales está opcionalmente sustituido.

25. El compuesto de la Reivindicación 24, en el que

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11},

cada R^{11} es un sustituyente seleccionado independientemente entre halógeno, haloalquilo, -R^o, -OR^o, -O(haloalquilo), 3,4-metileno-dioxi, 3,4-etileno-dioxi, -CO_2R^o, -$C(O)R^o$, -$N(R')_2$, -$C(O)N(R^o)_2$, -$OC(O)R^o$, -$NR'SO_2R^o$, y -$OC(O)N(R^o)_2$;

cada R' es independientemente H o alquilo; y

cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo

26 El compuesto de la reivindicación 25, en el que:

R^{10} es tetrahidrofuranilo, tetrahidropiranilo, morfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales está opcionalmente sustituido en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$ o -$N(R^{12})_2$ y cada uno de los cuales está opcionalmente sustituido en cualquier átomo de nitrógeno del anillo sustituible con alquilo, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)NR^{12}_2$,

R^{13} es triazolilo, imidazolilo, furanilo, pirrolilo, tienilo, cada uno de los cuales está opcionalmente sustituido en cualquier átomo de carbono del anillo sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$ o -$N(R^{12})_2$ y cada uno de los cuales está opcionalmente sustituido en cualquier átomo de nitrógeno del anillo sustituible con alquilo, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$R^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, $S(O)_2NR^{12}_2$, -$C(O)NR^{12}_2$, y

cada R^{12} es independientemente H, alquilo, haloalquilo o hidroxialquilo.

27 El compuesto de la Reivindicación 26, en el que.

R^3 es un grupo fenilo opcionalmente sustituido en la posición *para* o *meta* por uno o más grupos seleccionados independientemente representados por R11; y

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, $-R^o$, $-OR^o$, $-N(R')_2$, $-NR'SO_2R^o$ y -O(haloalquilo).

28 El compuesto de la Reivindicación 27, en el que:

R^{10} es piperidinilo, piperazinilo, dioxolanilo, tetrahidrofuranilo, o morfolinilo, cada un opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)NR^{12}_2$, cada uno opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$ o $-C(O)NR^{12}_2$;

R^{13} es triazolilo, imidazolilo o pirrolilo cada uno opcionalmente sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)N(R^{12})_2$ y cada uno opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2NR^{12}_2$, $-C(O)NR^{12}_2$.

29 El compuesto de la Reivindicación 28, en el que:

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14};

cada R^{14} es independientemente halógeno, R^o, $-OR^o$, $-CO_2R^o$, $-C(O)R^o$, -CN, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, $NHC(O)NR^o_2$, $(CH_2)_nOH$, $O(CH_2)_nOH$, $(CH_2)_nC(O)NR^o_2$, o $O(CH_2)_nC(O)NR^o_2$;

n es un número entero de 1-4,

R^3 es un grupo fenilo opcionalmente sustituido en la posición *para* por R^{11},

R^{11} es cloruro, fluoruro, bromuro, $-OR^o$, $-N(R')_2$, $-NR'SO_2R^o$ o $-R^o$;

R' es independientemente hidrógeno o un grupo alquilo C_{1-3}; y

R^0 es independientemente hidrógeno, haloalquilo, o un grupo alquilo C_1-3.

30. El compuesto de la Reivindicación 29, en el que:

R^{10} es piperidinilo, piperazinilo, o morfolinilo y está opcionalmente *N*-sustituido con metilo, etilo, $C(O)OR^{12}$, $C(O)NH_2$ o $-C(O)R^{12}$;

R^{13} es triazolilo y está opcionalmente *N*-sustituido con metilo, etilo, $-C(O)OR^{12}$, $C(O)NH_2$ o $-C(O)R^{12}$, y

cada R^{12} es independientemente -H, metilo o etilo.

31. El compuesto de la Reivindicación 22, en el que:

R^{10} es oxazolidinilo, oxazolidinonilo, tiazolidinilo, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo, cada uno de los cuales está *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquiera de uno o más átomos de carbono del anillo con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2NR^{12}_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)NR^{12}_2$, $-OC(O)NR^{12}_2$ o $-NR^{12}_2$,

cada R^{12} es independientemente H, alquilo, haloalquilo, o hidroxialquilo,

R^{13} es pirazolilo, triazolilo, imidazolilo o pirrolilo, cada uno de los cuales *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquiera de uno o más átomo de carbono del anillo con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-R^{12}C(O)OR^{12}$-, $-C(O)N(R^{12})_2$, $-NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $-S(O)_2COR^{12}$, $-S(O)_2NR^{12}_2$, $-S(O)_2OR^{12}$, $-S(O)OR^{12}$, $-OR^{12}$, $-SR^{12}$, -CN, $-NR^{12}C(O)N(R^{12})_2$, $-OC(O)NR^{12}_2$ o $-NR^{12}_2$;

T^2 es un alquileno C_{1-6} de cadena lineal opcionalmente sustituido en cualquiera de uno o más átomos de carbono sustituibles con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico

no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, alquilamina, dialquilamina o hidroxilo,

R^{Y1} es $-C(O)OR^5$, $-C(O)NR^5_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2NR^5_2$, $-NR^5S(O)_2R^5$, $-OR^5$, -CN, $-NR^5C(O)NR^5_2$, $-NR^5_2$, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8;

R^7 es un piperidinonilo, oxazolidinilo, oxazolidinonilo, tiazolidinilo, tetrahidrofuranilo, tetrahidropiranilo, tiazolidinilo, tetrahidrotiofeno, morfolinilo, tiomorfolinilo, imidazolidinilo, imidazolidinonilo, dioxanilo, dioxolanilo, ditiolanilo, pirrolidinilo, pirrolidinonilo, piperazinilo o pipendinilo opcionalmente sustituido; y

R^8 es un furanilo, tetrazolilo, oxazolilo, isoxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo, pirimidilo, tiazolilo, tienilo o imidazolilo opcionalmente sustituido

32. El compuesto de la Reivindicación 31, en el que.

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14};

cada R^{14} es independientemente halógeno, haloalquilo, R^o, $-OR^o$, $-O$(haloalquilo), $-SR^o$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$, $(CH_2)_nCO_2R^o$, $-O(CH_2)_nCO_2R^o$, $-(CH_2)_nOH$, $-(CH_2)_nOH$, $-(CH_2)_nC(O)N(R^o)_2$, o $O(CH_2)_nC(O)N(R^o)_2$,

n es un número entero de 1-4,

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} se selecciona independientemente entre halógeno, haloalquilo, $-R^o$, $-OR^o$, $-O$(haloalquilo), $-SR^o$, 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, $-NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, -

$C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$

33. El compuesto de la Reivindicación 32, en el que

R^3 es un grupo fenilo opcionalmente sustituido por uno o más grupos seleccionados independientemente representados por R^{11},

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), 3,4-metileno-dioxi, 3,4-etileno-dioxi, $-CO_2R^o$, $-C(O)R^o$, $-N(R')_2$, $-NR'SO_2R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, y $-OC(O)N(R^o)_2$,

cada R' es independientemente H o alquilo; y

cada R^o es independientemente hidrógeno, haloalquilo o un grupo alquilo.

34 El compuesto de la Reivindicación 33, en el que:

R^{Y1} es $-C(O)OR^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5C(O)N(R^5)_2$, -OH, un grupo heterocíclico no aromático opcionalmente sustituido representado por R^7 o un grupo heteroarilo opcionalmente sustituido representado por R^8,

cada R^5 es independientemente H o alquilo, o $N(R^5)_2$ es un grupo heterocíclico no aromático que contiene nitrógeno,

R^7 es piperidinonilo, morfolinilo, imidazolidinonilo, pirrolidinilo, pirrolidinonilo, piperazinilo o pipendinilo,

R^8 es tetrazolilo, oxazolilo, oxadiazolilo, pirrolilo, pirazolilo, piridinilo o imidazolilo;

T^2 es un alquileno C_{1-5} de cadena lineal opcionalmente sustituido en el átomo de carbono adyacente a R^Y con haluro, alquilo, gem dialquilo, gem dihalo, haloalquilo, espiro cicloalquilo, grupo heterocíclico no aromático espiro opcionalmente *N*-sustituido que contiene nitrógeno, amina, dialquilamina o hidroxilo,

el grupo representado por R^{10} es morfolinilo, tiomorfolino, imidazolidinilo, imidazolidinonilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales está *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$,-, $C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$ o -$N(R^{12})_2$, y

el grupo representado por R^{13} es triazolilo, imidazolilo o pirrolilo cada uno de los cuales está *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, -$C(O)OR^{12}$, -$C(O)R^{12}$, -$OC(O)R^{12}$, -$R^{12}C(O)OR^{12}$-, -$C(O)N(R^{12})_2$, -$NR^{12}C(O)R^{12}$, -$NR^{12}C(O)OR^{12}$, -$S(O)_2R^{12}$, -$S(O)_2COR^{12}$, -$S(O)_2N(R^{12})_2$, -$S(O)_2OR^{12}$, -$S(O)OR^{12}$, -OR^{12}, -SR^{12}, -CN, -$NR^{12}C(O)N(R^{12})_2$, -$OC(O)N(R^{12})_2$ o -$N(R^{12})_2$.

35. El compuesto de la Reivindicación 34, en el que:

R^3 es un grupo fenilo opcionalmente sustituido en la posición *meta* o *para* por uno o más grupos seleccionados independientemente representados por R^{11}; y

cada R^{11} es independientemente un sustituyente seleccionado entre halógeno, haloalquilo, -R^o, -OR^o, -$N(R')_2$, -$NR'SO_2R^o$ y -O(haloalquilo)

36 el compuesto de la Reivindicación 35, en el que:

R^{Y1} es -$C(O)OR^5$, -$C(O)N(R^5)_2$, -OH, *N*-morfolinilo, 2-morfolinilo, 3-morfolinilo, 2-morfolinilo *N*-sustituido, 3-morfolinilo *N*-sustituido, *N*-imidazolidinilo, 2-imidazolidinilo, 4-imidazolidinilo, 5-imidazolidinilo, 2-imidazolidinilo *N*-sustituido, *N*-imidazolidinilo *N'*-sustituido, 4-imidazolidinilo *N*-sustituido, 5-imidazolidinilo *N*-sustituido, *N*-imidazolidinonilo, 4-imidazolidinonilo, 5-imidazolidinonilo, 4-imidazolidinonilo *N*-sustituido, 5-imidazolidinonilo *N*-sustituido, *N*-pirrolidinilo, 2-pirrolidinilo, 3-pirrolidinilo, 2-pirrolidinilo *N*-sustituido, 3-pirrolidinilo *N*-sustituido, *N*-pirrolidin-2-onilo, 3-

pirrolidin-2-onilo, 4-pirrolidin-2-onilo, 5-pirrolidin-2-onilo, 3-pirrolidin-2-onilo *N*-sustituido, 4-pirrolidin-2-onilo *N*-sustituido, 5-pirrolidin-2-onilo *N*-sustituido, *N*-pirrolidin-3-onilo, 2-pirrolidin-3-onilo, 4-pirrolidin-3-onilo, 5-pirrolidin-3-onilo, 2-pirrolidin-3-onilo *N*-sustituido, 4-pirrolidin-3-onilo *N*-sustituido, 5-pirrolidin-3-onilo *N*-sustituido, *N*-piperidinilo, 2-piperidinilo, 3-piperidinilo, 4-piperidinilo, 2-piperidinilo *N*-sustituido, 3-piperidinilo *N*-sustituido, 4-piperidinilo *N*-sustituido, *N*-piperidin-2-onilo, 3-piperidin-2-onilo, 4-piperidin-2-onilo, 5-piperidin-2-onilo, 6-piperidin-2-onilo, 3-piperidin-2-onilo *N*-sustituido, 4-piperidin-2-onilo *N*-sustituido, 5-piperidin-2-onilo *N*-sustituido, 6-piperidin-2-onilo *N*-sustituido, *N*-pipendin-3-onilo, 2-piperidin-3-onilo, 4-pipendin-3-onilo, 5-piperidin-3-onilo, 6-piperidin-3-onilo, 2-piperidin-3-onilo *N*-sustituido, 4-piperidin-3-onilo *N*-sustituido, 5-piperidin-3-onilo *N*-sustituido, 6-pipendin-3-onilo *N*-sustituido, *N*-piperidin-4-onilo, 2-piperidin-4-onilo, 3-piperidin-4-onilo, 5-piperidin-4-onilo, 6-piperidin-4-onilo, 2-piperidin-4-onilo *N*-sustituido, 3-piperidin-4-onilo *N*-sustituido, 5-piperidin-4-onilo *N*-sustituido, 6-piperidin-4-onilo *N*-sustituido, *N*-piperazinilo, 2-piperazinilo, *N*-piperazinilo *N'*-sustituido, 2-piperazinilo *N*-sustituido, furanilo, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, 4-(1,2,3)oxadiazolilo, 5-(1,2,3)oxadiazolilo, 3-(1,2,4)oxadiazolilo, 5-(1,2,4)oxadiazolilo, 3-(1,2,5)oxadiazolilo, 4-(1,2,5)oxadiazolilo, 2-(1,3,4)oxadiazolilo, 5-(1,3,4)oxadiazolilo, *N*-pirrolilo, 2-pirrolilo, 3-pirrolilo, 2-pirrolilo *N*-sustituido, 3-pirrolilo *N*-sustituido, *N*-pirazolilo, 3-pirazolilo, 4-pirazolilo, 5-pirazolilo, 3-pirazolilo *N*-sustituido, 4-pirazolilo *N*-sustituido, 5-pirazolilo *N*-sustituido, 2-piridinilo, 3-piridinilo, 4-piridinilo, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido;

T^2 es un alquileno C_{1-3} de cadena lineal sustituido con flúor, metilo, gem dimetilo, gem difluoro fluorometilo, espiro ciclopropilo, espiro ciclobutilo, espiro azetidinilo opcionalmente *N*-sustituido, espiro aziridinilo opcionalmente *N*-sustituido, espiro pirrolidinilo opcionalmente *N*-sustituido, espiro piperidinilo opcionalmente *N*-sustituido, amina, metilamina, dimetilamina o hidroxilo;

el grupo representado por R^{10} es morfolinilo, pirrolidinilo, piperazinilo o piperidinilo cada uno de los cuales está *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$; y

el grupo que representa R^{13} es imidazolilo o pirrolilo cada uno de los cuales está *N*-sustituido con T^2-R^{Y1} y opcionalmente también sustituido en cualquier átomo de carbono sustituible con alquilo, haluro, haloalquilo, hidroxialquilo, $-C(O)OR^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$ o $-C(O)N(R^{12})_2$ y cada uno está opcionalmente sustituido en cualquier átomo de nitrógeno sustituible con alquilo, haloalquilo, hidroxialquilo, $C(O)OR^{12}$, $-C(O)R^{12}$, $-R^{12}C(O)OR^{12}$, $-S(O)_2R^{12}$, $S(O)_2N(R^{12})_2$, $-C(O)N(R^{12})_2$.

37 El compuesto de la Reivindicación 36, en el que:

El anillo A es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14},

cada R^{14} es independientemente halógeno, R^o, $-OR^o$, $-CO_2R^o$, $-C(O)R^o$, -CN, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^o$, $O(CH_2)_nCO_2R^o$, $NHSO_2R^o$, $NHC(O)NR^o_2$, $(CH_2)_nOH$, $O(CH_2)_nOH$, $(CH_2)_nC(O)NR^o_2$, o $O(CH_2)_nC(O)NR^o_2$,

n es un número entero de 1-4;

R^3 es un grupo fenilo opcionalmente sustituido en la posición *para* por R^{11};

R^{11} es cloruro, fluoruro, bromuro, $-OR^o$, $-N(R')_2$, $-NR'SO_2R^o$ o R^o;

R' es independientemente hidrógeno o un grupo alquilo C_{1-3}; y

R^o es independientemente hidrógeno, haloalquilo, o un grupo alquilo C_{1-3}.

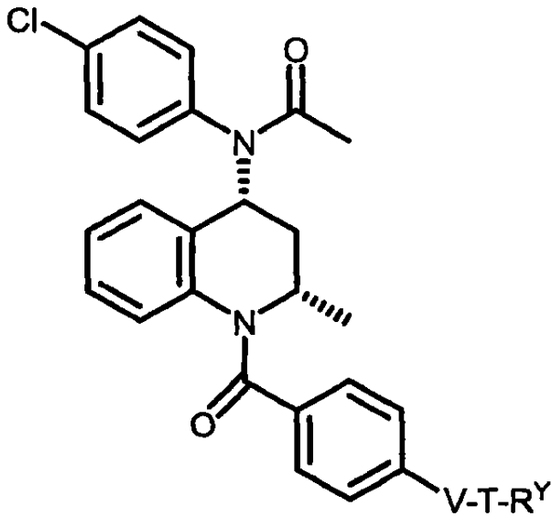
38. El compuesto de la Reivindicación 37, en el que:

R^{Y1} es $-C(O)OR^5$, $-C(O)NR^5_2$, -OH, *N*-tetrazolilo, 5-tetrazolilo, 5-tetrazolilo *N*-sustituido, *N*-imidazolilo, 2-imidazolilo, 4-imidazolilo, 5-imidazolilo; 2-imidazolilo *N*-sustituido, 4-imidazolilo *N*-sustituido o 5-imidazolilo *N*-sustituido,

el grupo representado por R^{10} es piperidinilo, piperazinilo, o morfolino, *N*-sustituido con T^2-R^{Y1} y sustituido opcionalmente también en el carbono alfa al átomo de nitrógeno con metilo o gem dimetilo; y

el grupo representado por R^{13} es tiazolilo *N*-sustituido con T^2-R^{Y1} y opcionalmente sustituido también en el carbono alfa al átomo de nitrógeno con metilo

39 Un compuesto representado por la siguiente fórmula estructural.



o una sal farmacéuticamente aceptable del mismo, en el que:

V es un enlace covalente o -O-

T es un alquileno C_{1-10} no sustituido de cadena lineal,

R^Y es $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, $-CN$, $-NR^5C(O)NR^5_2$, $-OC(O)NR^5_2$, $-NR^5_2$, $-OR^5$, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido,

con la condición de que T-R^Y sea distinto de $-CH_2R^{20}$, $-CH_2CH_2R^{21}$ o $-(CH_2)_3R^{22}$, donde

R^{20} es -COOH, -C(O)NH_2, -C(O)$NHCH_3$, C(O)$N(CH_3)_2$, 5-tetrazolilo, 4-piridinilo, *N*-etil-4-piperidinilo o C(O)*N*-morfolinilo;

R^{21} es -COOH, *N*-morfolinilo, C(O)NH_2, *N*-pirrolidin-2-onilo, *N*-imidazolilo o *N*-pirrolidinilo; y

R^{22} es -COOH, C(O)$N(CH_2CH_3)_2$, C(O)$NH(CH_2CH_3)$, C(O)NH_2, C(O)$NHS(O)_2CH_3$, C(O)NHOH, C(O)OCH_2CH_3, NH_2, C(O)CH_3, CN, $NHS(O)_2CF_3$, C(O)*N*-pirrolidinilo, *N*-pirrolidinilo, 5-tetrazolilo, 5-(1,2,4)oxadiazolilo, *N*-morfolinilo o *N*-imidazolilo

40 Un método para tratar una enfermedad, trastorno o síntoma inflamatorio en un sujeto en necesidad de tratamiento, que comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto representado por el compuesto de la Reivindicación 1

41. El método de la Reivindicación 40 en el que la enfermedad, trastorno o síntoma inflamatorio es rinitis alérgica, artritis reumatoide, enfermedad pulmonar obstructiva crónica o asma alérgica.

42. El método de la Reivindicación 41 en el que la enfermedad, trastorno o síntoma inflamatorio es rinitis alérgica o asma alérgica.

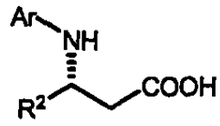
43 Un método para tratar una enfermedad, trastorno o síntoma inflamatorio en un sujeto en necesidad de tratamiento, que comprende la etapa de administrar al sujeto una cantidad eficaz de un compuesto representado por un compuesto de una cualquiera de las Reivindicaciones 2-38.

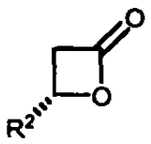
44 El método de la Reivindicación 43, en el que la enfermedad, trastorno o síntoma inflamatorio es rinitis alérgica, artritis reumatoide, enfermedad pulmonar obstructiva crónica o asma alérgica

45 El método de la Reivindicación 44 en el que la enfermedad, trastorno o síntoma inflamatorio es rinitis alérgica o asma alérgica.

46 Una composición farmacéutica que comprende un vehículo o diluyente farmacéuticamente aceptable y un compuesto de una cualquiera de las Reivindicaciones 1-38.

47 Un método para preparar un compuesto representado por la siguiente fórmula estructural.



que comprende la etapa de hacer reaccionar Ar-NH_2 con  en el que Ar es un grupo aromático monocíclico opcionalmente sustituido y R^2 es alquilo C1-C3

48 El método de la Reivindicación 47 en el que Ar es un grupo fenilo opcionalmente sustituido y R^2 es metilo o etilo

49 El método de la Reivindicación 48 en el que Ar es un grupo fenilo opcionalmente *para* o *meta* sustituido con R^{14},

cada R^{14} es independientemente halo, ciano, R^o, $-OR^{30}$, $-CO_2R^{31}$, $-C(O)R^o$, $-C(O)N(R^x)_2$, $-OC(O)R^o$, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)NR^x_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)NR^o_2$, $O(CH_2)_nC(O)NR^x_2$;

n es un número entero de 1-4;

R^o es independientemente hidrógeno, haloalquilo C1-C3 o un grupo alquilo C1-C3,

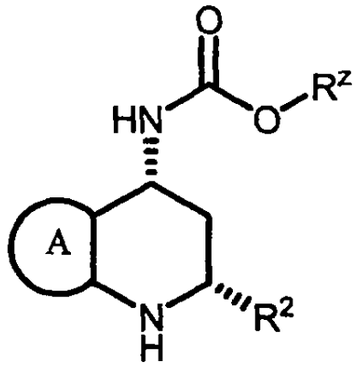
un R^x es -H o alquilo C_1-C_3 y el otro es un grupo protector de amina;

R^{30} es un grupo protector de alcohol; y

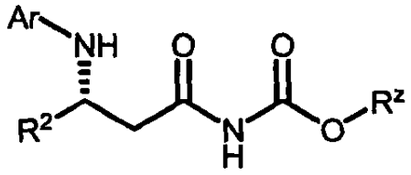
R^{31} es un grupo protector de ácido carboxílico.

50 El método de la reivindicación 49 en el que Ar es un grupo fenilo.

51 Un método para preparar un compuesto producto representado por la siguiente fórmula estructural



a partir de un compuesto de partida representado por la siguiente fórmula estructural.



comprendiendo dicho método la etapa de reducir el carbonilo de la amida del compuesto de partida para formar un intermedio y después ciclar el intermedio para formar el compuesto producto, donde $-C(O)OR^Z$ es un grupo protector de amida

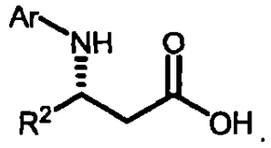
52 El método de la Reivindicación 51 en el que R^Z es un grupo alquilo, un grupo alilo o un grupo aromático sustituido o no sustituido.

53 El método de la Reivindicación 52 en el que el carbonilo de la amida del compuesto de partida se reduce haciendo reaccionar el compuesto de partida con borohidruro sódico y un ácido de Lewis y el intermedio se cicla en presencia de ácido.

54. El método de la Reivindicación 53 en el que Ar es un grupo fenilo opcionalmente sustituido y R^2 es metilo o etilo

55 El método de la Reivindicación 53 en el que R^2 es bencilo, metilo, etilo, alilo, 2,2,2-triclorometilo, 2,2,2-tricloro-*terc*-butilo, *terc*-butilo o fluorometilo

56 El método de la Reivindicación 51 en el que el compuesto de partida se prepara amidando un aminoácido con $H_2NC(O)OR^2$, en el que dicho aminoácido está representado por la siguiente fórmula estructural:

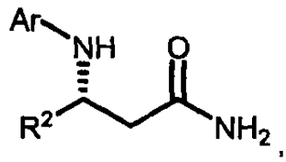


57 El método de la Reivindicación 56 en el que dicha amidación se realiza haciendo reaccionar el aminoácido con un reactivo de activación de ácido carboxílico para formar un intermedio activado y después haciendo reaccionar el intermedio activado con $H_2NC(O)OR^2$.

58. El método de la Reivindicación 57 en el que el agente de activación de ácido carboxílico es un carbonildiimidazol

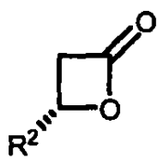
59 El método de la Reivindicación 56 en el que dicha amidación se realiza haciendo reaccionar el aminoácido con un reactivo de activación de ácido carboxílico para formar un intermedio activado y después haciendo reaccionar el intermedio activado con NH_3 o un equivalente funcional del mismo para

formar un intermedio carboxamida representado por la siguiente fórmula estructural:



haciendo reaccionar el intermedio carboxamida con X-C(O)OR^Z, donde X es un grupo saliente.

60 El método de la Reivindicación 56 en el que el aminoácido se prepara



haciendo reaccionar Ar-NH_2 con .

61 El método de la Reivindicación 60 en el que Ar es un grupo fenilo opcionalmente sustituido y R^2 es metilo o etilo.

62. El método de la Reivindicación 61 en el que Ar es un grupo fenilo opcionalmente sustituido en las posiciones seis y siete con R^{14};

cada R^{14} es independientemente halo, ciano, R^o, -OR^{30}, -CO_2R^{31}, -C(O)R^o, -C(O)N(R^x)$_2$, -OC(O)R^o, $(CH_2)_nCO_2R^{31}$, $O(CH_2)_nCO_2R^{31}$, $NHSO_2R^o$, $NHC(O)NR^x_2$, $(CH_2)_nOR^{30}$, $O(CH_2)_nOR^{30}$, $(CH_2)_nC(O)NR^x_2$, $O(CH_2)_nC(O)NR^x_2$,

n es un número entero de 1-4,

R^o es independientemente hidrógeno, un grupo haloalquilo C_{1-3} o un grupo alquilo C_{1-3},

un R^x es -H o alquilo C_1-C_3 y el otro es un grupo protector de amina,

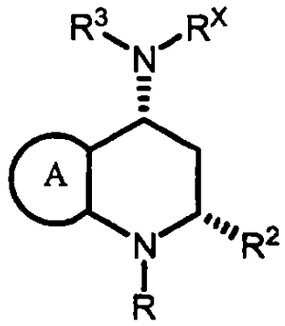
R^{30} es un grupo protector de alcohol; y

R^{31} es un grupo protector de ácido carboxílico.

63 El método de la Reivindicación 62 en el que Ar es un grupo fenilo.

RESUMEN DE LA DESCRIPCIÓN

En este documento se describen compuestos representados por la Formula Estructural (I).



También se describe el uso de dichos compuestos para inhibir el receptor acoplado a proteína G mencionados como molécula homóloga al receptor de quimioatracción expresada en Th2, o simplemente "CRTH2" para el tratamiento de trastornos inflamatorios Las variables en la Fórmula Estructural (I) se definen en este documento

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TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	07 April 2005
International Application No.	
Attorney Docket No	MPI04-007

EV528716580US

I. Certification under 37 CFR 1.10 (If applicable)

EV528716580US	07 April 2005
Express Mail Mailing Number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1 10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, P O Box 1450, Alexandria, VA 22313-1450

Signature of Person Mailing Correspondence	Sean Hunziker/ Beverly Sotiropoulos
	Typed or Printed Name of Person Mailing Correspondence

II. ☑ New International Application

TITLE	PGD2 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES	Earliest priority date (Day/Month/Year): 07 April 2004

SCREENING DISCLOSURE INFORMATION In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied (Note check as many boxes as apply)

A. ☐ The invention disclosed was not made in the United States

B. ☐ There is no prior U S application relating to this invention

C. ☑ The following prior U S. application(s) contain subject matter which is related to the invention disclosed in the attached international application *(NOTE priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority)*

application no.	60/560,410	filed on	07 April 2004	application no.		filed on	
application no.		filed on		application no.		filed on	
application no		filed on					

E. ☑ The present international application ☑ contains additional subject matter not found in the prior U.S application(s) identified in paragraph C above The additional subject matter is found on pages throughout and ☑ **DOES NOT ALTER** ☐ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U S application to have been made available for inspection by the appropriate defense agencies under 35 U S C 181 and 37 CFR 5 1 See 37 CFR 5 15

III. ☐ A response to an Invitation from the RO/US. The following document(s) is(are) enclosed

A. ☐ A Request for an Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages

D. ☐ Submission of Priority Documents

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ A Request for Rectification under PCT Rule 91 ☐ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☑ Other (please specify): PCT Request Form (6 pages-in duplicate), PCT Fee Calculation Sheet (1 page), 362 pages of Specification (pp 1-362), 28 pages of Claims (pp. 363-390), 1 page of Abstract (p 391), General Power of Attorney for Millennium Pharmaceuticals, Inc by Scott Brown (1 page); General Power of Attorney for Shomir Ghosh (2 pages), General Power of Attorney for Amy M. Elder (2 pages), General Power of Attorney for Kenneth G Carson (2 pages), General Power of Attorney for Kevin Sprott (2 pages), General Power of Attorney for Sean Harrison (2 pages), General Power of Attorney for Dominic Reynolds (1 page), and return postcard

The person signing this form is the	☐	Applicant	Karoline K. M. SHAIR
	☑	Attorney/Agent (Reg No) 44,332	Typed name of signer
	☐	Common Representative	Karoline K. M. Shair
			Signature

PTO-1382 (Rev 08-1997) U.S Department of Commerce Patent and Trademark Office

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PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty

For receiving Office use only
International Application No.
International Filing Date
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* *MP104-007*

Box No. I TITLE OF INVENTION

PGD2 RECEPTOR ANTAGONISTS FOR THE TREATMENT OF INFLAMMATORY DISEASES

Box No. II APPLICANT ☐ This person is also inventor

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
Cambridge, MA 02139
United States of America

Telephone No: (617) 679-7000

Facsimile No: (617) 551-8820

Applicant's Registration No with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

GHOSH, Shomir
134 Sewall Avenue, Unit C
Brookline, Massachusetts 02446
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's Registration No with the Office:

State *(that is, country)* of nationality: IN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as ☒ agent ☐ common representative

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country)*

SHAIR, Karoline K. M.
MILLENNIUM PHARMACEUTICALS, INC.
40 Landsdowne Street
Cambridge, MA 02139
United States of America

Telephone No: (617) 444-3227

Facsimile No: (617) 551-8820

Applicant's Registration No with the Office: 44,332

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

110544

552

Name and address *(Family name followed by given name, for a legal entity, full official designation The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below)*

ELDER, Amy M
15 Westminster Avenue
Arlington, Massachusetts 02474
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality US

State *(that is, country)* of residence US

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below)*

CARSON, Kenneth G.
96 Herrontown Road
Princeton, New Jersey 08540
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality US

State *(that is, country)* of residence US

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below)*

SPROTT, Kevin T.
67 Monument Avenue #2
Boston, Massachusetts 02129
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality US

State *(that is, country)* of residence US

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation The address must include postal code and name of country The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below)*

HARRISON, Sean J.
38 Grove Street
Belmont, Massachusetts 02478
United States of America

This person is
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality US

State *(that is, country)* of residence US

This person is applicant for the purposes of ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet

Continuation of Box No III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HICKS, Frederick A.
5 Woodbine Street
Somerville, Massachusetts 02143
United States of America

This person is
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RENOU, Christelle C
74 Josephine Avenue, Unit A
Somerville, Massachusetts 02144
United States of America

This person is
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: US

This person is applicant for the purposes of
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

REYNOLDS, Dominic
304 Allston Street, Apt. 6
Cambridge, Massachusetts 01239
United States of America

This person is
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: US

This person is applicant for the purposes of
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address *(Family name followed by given name, for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's Registration No with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet

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Box No. V **DESIGNATION C TATES** *Mark the applicable check-boxes below, at least o ust be marked.*

The filing of this request **constitutes under Rule 4.9(a), the designation** of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents

However,

☐ DE Germany **is not designated** for any kind of national protection

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☐ KR Republic of Korea **is not designated** for any kind of national protection

☐ RU Russian federation **is not designated** for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law of an earlier national application from which priority is claimed See the Notes to Box No V as to the consequences of such national law provisions in these and certain other States)

Box No. VI **PRIORITY CLAIM**

The priority of the following earlier application(s) is hereby claimed

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is		
		national application country or Member of WTO	regional application * regional Office	international application receiving Office
item (1) 07 April 2004 (07.04 2004)	60/560,410	US		

☐ Further priority claims are indicated in the Supplemental Box

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as

☒ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4 10(b)(ii))*

Box No. VII **INTERNATIONAL SEARCHING AUTHORITY**

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen, the two-letter code may be used)*

ISA / EP

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII **DECLARATIONS**

The following **declarations** are contained in Boxes Nos VIII(i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)* Number of declarations

☐	Box No VIII(i)	Declaration as to the identity of the inventor
☐	Box No VIII(ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent
☐	Box No VIII(iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application
☐	Box No VIII(iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)
☐	Box No VIII(v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty

Supplemental Box

00547

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CONTINUATION of Box No. IV (AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE)

BROWN, Scott A., Reg. No. 32,724
SILVERMAN, Ian Robert, Reg. No. 37,443
SILVERI, Jean M., Reg. No. 39,030
KLUNDER, Janice M., Reg. No. 41,121
SCHRAY, Kerri Pollard, Reg. No. 47,066
SIOUSSAT, Tracy M., Reg. No. 50,609

All of MILLENNIUM PHARMACEUTICALS, INC., 40 Landsdowne Street, Cambridge, MA, 02139, United States of America

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains

(a) In paper form, the following	number of sheets	
request (including declaration sheets)	6	
description (excluding sequence listing part and/or tables related thereto)	362	
Claims	28	
Abstract	1	
Drawings	0	
Sub-total number of sheets	397	
sequence listing		
tables related thereto		
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form, see (c) below)		
Total number of sheets	397	

(b) ☐ **only in computer readable form** (Section 801(a)(i))

(i) ☐ sequence listing
(ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))

(i) ☐ sequence listing
(ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the

☐ sequence listing
☐ tables related thereto

(additional copies to be indicated under item 9(ii), and/or 10(ii), in right column)

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*

			Number of items
1	☒	fee calculation sheet	1
2	☐	original separate power of attorney	
3	☐	original general power of attorney	
4	☒	7 copies of general powers of attorney (12 pgs), reference number, if any	12
5	☐	statement explaining lack of signature	
6	☐	priority document(s) identified in Box No VI as item(s)	
7	☐	translation of international application into *(language)*	
8	☐	separate indications concerning deposited microorganism or other biological material	
9	☐	sequence listing in computer readable form (indicate type and number of carriers)	
	(i) ☐	Copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	
	(ii) ☐	*(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule13ter	
	(iii) ☐	Together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in the left column	
10	☐	Tables in computer readable form related to sequence listing *(indicate type and number of carriers)*	
	(i) ☐	copy submitted for the purposes of international search under Section 802 (b-*quarter*) only (and not as part of the international application)	
	(ii) ☐	*(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quarter*)	
	(iii) ☐	together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	
11	☒	other *(specify)* *Transmittal Letter/Postcard*	2

Figure of the drawings which Should accompany the abstract: none

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

Karoline K. M. Shair

Karoline K. M. SHAIR, Registration No. 44,332
Agent for Applicants

For receiving Office use only

1 Date of actual receipt of the purported international application		2 Drawings ☐ received ☐ not received
3 corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application		
4 Date of timely receipt of the required corrections under PCT Article 11(2)		
5 International Searching Authority (if two or more are competent) ISA /	6 ☐ Transmittal of search copy delayed until search fee is paid	

For International Bureau use only

Date of receipt of the record copy by the International Bureau

PCT

FEE CALCULATION SHEET

Annex to the Request

For receiving Office use only

International application No

00549

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Applicant's or agent's file reference MP104-007

Date stamp of the receiving Office

Applicant MILLENNIUM PHARMACEUTICALS, INC et al

CALCULATION OF PRESCRIBED FEES

1 TRANSMITTAL FEE | USD 300 [T]

2 SEARCH FEE | 1920 [S]
International search to be carried out by ISA/EP
(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search)

3 INTERNATIONAL FEE

Where items (b) and/or (c) of Box No IX apply, enter Sub-Total number of Sheets _____
Where items (b) and (c) of Box No IX do not apply, enter Total number of Sheets 397

[11] First 30 sheets | 1134 [11]

[12] 367 (number of sheets in excess of 30) x 12 (fee per sheet) = | 4404 [12]

[13] additional components (only if sequence listing and/or tables related thereto are filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)

400 x _____ = | _____ [13]

Add amounts entered at 11, 12 and 13 and enter total a I | 5538 [I]

(Applicants from certain States are entitled to a reduction of 75% of the international filing fee Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the international filing fee)

4 FEE FOR PRIORITY DOCUMENT (if applicable) | 20 [P]

5 TOTAL FEES PAYABLE TOTAL | 7778
Add amounts entered at T, S, I and P, and enter total in the Total box

MODE OF PAYMENT

☒ Authorization to charge deposit account (see below) ☐ bank draft ☐ coupons
☐ cheque ☐ cash ☐ other *(specify)*
☐ postal money order ☐ revenue stamps

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT *(this mode of payment may not be available at all receiving Offices)*

Receiving Office RO/US

☒ Authorization to charge the total fees indicated above

Deposit Account No 501668

☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any over payment in the total fees indicated above

Date April 7, 2005

Name Karoline K M SHAIR, Reg No 44,332

☒ Authorization to charge the fee for the priority document

Signature Karoline K. M Shair

PATENT COOPERATION TREATY

FR 00550

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To
MILLENNIUM PHARMACEUTICALS, INC.
Attn. Shair, Karoline K. M.
40 Landsdowne Street
Cambridge MA 02139
UNITED STATES OF AMERICA

RECEIVED
MILLENNIUM PHARMACEUTICALS
AUG 1 2005
DOCKETING DEPARTMENT
DOCKETED BY BRS

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference MP104-007	Date of mailing (day/month/year) 28/07/2005
International application No PCT/US2005/011643	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant MILLENNIUM PHARMACEUTICALS, INC.	International filing date (day/month/year) 07/04/2005

1 [x] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46)

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report, however, for more details, see the notes on the accompanying sheet

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Fascimile No (41-22) 740 14 35

For more detailed instructions, see the notes on the accompanying sheet.

2 [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith

3 [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made

4 **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis* 3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later), otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority 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 Josef Ullrich

NOTES TO FORM PCT/ISA/220

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19 The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty In case of discrepancy between these Notes and those requirements, the latter are applicable For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e g the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication Furthermore, it should be emphasized that provisional protection is available in some States only

What parts of the international application may be amended?

Under Article 19, only the claims may be amended

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority The description and drawings may only be amended under Article 34 before the International Examining Authority

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46 1)

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46 2).

Where a demand for international preliminary examination has been/is filed, see below

How? Either by canceling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed

All the claims appearing on a replacement sheet must be numbered in Arabic numerals Where a claim is cancelled, no renumbering of the other claims is required In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b))

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter

The letter will not be published with the international application and the amended claims It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

BNSDOCID <XS____ISA220NOENP4_I_>

The letter must indicate the differences between the claims as filed and the claims as amended It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged,

(ii) the claim is cancelled,

(iii) the claim is new,

(iv) the claim replaces one or more claims as filed,

(v) the claim is the result of the division of a claim as filed

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1 [Where originally there were 48 claims and after amendment of some claims there are 51]
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged, new claims 49 to 51 added."

2 [Where originally there were 15 claims and after amendment of all claims there are 11]
"Claims 1 to 15 replaced by amended claims 1 to 11 "

3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
"Claims 1 to 6 and 14 unchanged, claims 7 to 13 cancelled, new claims 15, 16 and 17 added " or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added, all other claims unchanged "

4 [Where various kinds of amendments are made]
"Claims 1-10 unchanged, claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17, new claims 20 and 21 added "

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1))

The statement will be published with the international application and the amended claims

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1) "

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62 2(a), first sentence)

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide

BNSDOCID <XS____ISA220NOENP4_I_>

PATENT COOPERATION TREATY

PCT

~~8550~~

561

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below
MP104-007		
International application No	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US2005/011643	07/04/2005	07/04/2004

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 3 sheets

[X] 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, unless otherwise indicated under this item

[ ] The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 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 II)

3 [ ] **Unity of invention is lacking** (see Box III)

4 With regard to the **title,**

[X] 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,**

[X] 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 No _____

[ ] 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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/011643

A CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/44 C07D401/10 C07D401/12 A61K31/4709 A61P29/00

562

00554

According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	EP 1 069 122 A (SHIONOGI & CO., LTD) 17 January 2001 (2001-01-17) page 2, line 10 - line 40	1-70
A	WO 02/088069 A (PFIZER PRODUCTS INC; DAMON, DAVID, BURNS; DUGGER, ROBERT, WAYNE; SCOTT) 7 November 2002 (2002-11-07) Scheme B, claim 4	54-70
X,P	EP 1 435 356 A (WARNER-LAMBERT COMPANY LLC) 7 July 2004 (2004-07-07) claim 1; examples 1-102	1-70
X,P	WO 2004/032848 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 22 April 2004 (2004-04-22) claim 1; examples A-E	1-70

☐ Further documents are listed in the continuation of box C

☒ Patent family members are listed in annex

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 July 2005	28/07/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel (+31-70) 340-2040 Tx 31 651 epo nl, Fax (+31-70) 340-3016	Seelmann, I

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No PCT/US2005/011643

563 00555

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1069122 A	17-01-2001	AU 745129 B2	14-03-2002
		AU 2960199 A	18-10-1999
		BR 9909290 A	05-12-2000
		CA 2326419 A1	07-10-1999
		EP 1069122 A1	17-01-2001
		HU 0101728 A2	28-12-2001
		JP 3455181 B2	14-10-2003
		NO 20004919 A	28-11-2000
		PL 343316 A1	13-08-2001
		US 6320060 B1	20-11-2001
		CN 1431208 A	23-07-2003
		CN 1117743 C	13-08-2003
		EP 1528060 A1	04-05-2005
		ID 26346 A	14-12-2000
		WO 9950260 A1	07-10-1999
		JP 3621373 B2	16-02-2005
		JP 2002167383 A	11-06-2002
		RU 2186065 C1	27-07-2002
		TR 200002839 T2	22-01-2001
		TR 200101628 T2	22-07-2002
		US 2002016476 A1	07-02-2002
		US 2002026061 A1	28-02-2002
		ZA 200004720 A	09-03-2001
WO 02088069 A	07-11-2002	BR 0209238 A	15-06-2004
		BR 0209291 A	13-07-2004
		CA 2445623 A1	07-11-2002
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		CN 1529696 A	15-09-2004
		CN 1505609 A	16-06-2004
		CZ 20032898 A3	14-07-2004
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		EP 1425270 A2	09-06-2004
		EP 1383734 A2	28-01-2004
		HU 0304039 A2	29-03-2004
		HU 0304041 A2	28-04-2004
		WO 02088085 A2	07-11-2002
		WO 02088069 A2	07-11-2002
		JP 2004527556 T	09-09-2004
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		MX PA03009935 A	29-01-2004
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		PL 366584 A1	07-02-2005
		PL 366700 A1	07-02-2005
		US 2003073843 A1	17-04-2003
		US 2002177716 A1	28-11-2002
		US 2003216576 A1	20-11-2003
		ZA 200306599 A	22-10-2004
		ZA 200306600 A	25-08-2004
EP 1435356 A	07-07-2004	EP 1435356 A1	07-07-2004
WO 2004032848 A	22-04-2004	AU 2003277285 A1	04-05-2004
		CA 2500582 A1	22-04-2004
		WO 2004032848 A2	22-04-2004
		US 2004082609 A1	29-04-2004

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

To

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis* 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	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2005/011643	07 04 2005	07 04 2004

International Patent Classification (IPC) or both national classification and IPC
C07D215/44, C07D401/10, C07D401/12, A61K31/4709, A61P29/00

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 43*bis* 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") However, 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 1*bis*(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 three 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
D-80298 Munich
Tel +49 89 2399 - 0 Tx 523656 epmu d
Fax +49 89 2399 - 4465

Authorized Officer

Seelmann, I

Telephone No +49 89 2399-7480

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US2005/011643

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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, unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12 3 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

☐ in written format

☐ in computer readable form

c time of filing/furnishing

☐ contained in the international application as filed

☐ filed together with the international application in computer readable 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
PCT/US2005/011643

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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. 51-53 (industrial applicability)

because

☒ the said international application, or the said claims Nos 51-53 relate to the following subject matter which does not require an international preliminary examination *(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

☐ no international search report has been established for the whole application or for said claims Nos

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions

☒ See separate sheet for further details

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US2005/011643

567

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

1 Statement

Novelty (N)	Yes	Claims	1-70
	No	Claims	
Inventive step (IS)	Yes	Claims	1-70
	No	Claims	
Industrial applicability (IA)	Yes	Claims	1-50,54-70
	No	Claims	

2 Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1 Certain published documents (Rules 43*bis* 1 and 70 10)

and / or

2 Non-written disclosures (Rules 43*bis*.1 and 70 9)

see form 210

Re Item III

Claims 51-53 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

1. PRIOR ART

Reference is made to the following documents

D1 EP 1 069 122 A
D2: WO 02/088069 A

2. NOVELTY

The subject-matter of the claims is considered to be novel (Article 33(2) PCT). The essential structural difference between the compounds of claim 1 and those of D1 resides in the basic ring system, D1 discloses benzothiophenes whereas the application relates to condensed piperidines (i a. quinolines) The difference between the process for the preparation of intermediates according to claim 54-70 and D2 resides i.a. in the stereochemistry of compound VII of D1 vis-a-vis the title compound of claim 58.

3. INVENTIVE STEP

The subject-matter of the claims can be considered as involving an inventive step (Article 33(3) PCT).

The document D1 is regarded as being the closest prior art to the subject-matter of claim 1 It discloses benzothiophene derivatives with PGD2 activity. The structural difference to the present compounds is as outlined above. The problem to be solved by the present invention is seen in the provision of further compounds with PGD2 activity.

In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved for those compounds as disclosed in the claims. The prior art D1 gives no information, which would motivate a man skilled in the art to arrive at the present invention.

The document D2 is regarded as being the closest prior art to the subject-matter of claims 54-70 It discloses i a a process for the preparation of compound VII, which is the title compound of present claim 58 and an important intermediate in the preparation of the compounds of present claim 1. However, D2 discloses only a different stereoisomer. The problem to be solved by the present invention is seen in the provision of a process for the preparation of intermediates for the preparation of compounds of claim 1. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved by the claimed process The prior art D2 gives no information, which would motivate a man skilled in the art to arrive at the present invention

If the compounds of claims 47-49 fall within the scope of claim 1, these claims should contain a reference to claim 1.

4. INDUSTRIAL APPLICABILITY

For the assessment of the present claims 51-53 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

The documents D3: EP-A-1 435 356 and D4· WO 2004/032848 were filed before the priority date but published only between the priority and the filing date of the present application. Therefore, in the regional phase they could become relevant to assess

whether the subject-matter satisfies the criteria set forth in Article 33(2) PCT

PATENT COOPERATION TREAT

PCT/US2005/011643

RECEIVED
MILLENNIUM PHARMACEUTICALS
JUL 18 2005
DOCKETING DEPARTMENT
DOCKETED BY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To

SHAIR, Karoline, K , M
Millenium Pharmaceuticals, Inc
40 Landsdowne Street
Cambridge, MA 02139
ETATS-UNIS D'AMERIQUE

00563

571

Date of mailing *(day/month/year)* 06 July 2005 (06 07 2005)	
Applicant's or agent's file reference MP104-007	**IMPORTANT NOTIFICATION**
International application No PCT/US2005/011643	International filing date *(day/month/year)* 07 April 2005 (07 04 2005)
International publication date *(day/month/year)*	Priority date *(day/month/year)* 07 April 2004 (07 04 2004)
Applicant MILLENNIUM PHARMACEUTICALS, INC et al	

1 By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b)

2 *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17 1(a) or (b) Where, under Rule 17 1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances

3 *(If applicable)***An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17 1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17 1(b)) Even though the priority document was not furnished in compliance with Rule 17 1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration In case such a copy is not accepted by the designated Office as the priority document, Rule 17 1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
07 April 2004 (07 04 2004)	60/560,410	US	20 May 2005 (20 05 2005)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No +41 22 338 82 70	Authorized officer Lulu HENRIOD (Fax 338 8965) Facsimile No (41-22) 338 89 65 Telephone No +41 22 338 8767

572

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-112392- -00000-0000
Fec 2006-11-03 15 36 36 Dep. 2020 NUECREACIONES
Tra 11 PATENTEIYII
Eve 378 FASENACIONALI
Act 411 PRESENTACION _ _Folios 554_

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 84,888
FECHA : NOVIEMBRE 2 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GUSTAVO HOLLMANN G	CONSIGNACION	BANCO POPULAR	050-00110-6	50105009	02/11/2006	1,389,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-112392- -00000-0000
Fec. 2006-11-03 15:36:36 Dep. 2020 NUEVAS CREACIONES
Tra. 11 PATENTES Y II
Exe: 378 FASE NACIONAL
Act 411 PRESENTACION Folios: 564

Industria y Comercio
SUPERINTENDENCIA

573

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha Noviembre 03 de 2006

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-112392- -00000-0000
Fec: 2006-11-03 15:38:35 Dep: 2020 NUEGREACIONES
Tra: 11 PATENTEIYII
Eve: 378 FASENACIONALI
ACTA 11 PRESENTACION Folios: 554

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

7/11/06

① **SOLICITUD DE :**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☒ Capitulo I. ☐ Capitulo II.

② **SOLICITANTE (71)**	Nombre: **MILLENNIUM PHARMACEUTICALS, INC.** Dirección: 40 Landsdowne Street, Cambridge, MA 02139 Estados Unidos Nacionalidad o Domicilio: Cambridge, Massachussets Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail:	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
③ **REPRESENTANTE O APODERADO**	Nombre: LUIS PATIÑO LEYVA Dirección Cra. 11ª No. 94-76 – Of. 308 Teléfono: 6161948 Fax: 6163976 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☒ Cual _____ Número 2.930.616 TP 2698
④ **INVENTOR (ES) (72)**	Nombre: GHOSH, Shomir Dirección: 134 Sewall Avenue, Unit C, Nacionalidad o Domicilio: Brookline, Massachussetts 02446, Estados Unidos	

⑤ **PCT (86)**

Solicitud Internacional No. PCT/US2005/011643 Fecha: Abril 7 de 2005

Publicación Internacional No. WO 2005/100321 A1 Fecha Octubre 27 de 2005

⑥ **Titulo (54)** **ANTAGONISTAS DEL RECEPTOR DE PGD2 PARA EL TRATAMIENTO DE ENFERMEDADES INFLAMATORIAS.**

⑦ **Clasificación Internacional (51)** C07D 215/44 A61K 31/47 // A61P 37/00

⑧ **PRIORIDAD:**	(33) País de Origen	(32) Fecha	(31) Numero de Solicitud
SI ☒ NO ☐	Estados Unidos	Abril 7 de 2004	60/560,410

⑨ **Comprobante de pago No.** **Fecha**

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

Continuación nombre, dirección y domicilio de inventores:

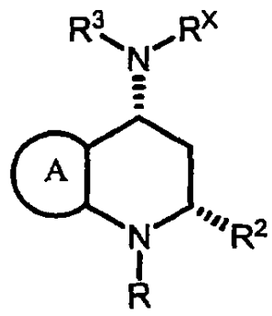
Nombre	Dirección	Domicilio
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REIVINDICACIONES

1 Un compuesto representado por la siguiente fórmula estructural:



o una sal farmacéuticamente aceptable del mismo, en la que.

El anillo A es un aromático monocíclico opcionalmente sustituido;

R es $-X_1-R^1$;

R^X es $-X_2-R^4$;

cada uno de X_1 y X_2 son independientemente $-S(O)_2-$, -C(O)-, o -C(O)NH-,

R^1 es A) un grupo aromático o heteroaromático que tiene 5-6 átomos en el anillo, sustituido con.

i) T^1-V-T-R^Y;

ii)T^1-V-T-M-R^Y, o

iii) V-R^9 en el que R^9 es un grupo carbocíclico o heterocíclico no aromático opcionalmente sustituido;

y en el que el grupo aromático o heteroaromático representado por R1 está opcionalmente sustituido también con 1-2 grupos seleccionados independientemente representados por R^Z; o

B) un grupo aromático o un grupo heteroaromático que tiene 5-6 átomos en el anillo, condensado con un anillo heterocíclico no aromático monocíclico o con un anillo monocíclico aromático en el que el anillo heterocíclico no aromático monocíclico o el anillo aromático está opcionalmente sustituido;

cada R^Z se selecciona independientemente entre halógeno, haloalquilo, R^o, $-OR^o$, -O(haloalquilo), $-SR^o$, $-NO_2$, -CN, $-N(R')_2$, $-NR'CO_2R^o$, $-NR'C(O)R^o$, -

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$NR'NR'C(O)R^o$, $-N(R')C(O)N(R')_2$, $-NR'NR'C(O)N(R')_2$, $-NR'NR'CO_2R^o$, $-C(O)C(O)R^o$, $-C(O)CH_2C(O)R^o$, $-CO_2R^o$, $-C(O)R^o$, $-C(O)N(R^o)_2$, $-OC(O)R^o$, $-OC(O)N(R^o)_2$, $-S(O)_2R^o$, $-SO_2N(R')_2$, $-S(O)R^o$, $-NR'SO_2N(R')_2$, $-NR'SO_2R^o$, $-C(=S)N(R')_2$ y $-C(=NH)-N(R')_2$,

cada R' es independientemente hidrógeno, alquilo, $-C(O)OR^o$, $S(O)_2R^o$ o $-C(O)R^o$;

cada R^o es independientemente hidrógeno o un grupo alquilo, grupo heterocíclico no aromático o grupo aromático y el alquilo, el grupo heterocíclico no aromático y el grupo aromático representados por R^o están opcionalmente sustituidos con uno o más grupos seleccionados independientemente representados por $R^{\#}$;

$R^{\#}$ es R^+, $-OR^+$, -O(haloalquilo), $-SR^+$, $-NO_2$, -CN, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$ o $-C(=NH)-N(R^+)_2$,

R^+ es -H, un grupo alquilo C_1-C_3, un grupo heteroarilo monocíclico, un grupo heterocíclico no aromático o un grupo fenilo opcionalmente sustituido con alquilo, haloalquilo, alcoxi, haloalcoxi, halo, -CN, $-NO_2$, amina, alquilamina o dialquilamina, o $-N(R^+)_2$ es un grupo heterocíclico no aromático, con la condición de que los grupos heterocíclicos no aromáticos representados por R^+ y $-N(R^+)_2$ que comprenden una amina de anillo secundario están opcionalmente acilados o alquilados,

R^Y es $-C(O)OR^5$, $-C(O)R^5$, $-OC(O)R^5$, $-C(O)N(R^5)_2$, $-NR^5C(O)R^5$, $-NR^5C(O)OR^5$, $-S(O)_2R^5$, $-S(O)_2COR^5$, $-S(O)_2N(R^5)_2$, $-NR^5S(O)_2R^5$, $-NR^5S(O)_2R^5$, $S(O)_2OR^5$, $-S(O)OR^5$, $-S(O)R^5$, $-SR^5$, $-C(O)NR^5S(O)_2R^5$, -CN, $-NR^5C(O)NR^5_2$, $-OC(O)NR^5_2$, $-NR^5_2$, $-OR^5$, un grupo heterocíclico no aromático opcionalmente sustituido o un grupo heteroarilo opcionalmente sustituido;

V es un enlace covalente, -O-, -C(O)-, -N(R')-, -S-, -S(O)-, $-C(O)NR^5$-, $-NR^5C(O)$-, $-S(O)_2NR^5$-, $-NR^5S(O)_2$- o $-S(O)_2$-,

REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
PATIÑO LEYVA LUIS
Apoderado(a) y/o Representante de
MILLENNIUM PHARMACEUTICALS, INC.

REFERENCIA	Radicación No.	6 112392
	Solicitud internacional	PCT/US2005/011643
	Fecha inicio fase nacional	07/11/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	14645

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. Debe aclarar el número de reivindicaciones, por cuanto la publicación internacional difiere del petitorio presentado en fase nacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 22 DIC. 2006
aalvarado