



No. 07-134572-00000-0000

Fecha: 2007-12-20 14:11:52 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 176

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT**

ENTRADA EN FASE NACIONAL

P2007/000206

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: MERCK & CO., INC.

Dirección: 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907

Nacionalidad o Domicilio: ESTADOS UNIDOS
Lugar de Constitución: ESTADOS UNIDOS

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

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10

Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79782747Bta
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/US2006/024740

Fecha Junio 26, 2006

Publicación Internacional No. WO 2007/002557

Fecha Enero 4, 2007

6

Título (54) AGONISTAS DEL RECEPTOR DE NIACINA, COMPOSICIONES QUE
CONTIENEN TALES COMPUESTOS Y PROCEDIMIENTOS PARA TRATAMIENTO

7

Clasificación Internacional (51) A61K 31/196, A61K 31/33, C07C 233/45, C07C
233/46, C07D 231/12, C07D 249/06, C07D 257/04, C07D 261/20, C07D 271/06, C07D
277/30, C07D 309/28, C07D 401/04, C07D 413/04, C07D 417/04, C07D 513/04

8

Prioridad

SI ☒ NO ☐

(33) País de Origen

US

(32) Fecha

Junio 28, 2005

(31) Número de Solicitud

60/694.711

9

Comprobante de pago No. 07-100.915

Fecha Diciembre 12, 2007

10

ANEXOS☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso. Adjunto copia simple ver Exp. N° 07.055.540

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 12 x 12.

☐

De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

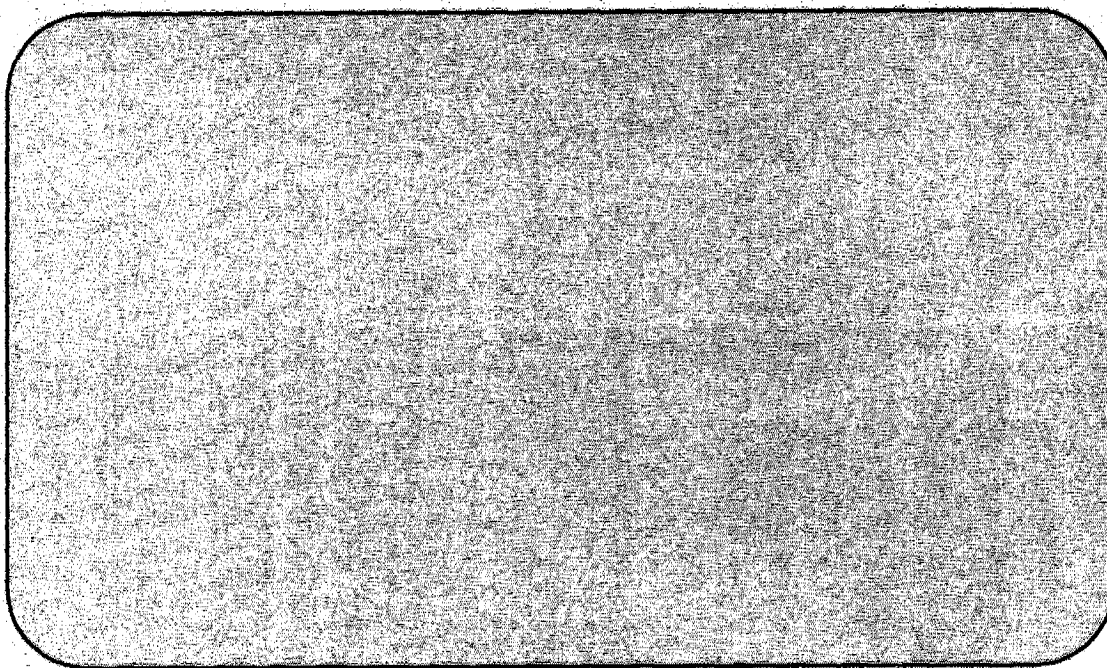
☐

De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEFIRMA: C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/US2006/024740

SUBHAREKHA RAGHAVAN,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

STEVEN L. COLLETTI,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

FA-XIANG DING,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Canadiense

HONG SHEN,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Canadiense

JAMES R. TATA,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

ASHLEY ROUSE LINS,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

ABIGAIL LEE SMENTON,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

WEICHUN CHEN,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

DARBY RYE SCHMIDT,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

GEORGE SCOTT TRIA,
126 East Lincoln Avenue,
Rahway, New Jersey 07065-0907
Estados Unidos de América
Nacionalidad: Estaunidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176009-2

RECIBO OFICIAL DE CAJA : 07 - 100.915
FECHA : DICIEMBRE 12 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-134572-00000-0000

Fecha: 2007-12-20 14:11:52 Dep: 2020 NULCACIONE
Lr: 11 PATENTEYII Lve: 379 FASENACIONALII
Act: 411 PRESENTACION Folios: 176

******* CONSIGNACION *******

DEPOSITANTE	Tipo Pago	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
OLARTE RAISNEY	CONSIGNACION	BANCO POPULAR	050-00130-6	57708169	11/13/2007	6,040,000.00

******* CONCEPTO *******

CANT. IDENTIFICADO	CONCEPTO	TOTAL CONCEPTO
1 0005-01-01	SOLICITUDES	
	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
	TOTAL :	482,000.00

ON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

LIBRO DE CADA RESOLUCION DE EXPEDIENTE No. _____

96

PODER ESPECIAL

Yo el abajo firmante, J. Ian Raisbeck, identificado con cédula de ciudadanía No. 79.376.996 de Bogotá, representante legal de OLARTE RAISBECK & FRIERI LTDA., sociedad limitada constituida en la República de Colombia, y obrando bajo las facultades otorgadas por el Poder General adjunto por la sociedad MERCK & Co. Inc., constituida de acuerdo a las leyes de New Jersey, Estados Unidos de América domiciliada en 126 East Lincoln Avenue, Rahway, NJ 07065-0907, Estados Unidos de América, nombro por el presente a los Doctores CARLOS R. OLARTE y/o ANA MARIA FRIERI DEL CASTILLO y/o JUAN GUILLERMO MOURE PEREZ y/o NATALIA CASTRO VELEZ, para que representen a la sociedad MERCK & Co. Inc., en la Republica de Colombia, en materia de patentes, y ante las autoridades ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y recon convenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses. Por el presente instrumento se revoca todo poder anteriormente otorgado por mi representada para realizar las gestiones antes mencionadas.

Dado y firmado el 28 de Mayo de 2007



J. IAN RAISBECK

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA
NOTARIA EL ANTERIOR ESCRITO INVENTARIO A:

27

FUE PRESENTADO POR EL PRESENTE
ANTE EL PODERADO POR VEINTISIETE
DE MAYO DE 2001

Con C.C.

Y ADEMAS DEL PRESENTE CONTENIDO
BUENAMENTE SE LE EXPLICA LA FIRMA QUE
ANTERIORMENTE FUE PUESTA POR EL

EL ENCARGADO:

[Signature]

HUY:

31 MAY 2001

HUELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPÚBLICA DE COLOMBIA

REPÚBLICA DE COLOMBIA



MARIA EUGENIA ROJAS DE URUETA
NOTARIA

Notaria 27 Bogotá DC

San Basilio
79376998
361357993

WK 4682369



ESCRITURA PUBLICA NUMERO -----
TRESCIENTOS DOCE (312).-----

En la ciudad de Bogotá, Distrito
Capital, República de Colombia, a los
Veintidos - - - (22) días del mes de
Marzo - - - - - de dos mil siete (2007),

ante mi, MARIA EUGENIA ROJAS DE URUETA - -

-----NOTARIA(O) VEINTISIETE (27) DEL
CIRCULO DE BOGOTA, - - - se otorgó la escritura pública que se
consigna en los siguientes términos:-----

CLASE(S) DE ACTO: PROTOCOLIZACION:-----

OLARTE RAISBECK & FRIERI LTDA-----

NIT: 830122870-6.-----

Compareció CARLOS REINALDO OLARTE GARCIA mayor edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.782.747, obrando en nombre y representación OLARTE RAISBECK & FRIERI LTDA, con número de identificación tributaria (NIT) 830122870-6 entidad legalmente constituida mediante escritura pública número mil ciento diecinueve (1119) de la notaría treinta y nueve (39) de Bogotá del diez (10) de junio de dos mil tres (2003), como lo acredita con el certificado de constitución y gerencia expedido por la Cámara de Comercio de Bogotá que presenta para su protocolización y declaró-----

PRIMERO.- Que presenta para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en cinco (5) folios autenticados, un poder con su traducción la cual es del siguiente tenor:-----

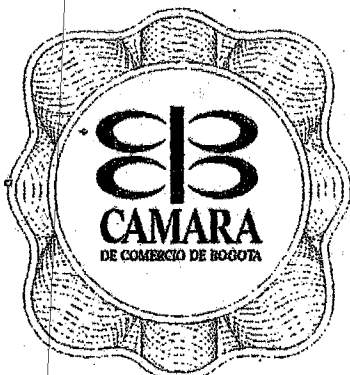
PODER GENERAL-----

NOTARIA VEINTISIETE
Maria Eugenia Rojas de Urueta

El suscrito, MERCK & CO., INC, domiciliado en 126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.-----

nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con Oficinas en el World Trade Center Torre A, Calle 100 No. 8A-37, piso 10, Bogotá D.C. nuestro representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia y la República del Ecuador, la Republica del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de Policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales, elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvencciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento allanarse a la pretensión, recibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeran conducentes al resguardo de nuestros intereses.-----

Firma: Donna L. Margiotto, Senior Manager, "Patent-----



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* 5 8 4 7 1 8 1 1 *

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE FEBRERO DE 2007

HORA 09:15:34

02C25020105804PCT0708

HOJA : 001

* * * * *

CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O INSCRIPCION DE DOCUMENTOS.

LA CAMARA DE COMERCIO DE BOGOTA, CON FUNDAMENTO EN LAS MATRICULAS E INSCRIPCIONES DEL REGISTRO MERCANTIL,

CERTIFICA :

NOMBRE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

N.I.T. : 830122870-6 ADMINISTRACION: BOGOTA PERSONAS JURIDICAS, REGIMEN COMUN.

DOMICILIO : BOGOTA D.C.

CERTIFICA :

MATRICULA NO. 01284164

CERTIFICA :

CONSTITUCION : QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX, SE CONSTITUYO LA SOCIEDAD COMERCIAL DENOMINADA: OR LEGAL LTDA

CERTIFICA :

QUE POR ESCRITURA PUBLICA NO. 0001328 DE NOTARIA 39 DE BOGOTA D.C. DEL 4 DE JULIO DE 2003 , INSCRITA EL 9 DE JULIO DE 2003 BAJO EL NUMERO 00887749 DEL LIBRO IX, LA SOCIEDAD CAMBIO SU NOMBRE DE : OR LEGAL LTDA POR EL DE : OLARTE RAISBECK & FRIERI LTDA PERO PARA TODOS LOS EFECTOS PODRA OPERAR BAJO EL NOMBRE OLARTERAISBECK

CERTIFICA :

REFORMAS:

ESCRITURA	FECHA	NOTARIA	CIUDAD	INSCRIPCION	FECHA
0001328	2003/07/04	00039	BOGOTA D.C.	00887749	2003/07/09

CERTIFICA :

VIGENCIA: QUE LA SOCIEDAD NO SE HALLA DISUELTA. DURACION HASTA EL 10 DE JUNIO DE 2103 .

CERTIFICA :

OBJETO SOCIAL : LA SOCIEDAD TENDRA POR OBJETO PRINCIPAL LA PRESTACION DE SERVICIOS DE ASESORIA EN EL AREA SOCIAL, TECNICA, COMERCIAL Y JURIDICA, DE PERSONAS NATURALES O JURIDICAS, NACIONALES O EXTRANJERAS, PUBLICAS O PRIVADAS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA : A. PRESTAR ASESORIA Y EJERCER LA REPRESENTACION JUDICIAL DE PERSONAS NATURALES O JURIDICAS ANTE LAS DIFERENTES JURISDICCIONES Y PARTICIPAR EN SU NOMBRE Y REPRESENTACION EN TRIBUNALES DE ARBITRAMIENTO, AMIGABLE COMPOSICION, CONCILIACION Y MEDIACION. B. CONFORMAR Y PARTICIPAR EN CENTROS DE ARBITRAJE Y CONCILIACION. C. CELEBRAR Y EJECUTAR TODAS LAS OPERACIONES DE CAMBIO Y COMERCIO EXTERIOR QUE REQUIERA EL BUEN FUNCIONAMIENTO DE LA COMPAÑIA ; D. ADQUIRIR, ENAJENAR, GRAVAR, DAR O TOMAR EN ARRENDAMIENTO TODA CLASE DE BIENES, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ;

NOTARIA VEINTISIETE
Maria Eugenia Rojas de Urueta

E. INTERVENIR COMO DEUDORA O ACREEDORA EN TODA CLASE DE OPERACIONES DE CREDITO, DANDO O RECIBIENDO LAS GARANTIAS DEL CASO CUANDO HAYA LUGAR A ELLAS ; F. CELEBRAR CON ESTABLECIMIENTOS DE CREDITO NACIONALES O EXTRANJEROS Y CON COMPAÑIAS ASEGURADORAS TODAS LAS OPERACIONES QUE SE RELACIONEN CON LOS NEGOCIOS Y BIENES SOCIALES. G. ABRIR, OPERAR Y CERRAR CUALQUIER TIPO DE CUENTAS BANCARIAS ; H. GIRAR, ACEPTAR, ENDOSAR, ASEGURAR, COBRAR, RECHAZAR, PROTESTAR, AVALAR GARANTIZAR Y NEGOCIAR EN GENERAL TODA CLASE DE INSTRUMENTOS NEGOCIABLES Y CUALQUIER OTRA CLASE DE TITULOS DE CREDITO ; I. ORGANIZAR, PROMOVER, FORMAR Y FINANCIAR SOCIEDADES O EMPRESAS NACIONALES O EXTRANJERAS QUE TIENDAN A FACILITAR, ENSANCHAR, O COMPLEMENTAR LOS NEGOCIOS SOCIALES DENTRO Y FUERA DEL PAIS Y SUSCRIBIR ACCIONES O CUOTAS EN ELLAS, Y EJERCER TODOS LOS DERECHOS Y OBLIGACIONES ECONOMICOS Y CORPORATIVOS QUE SURJAN DE DICHA PARTICIPACION. J. CREAR CONSORCIOS Y UNIONES TEMPORALES. K. SERVIR DE COMISIONISTA O INTERMEDIARIO COMERCIAL A TITULO DE CORRETAJE O A CUALQUIER OTRO TITULO ; L. SER CORRESPONSAL Y TENER CORRESPONSALES INTERNACIONALES ; M. EFECTUAR AVALUOS COMERCIALES DE TODA CLASE DE BIENES. N. ADQUIRIR Y CONSTRUIR TODA CLASE DE INSTALACIONES INDUSTRIALES O COMERCIALES COMO FABRICAS, TALLERES, ALMACENES DE DISTRIBUCION O VENTA ESTABLECIMIENTOS DE COMERCIO, ETC. O. DISTRIBUIR O VENDER TODO TIPO DE PRODUCTOS Y ABRIR Y ADMINISTRAR, DIRECTA O INDIRECTAMENTE, LOS ESTABLECIMIENTOS DE COMERCIO QUE SEAN NECESARIOS PARA ELLO. P. ENAJENAR, ARRENDAR, GRAVAR Y ADMINISTRAR EN GENERAL LOS BIENES QUE COMPONEN EL PATRIMONIO SOCIAL. Q. APORTAR SUS BIENES, EN TODO O EN PARTE, A OTRA U OTRAS SOCIEDADES A QUE LE CONVENGA VINCULARSE PARA UN MEJOR DESARROLLO DE SUS NEGOCIOS. R. TRANSIGIR, DESISTIR O SOMETER A DECISIONES ARBITRALES LAS CUESTIONES EN QUE TENGA INTERES FRENTE A TERCEROS. ; S. SOLICITAR, CONSEGUIR LOS REGISTROS RESPECTIVOS ANTE LA AUTORIDAD COMPETENTE Y EXPLOTAR EL DERECHO SOBRE MARCAS, NOMBRES COMERCIALES O CUALQUIER SIGNO DISTINTIVO, DIBUJOS, INSIGNIAS, PATENTES Y CUALQUIER OTRO DERECHO DE PROPIEDAD INDUSTRIAL O INTELECTUAL YA SEA A NOMBRE DE LA SOCIEDAD O DE UN TERCERO. T. HACER PUBLICACIONES Y COMUNICACIONES RELACIONADAS CON EL OBJETO SOCIAL. U. CELEBRAR Y EJECUTAR CON SU PROPIO NOMBRE Y POR CUENTA DE TERCEROS O EN PARTICIPACION CON ELLOS, ACTOS O CONTRATOS Y OPERACIONES EN GENERAL, TODO ACTO O CONTRATO QUE SEA NECESARIO O CONVENIENTE PARA CUMPLIR O FACILITAR LOS ACTOS Y OPERACIONES PREVISTAS EN LOS ESTATUTOS Y QUE DE MANERA DIRECTA SE RELACIONEN CON EL OBJETO SOCIAL, TAL COMO QUEDA DETERMINADO.

CERTIFICA :

CAPITAL Y SOCIOS : \$ 120,000,000.00 DIVIDIDO EN 12,000.00 CUOTAS CON VALOR NOMINAL DE \$ 10,000.00 CADA UNA, DISTRIBUIDO ASI :

- SOCIOS CAPITALISTA(S)

FRIERI DEL CASTILLO ANA MARIA	C.C. 00045483209
NO. CUOTAS: 4,000.00	VALOR:\$40,000,000.00
RAISBECK LLINAS JAMES IAN	C.C. 00079376996
NO. CUOTAS: 4,000.00	VALOR:\$40,000,000.00
OLARTE GARCIA CARLOS REINALDO	C.C. 00079782747
NO. CUOTAS: 4,000.00	VALOR:\$40,000,000.00
TOTALES	
NO. CUOTAS: 12,000.00	VALOR :\$120,000,000.00

CERTIFICA :

REPRESENTACION LEGAL : LA SOCIEDAD TENDRA UN GERENTE GENERAL, EL CUAL TENDRA UN PRIMER SUPLENTE Y UN SEGUNDO SUPLENTE QUE LO

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* 5 6 4 7 1 8 1 2 *

CAMARA DE COMERCIO DE BOGOTA

SEDE NORTE

1 DE FEBRERO DE 2007

HORA 09:15:35

02C25020105804PCT0708

HOJA : 002

REEMPLAZARA EN SUS FALTAS ABSOLUTAS, TEMPORALES O ACCIDENTALES, Y CUYA DESIGNACION Y REMOCION CORRESPONDERA TAMBIEN A LA JUNTA DE SOCIOS.

CERTIFICA :

** NOMBRAMIENTOS : **

QUE POR ESCRITURA PUBLICA NO. 0001119 DE NOTARIA 39 DE BOGOTA D.C. DEL 10 DE JUNIO DE 2003 , INSCRITA EL 25 DE JUNIO DE 2003 BAJO EL NUMERO 00885810 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
GERENTE	
OLARTE GARCIA CARLOS REINALDO	C.C.00079782747
PRIMER SUPLENTE DEL GERENTE	
RAISBECK LLINAS JAMES IAN	C.C.00079376996
SEGUNDO SUPLENTE DEL GERENTE	
FRIERI DEL CASTILLO ANA MARIA	C.C.00045483209

CERTIFICA :

FACULTADES DEL REPRESENTANTE LEGAL : EL GERENTE GENERAL ES EL REPRESENTANTE LEGAL DE LA SOCIEDAD, Y EN CASO DE FALTA TEMPORAL ABSOLUTA HARA SUS VECES EL PRIMER SUPLENTE O EN SU DEFECTO EL SEGUNDO SUPLENTE, TAMBIEN ELEGIDOS POR LA JUNTA DE SOCIOS. EL GERENTE REPRESENTARA Y COMPROMETERA A LA SOCIEDAD FRENTE A TERCEROS, SEAN PERSONAS O ENTIDADES PARTICULARES, OFICIALES O JUDICIALES. ASI MISMO, PODRA CELEBRAR EN SU NOMBRE CONTRATO DE ARRENDAMIENTO COMO ARRENDADOR O ARRENDATARIO. CONSTITUIR APODERADOS DE LA SOCIEDAD, DESISTIR, INTERPONER TODA CLASE DE RECURSOS RECIBIR DINERO EN MUTUO, HACER DEPOSITOS BANCARIOS O DE CUALQUIER OTRA INDOLE, FIRMAR TITULOS VALORES Y NEGOCIARLOS, TENERLOS, CONTRATARLOS, PAGARLOS, ENDOSARLOS, DESCARGARLOS, CELEBRAR CONTRATOS COMERCIALES, EJECUTAR LOS ACUERDOS DE LA JUNTA DE SOCIOS Y CONVOCARLA A REUNIONES ORDINARIAS O EXTRAORDINARIAS, SUSCRIBIR CONTRATOS LABORALES A NOMBRE DE LA SOCIEDAD, Y EN GENERAL TODAS LAS GESTIONES QUE OBEDEZCAN A LA NATURALEZA DE SU ENCARGO Y QUE SE RELACIONEN DIRECTAMENTE CON EL GIRO ORDINARIO DE LOS NEGOCIOS SOCIALES. EL GERENTE REQUERIRA APROBACION DE LA JUNTA DE SOCIOS PARA CELEBRAR ACTOS CUYA CUANTIA SEA O EXCEDA LA SUMA DE DIEZ MILLONES DE PESOS (\$10,000,000) MONEDA CORRIENTE.

CERTIFICA :

** REVISOR FISCAL: **

QUE POR ACTA NO. 0000006 DE JUNTA DE SOCIOS DEL 5 DE MARZO DE 2004 , INSCRITA EL 8 DE JULIO DE 2004 BAJO EL NUMERO 00942232 DEL LIBRO IX , FUE(RON) NOMBRADO(S):

NOMBRE	IDENTIFICACION
REVISOR FISCAL	
LACHE NUÑEZ JOSE LUCIO	C.C.00006763005

CERTIFICA :

DIRECCION DE NOTIFICACION JUDICIAL : CLL 100 NO 8A-37 P 10 W.T.C.

NOTARIA 39 DE BOGOTA
Maria Eugenia Rojas de Urzeta

T A

MUNICIPIO : BOGOTA D.C.
DIRECCION COMERCIAL : CLL 100 NO 8A-37 P 10 W.T.C. T A
MUNICIPIO : BOGOTA D.C.
E-MAIL : ELIZABETH.BARBOSA@OLARTERAISBECK.COM

CERTIFICA :

QUE LA SOCIEDAD TIENE MATRICULADOS LOS SIGUIENTES ESTABLECIMIENTOS :

NOMBRE : OR LEGAL LIMITADA

MATRICULA NO. 01284255

RENOVACION DE LA MATRICULA : EL 27 DE MARZO DE 2006

ULTIMO AÑO RENOVADO : 2006

CERTIFICA :

DE CONFORMIDAD CON LO ESTABLECIDO POR LA LEY 962 DE 2005, LOS ACTOS DE REGISTRO AQUI CERTIFICADOS QUEDAN EN FIRME CINCO (5) DIAS HABILES DESPUES DE LA FECHA DE INSCRIPCION, SIEMPRE QUE NO SEAN OBJETO DE RECURSOS EN LA VIA GUBERNATIVA.

INFORMACION COMPLEMENTARIA

LOS SIGUIENTES DATOS SOBRE RIT Y PLANEACION DISTRITAL SON INFORMATIVOS

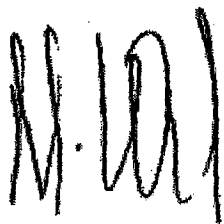
CONTRIBUYENTE INSCRITO EN EL REGISTRO RIT DE LA DIRECCION DISTRITAL DE IMPUESTOS, FECHA DE INSCRIPCION 2003/06/24

FECHA DE ENVIO DE INFORMACION A PLANEACION DISTRITAL: 10 DE JULIO DE 2004

EL SECRETARIO DE LA CAMARA DE COMERCIO,

VALOR : \$ 3,000.00

DE CONFORMIDAD CON EL DECRETO 2150 DE 1995 Y LA AUTORIZACION IMPARTIDA POR LA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, MEDIANTE EL OFICIO DEL 18 DE NOVIEMBRE DE 1996, LA FIRMA MECANICA QUE APARECE A CONTINUACION TIENE PLENA VALIDEZ PARA TODOS LOS EFECTOS LEGALES.



(Firmado)

573217

Apostilla adjunta:

(Convention de La Haye du 5 octobre 1961)

- NOMBRE** NO SE ASUME
RESPONSABILIDAD DEL TEXTO
- FECHA** 2007 MAR 1 A 8:49
HORA 2103
- OFICINA** JEFE DE REGALAZACIONES Y
BENEFICIARIOS D.C.
- SERIAL** W J 1056

Matia Eugenia Rojas de Queta

Traductor Oficial
JORGE E. SIERRA REYES
teléfono 376 - 1993 Minjust

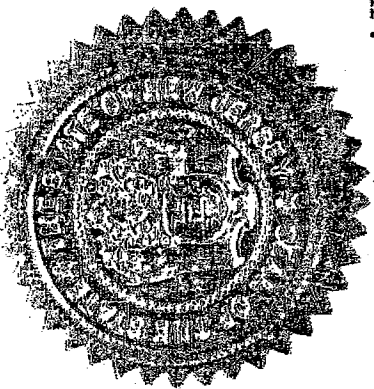
APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
BARBARA ANN COZZI
3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
BARBARA ANN COZZI, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 6TH DAY OF FEBRUARY 2007
7. BY: Bradley Abelow, NEW JERSEY TREASURER
8. NO. A282565
9. SEAL/STAMP:
10. SIGNATURE



Bradley Abelow

2/1

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

General Power

The undersigned,

domiciled in

126 EAST LINCOLN AVENUE, RAHWAY, NJ 07065-0907, USA.

hereby appoint Olarte Raisbeck & Frieri Ltda. with offices in the World Trade Center - Torre A, Calle 100 No. 8A-37, Piso 10, Bogota D.C., legal representatives with authority to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the authority to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

El suscrito,
MERCK & CO., INC.

domiciliado en

nombramos por el presente a Olarte Raisbeck & Frieri Ltda. con oficinas en el World Trade Center - Torre A, Calle 100 No. 8A-37, Piso 10, Bogotá D.C., nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

Signature/Firma: X

Donna L. Margiotto
Donna L. Margiotto, Senior Manager, Patent Administration

Date/Fecha:

February 1, 2007

City/Country/Ciudad,País: Rahway, NJ, USA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
José Luis Londoño
Felipe Mendoza
Simón Salinas
Alexander Agudelo
Camilo A. Rodríguez

Of Counsel
Guillermo Chahin
Graciela Melo
Jacqueline Chaparro
Cruz E. de Moncaleano

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MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

Certificación Notarial

On this date, February 1, 2007
The undersigned Notary Public certifies:

En esta fecha,
el Notario Público suscrito certifica:

1. That

Donna L. Margiotto

of legal age and domiciled in

126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA.

signed the foregoing document.

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

2. That the grantor has executed the foregoing
document as Senior Manager, Patent
Administration
of MERCK & CO., INC.

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

de

3. That MERCK & CO., INC.,
having its principal place of business located in
New Jersey, USA.

is duly incorporated, is currently in existence, and
that the purposes for which the General Power is
granted are within the scope of its corporate
purposes.

4. Que

con sede principal ubicada en

está legalmente constituida, que tiene existencia
legal vigente y que los propósitos para los cuales
se otorga el poder se encuentra dentro de los que
comprenden su objeto social.

4. That the grantor has the authority to execute the
General Power and that his/her representation is
legal.

4. Que el otorgante tiene la representación para
suscribir el poder, y que ésta es legítima.

5. The foundation for my certifications contained in
points 2, 3 and 4 was the exhibition of the following
authentic document(s):

5. El fundamento de mis certificaciones
contenidas en los puntos 2, 3 y 4 fue la exhibición
de los (del) siguiente(s) documento(s) auténtico(s):

Corporate Resolution No. 5 – Patent
Matters, amended October 24, 2006 by the
Board of Directors of Merck & Co., Inc. at
a meeting held on October 24, 2006.

NOTARY PUBLIC (Signature): X

Barbara Ann Cozzi

BARBARA ANN COZZI
Notary Public of New Jersey
My Commission Expires Nov. 30, 2008

NOTARIA VEINTISIETE
María Eugenia Rojas de Urueña

WK

4682370



Aministration. -----

Fecha febrero 2007 -----

Ciudad País: Rahway, NJ, USA-----

CERTIFICACION NOTARIAL -----

En esta fecha, -----

El notario público suscrito certifica: -----

1. Que Donna L. Margiotto mayor de edad, y domiciliado 126 East Lincoln Avenue, Rahway, NJ 07065-0907, USA. Suscribió el documento que antecede. -----

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

4. Que -----

con sede principal ubicada en -----

está legalmente constituida, que tiene existencia legal vigente que los propósitos para los cuales se otorga el poder se encuentren dentro de los que comprenden su objeto social.-----

4. Que el otorgante tiene la representación para suscribir poder, y que ésta es legítima. -----

5. El fundamento de mis certificaciones contenidas en los puntos 2,3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s): -----

NOTARY PUBLIC (fdo. ilegible) BARBARA ANN COZZI Notary Public Of New Jersey My Comisión Expires Nov. 30, 2006 -----

TRADUCCION OFICIAL DE UN DOCUMENTO QUE ESTA ORIGINALMENTE EN INGLES -----

El documento de Poder de Merck & Co., Inc. a Olarte Raisbeck & Frieri Ltda. lleva una certificación notarial con el siguiente sello en inglés:-----

(Firmado) -----

Sello: " Barbara Ann Cozzi, Notario Público de New Jersey- Mi comisión vence el 30 de Noviembre de 2008".-----

APOSTILLA



(Convention de La Haye Du 5 octobre 1961)

1. País: Estados Unidos de América -----

El presenté documento público -----

2. Ha sido firmado por: Barbara Ann Cozzi-----

3. Actuando en calidad de: Notario Público de New Jersey.-----

4 Lleva el sello/ estampilla de: Barbara Ann Cozzi, notario -----

Certificado

5. En: Trenton, New Jersey} -----

6) El 6 de February de 2007 -----

7. Por: Bradley Abelow, Tesorero de New Jesery. -----

8 Bajo el No. A282565 -----

9. Sello/ estampilla: El Estado de New Jesery- Sello del Estado--

10. Firma: Bradley Abelow -----

Certificación: -----

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Merck & Co. Inc.- Apost"-----

Fecha: 15 de Febrero de 2007.-----

Traductor: Jorge Enrique Sierra Reyes.- -----

Licencia No. 376 de 1993, del Ministerio de Justicia.- -----

Dirección Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia. ---

Teléfono: (57-1) 2182308, (57-1) 6232925.- -----

E-mail: treseser1@yahoo.com 9508- -----

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dicho documentos al protocolo de ésta notaría para que de su tenor se expidan las copias que más adelante se soliciten -----

El(los) compareciente(s) hace(n) constar que han verificado cuidadosamente sus nombres completos, estado(s) civil(es), los número(s) de sus documentos de identidad; Declara(n) que todas las informaciones consignadas en el presente instrumento son correctas y, en consecuencia, asumen la responsabilidad que

WK 4682371



se derive de cualquier inexactitud en los mismos. Conocen la ley y saben que el Notario responde de la regularidad formal de los instrumentos que autoriza, pero no de la veracidad de las declaraciones de los interesados.

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. A los otorgantes se les advirtió finalmente que una vez firmado el presente instrumento, La(el) Notaria(o) no acepta correcciones o modificaciones sino en la forma y casos previstos por la Ley. ---Se utilizaron las hojas de papel Notarial Nos: WK 4682369, WK 4682370, WK 4682371.-----

DERECHOS LEGALES: \$ 38.110.00 ✓

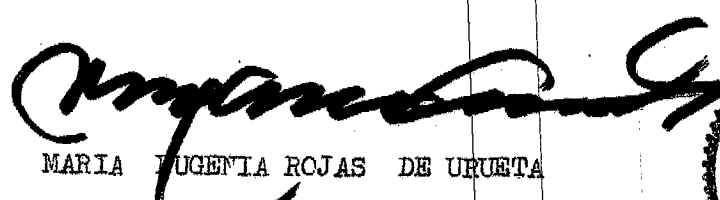
RESOLUCION 7880 DE 2006

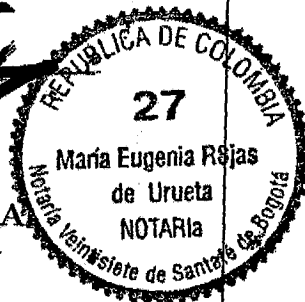
IVA \$ 14.642.00 ✓

CARLOS REINALDO OLARTE GARCIA

C.C.No. 79'782.747 Bogotá

TEL: 601-7700


MARIA EUGENIA ROJAS DE URUETA
NOTARIA(O) VENTISIETE (27) DE BOGOTA

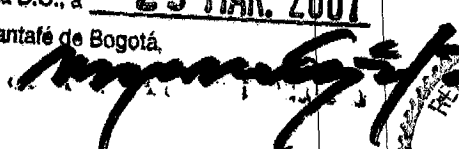


redb.

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fotocopia de la Escritura Publica No. 312
de fecha 22 de Marzo de 2007
tomada de su original que expido en
Ocho (8) hojas útiles de papel
común autorizado (Decreto 1343 de 1970) con destino a

Interesado

Dado en Santafé de Bogotá D.C., a 29 MAR. 2007
El Notario Veintisiete de Santafé de Bogotá.





ESTADO EN BLANCO

PATENT COOPERATION TREATY

WO 2007/002557
PCT/US2006/024740

From the INTERNATIONAL BUREAU

JAN 23 2007

PCT

RICHARD C. BILLUPS
JAN 24 2007
PATENT DEPT.NOTIFICATION CONCERNING
AVAILABILITY OF THE PUBLICATION
OF THE INTERNATIONAL APPLICATIONMERCK & CO., INC.
126 East Lincoln Avenue
Rahway, New Jersey 07065-0907
ETATS-UNIS D'AMERIQUEPAT. REG. COORD.
DOCKET
ATTORNEY
MAINTENANCECASE REFERENCE CLERK
OTHER IMPORTANT NOTICE

Date of mailing (day/month/year)

04 January 2007 (04.01.2007)

Applicant's or agent's file reference

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International application No.

PCT/US2006/024740

International filing date (day/month/year)

26 June 2006 (26.06.2006)

Priority date (day/month/year)

28 June 2005 (28.06.2005)

Applicant

MERCK & CO., INC. et al

The applicant is hereby notified that the International Bureau:

has published the above-indicated international application on 04 January 2007 (04.01.2007) under
No. WO 2007/002557has republished the above-indicated international application on under
No. WOFor an explanation as to the reason for this republication of the international application, reference is made to INID codes (15), (48)
or (88) (as the case may be) on the front page of the published international application.A copy of the international application is available for viewing and downloading on WIPO's website at the following address:
<http://www.wipo.int/pctdb> (under "Query" enter the PCT or WO number).The applicant may also request a paper copy of the published international application from the International Bureau by submitting a written
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2007 JAN 23 AM 10:34

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Nora Lindner

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Weichun [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). SCHMIDT, Darby Rye [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). TRIA, George Scott [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): RAGHAVAN, Subharekha [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). COLLETTI, Steven, L. [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). DING, Fa-Xiang [CN/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). SHEN, Hong [CN/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). TATA, James, R. [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). LINS, Ashley Rouse [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). SMENTON, Abigail Lee [US/US]; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US). CHEN,

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (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, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

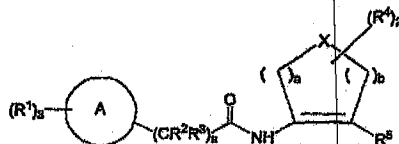
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Published:

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

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

(54) Title: NIACIN RECEPTOR AGONISTS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT



(I)

(57) Abstract: The present invention encompasses compounds of Formula (I): as well as pharmaceutically acceptable salts and hydrates thereof, that are useful for treating atherosclerosis, dyslipidemias and the like. Pharmaceutical compositions and methods of use are also included.

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NIACIN RECEPTOR AGONISTS, COMPOSITIONS CONTAINING SUCH COMPOUNDS AND METHODS OF TREATMENT

5 BACKGROUND OF THE INVENTION

The present invention relates to cycloalkene compounds, their derivatives, compositions containing such compounds and methods of treatment or prevention in a mammal relating to dyslipidemias. Dyslipidemia is a condition wherein serum lipids are abnormal. Elevated cholesterol and low levels of high density lipoprotein (HDL) are independent risk factors for atherosclerosis associated with a greater-than-normal risk of atherosclerosis and cardiovascular disease. Factors known to affect serum cholesterol include genetic predisposition, diet, body weight, degree of physical activity, age and gender. While cholesterol in normal amounts is a vital building block for cell membranes and essential organic molecules such as steroids and bile acids, cholesterol in excess is known to contribute to cardiovascular disease. For example, cholesterol, through its relationship with foam cells, is a primary component of plaque which collects in coronary arteries, resulting in the cardiovascular disease termed atherosclerosis.

Traditional therapies for reducing cholesterol include medications such as statins (which reduce production of cholesterol by the body). More recently, the value of nutrition and nutritional supplements in reducing blood cholesterol has received significant attention. For example, dietary compounds such as soluble fiber, vitamin E, soy, garlic, omega-3 fatty acids, and niacin have all received significant attention and research funding.

Niacin or nicotinic acid (pyridine-3-carboxylic acid) is a drug that reduces coronary events in clinical trials. It is commonly known for its effect in elevating serum levels of high density lipoproteins (HDL). Importantly, niacin also has a beneficial effect on other lipid profiles. Specifically, it reduces low density lipoproteins (LDL), very low density lipoproteins (VLDL), and triglycerides (TG). However, the clinical use of nicotinic acid is limited by a number of adverse side-effects including cutaneous vasodilation, sometimes called flushing.

Despite the attention focused on traditional and alternative means for controlling serum cholesterol, serum triglycerides, and the like, a significant portion of the population has total cholesterol levels greater than about 200 mg/dL, and are thus candidates for dyslipidemia therapy. There thus remains a need in the art for compounds, compositions and alternative methods of reducing total cholesterol, serum triglycerides, and the like, and raising HDL.

The present invention relates to compounds that have been discovered to have effects in modifying serum lipid levels.

The invention thus provides compositions for effecting reduction in total cholesterol and triglyceride concentrations and raising HDL, in accordance with the methods described.

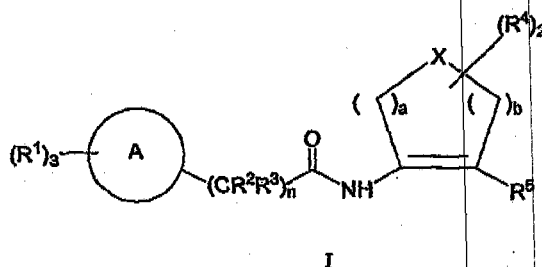
Consequently one object of the present invention is to provide a nicotinic acid receptor agonist that can be used to treat dyslipidemias, atherosclerosis, diabetes, metabolic syndrome and related conditions while minimizing the adverse effects that are associated with niacin treatment.

Yet another object is to provide a pharmaceutical composition for oral use.

These and other objects will be apparent from the description provided herein.

SUMMARY OF THE INVENTION

A compound represented by formula I:



or a pharmaceutically acceptable salt or solvate thereof is disclosed wherein:

X represents CH₂, O, S, S(O), SO₂ or NH, such that when X represents NH, the nitrogen atom may be optionally substituted with R⁶, C(O)R⁶, or SO₂R⁶, wherein:

R⁶ represents C₁₋₃alkyl optionally substituted with 1-3 groups, 0-3 of which are halo, and 0-1 of which are selected from the group consisting of: OC₁₋₃alkyl, OH, NH₂, NHC₁₋₃alkyl, N(C₁₋₃alkyl)₂, CN, Hetcy, Aryl and HAR,

said Aryl and HAR being further optionally substituted with 1-3 groups, 1-3 of which are halo, and 0-1 of which are selected from the group consisting of: OH, NH₂, C₁₋₃alkyl, C₁₋₃alkoxy, haloC₁₋₃alkyl and haloC₁₋₃alkoxy groups;

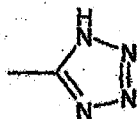
a and b are each integers 1, 2 or 3, such that the sum of a and b is 2, 3 or 4;

ring A represents a 6-10 membered aryl, a 5-13 membered heteroaryl or a partially aromatic heterocyclic group, said heteroaryl and partially aromatic heterocyclic group containing at least one heteroatom selected from O, S, S(O), S(O)₂ and N, and optionally containing 1 other heteroatom selected from O and S, and optionally containing 1-3 additional N atoms, with up to 5 heteroatoms being present;

each R² and R³ is independently H, C₁₋₃alkyl, haloC₁₋₃alkyl, OC₁₋₃alkyl, haloC₁₋₃alkoxy, OH or F;

n represents an integer of from 1 to 5;

each R⁴ is H or is independently selected from halo and R⁶;



R^5 represents $-CO_2H$,

or

$-C(O)NHSO_2R^6$ wherein R^6

represents C_{1-4} alkyl or phenyl, said C_{1-4} alkyl and phenyl each being optionally substituted with 1-3 groups, 1-3 of which are selected from halo and C_{1-3} alkyl, and 1-2 of which are selected from the group consisting of: OC_{1-3} alkyl, $haloC_{1-3}$ alkyl, $haloC_{1-3}$ alkoxy, OH, NH_2 and NHC_{1-3} alkyl;

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and each R^1 is H or is independently selected from the group consisting of:

a) halo, OH, CO_2H , CN, NH_2 , $S(O)_{0-2}R^6$, $C(O)R^6$, $OC(O)R^6$ and CO_2R^6 , wherein R^6 is as previously defined;

10 b) C_{1-6} alkyl and OC_{1-6} alkyl, said C_{1-6} alkyl and alkyl portion of OC_{1-6} alkyl being optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, CO_2H , CO_2C_{1-4} alkyl, $CO_2C_{1-4}haloalkyl$, OCO_2C_{1-4} alkyl, NH_2 , NHC_{1-4} alkyl, $N(C_{1-4}alkyl)_2$, Hetcy and CN;

c) NHC_{1-4} alkyl and $N(C_{1-4}alkyl)_2$, the alkyl portions of which are optionally substituted as set forth in (b) above;

15 d) $C(O)NH_2$, $C(O)NHC_{1-4}alkyl$, $C(O)N(C_{1-4}alkyl)_2$, $C(O)Hetcy$, $C(O)NHOC_{1-4}alkyl$ and $C(O)N(C_{1-4}alkyl)(OC_{1-4}alkyl)$, the alkyl portions of which are optionally substituted as set forth in (b) above;

e) $NR'C(O)R''$, $NR'SO_2R''$, $NR'CO_2R''$ and $NR'C(O)NR''R'''$ wherein:

R' represents H, C_{1-3} alkyl or $haloC_{1-3}$ alkyl,

20 R'' represents (a) C_{1-6} alkyl optionally substituted with 1-4 groups, 0-4 of which are halo, and 0-1 of which are selected from the group consisting of: OC_{1-6} alkyl, OH, CO_2H , CO_2C_{1-4} alkyl, $CO_2C_{1-4}haloalkyl$, NH_2 , $NHC_{1-4}alkyl$, $N(C_{1-4}alkyl)_2$, CN, Hetcy, Aryl and HAR,

said Hetcy, Aryl and HAR being further optionally substituted with 1-3 halo, C_{1-4} alkyl, C_{1-4} alkoxy, $haloC_{1-4}alkyl$ or $haloC_{1-4}alkoxy$ groups;

25 (b) Hetcy, Aryl or HAR, each being optionally substituted with 1-3 members selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, $haloC_{1-4}alkyl$ and $haloC_{1-4}alkoxy$ groups;

and R''' representing H or R'' ;

30 f) phenyl or a 5-6 membered heteroaryl or a Hetcy group attached at any available ring atom and each being optionally substituted with 1-3 groups, 1-3 of which are selected from halo, C_{1-3} alkyl and $haloC_{1-3}$ alkyl groups, and 1-2 of which are selected from OC_{1-3} alkyl and $haloOC_{1-3}$ alkyl groups, and 0-1 of which is selected from the group consisting of:

i) OH; CO_2H ; CN; NH_2 and $S(O)_{0-2}R^6$ wherein R^6 is as described above;

ii) $\text{NHC}_{1-4}\text{alkyl}$ and $\text{N}(\text{C}_{1-4}\text{alkyl})_2$, the alkyl portions of which are optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH , CO_2H , $\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $\text{CO}_2\text{C}_{1-4}\text{haloalkyl}$, NH_2 , $\text{NHC}_{1-4}\text{alkyl}$, $\text{N}(\text{C}_{1-4}\text{alkyl})_2$ and CN ;

iii) $\text{C}(\text{O})\text{NH}_2$, $\text{C}(\text{O})\text{NHC}_{1-4}\text{alkyl}$, $\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})_2$, $\text{C}(\text{O})\text{NHOC}_{1-4}\text{alkyl}$ and $\text{C}(\text{O})\text{N}(\text{C}_{1-4}\text{alkyl})(\text{OC}_{1-4}\text{alkyl})$, the alkyl portions of which are optionally substituted as set forth in b) above; and

iv) $\text{NR}'\text{C}(\text{O})\text{R}''$, $\text{NR}'\text{SO}_2\text{R}''$, $\text{NR}'\text{CO}_2\text{R}''$ and $\text{NR}'\text{C}(\text{O})\text{NR}''\text{R}'''$ wherein R' , R'' and R''' are as described above.

10 DETAILED DESCRIPTION OF THE INVENTION

The invention is described herein in detail using the terms defined below unless otherwise specified.

"Alkyl", as well as other groups having the prefix "alk", such as alkoxy, alkanoyl and the like, means carbon chains which may be linear, branched, or cyclic, or combinations thereof, containing the indicated number of carbon atoms. If no number is specified, 1-6 carbon atoms are intended for linear and 3-7 carbon atoms for branched alkyl groups. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and the like. Cycloalkyl is a subset of alkyl; if no number of atoms is specified, 3-7 carbon atoms are intended, forming 1-3 carbocyclic rings that are fused. "Cycloalkyl" also includes monocyclic rings fused to an aryl group in which the point of attachment is on the non-aromatic portion. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, decahydronaphthyl, indanyl and the like. Haloalkoxy and haloalkyl are used interchangeably and refer to halo substituted alkyl groups linked through the oxygen atom. Haloalkyl and haloalkoxy include mono- substituted as well as multiple substituted alkyl and alkoxy groups, up to perhalo substituted alkyl and alkoxy. For example, trifluoromethyl and trifluoromethoxy are included.

"Alkenyl" means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-butenyl, and the like.

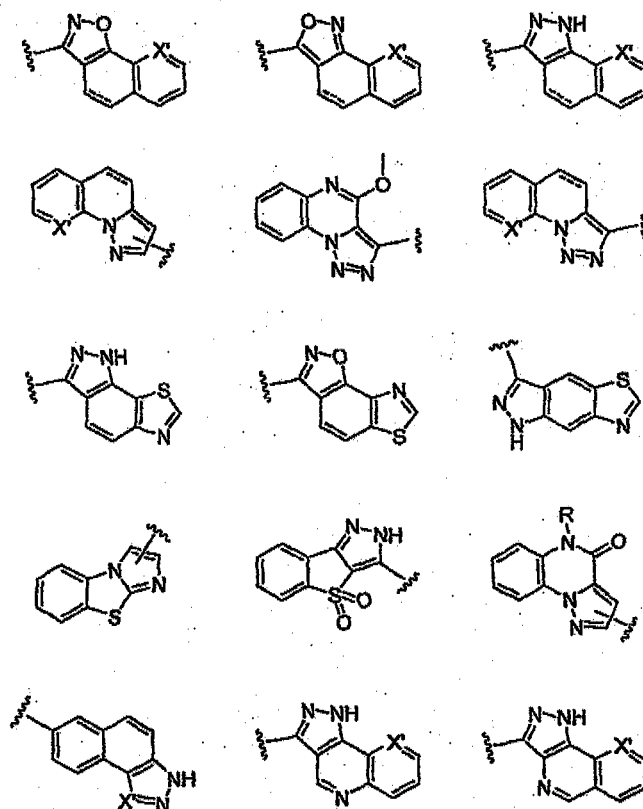
"Alkynyl" means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

"Aryl" (Ar) means mono- and bicyclic aromatic rings containing 6-10 carbon atoms. Examples of aryl include phenyl, naphthyl, indenyl and the like.

"Heteroaryl" (HAR) unless otherwise specified, means mono-, bicyclic and tricyclic aromatic ring systems containing at least one heteroatom selected from O, S, S(O), SO_2 and N, with each ring containing 5 to 6 atoms. HAR groups may contain from 5-14, preferably 5-13 atoms. Examples include, but are not limited to, pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl,

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thiadiazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzopyrazolyl, benzotriazolyl, furo(2,3-b)pyridyl, benzoxazinyl, tetrahydrohydroquinolyl, tetrahydroisoquinolyl, quinolyl, isoquinolyl, indolyl, dihydroindolyl, quinoxalyl, quinazolyl, naphthyridinyl, pteridinyl, 2,3-dihydrofuro(2,3-b)pyridyl and the like. Heteroaryl also includes aromatic carbocyclic or heterocyclic groups fused to heterocycles that are non-aromatic or partially aromatic, and optionally containing a carbonyl. Examples of additional heteroaryl groups include indolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, and aromatic heterocyclic groups fused to cycloalkyl rings. Examples also include the following:



--- is a single or double bond
 X' = CH or N
 R = H or CH₃

Heteroaryl also includes such groups in charged form, e.g., pyridinium.

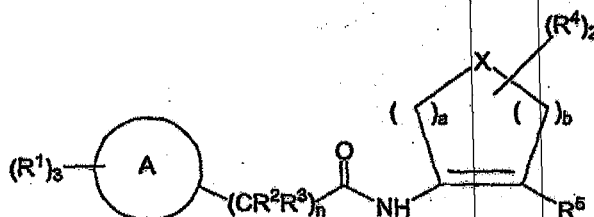
"Heterocyclyl" (Hetcy) unless otherwise specified, means mono- and bicyclic saturated and partially saturated rings and ring systems containing at least one heteroatom selected from N, S and O, each of said ring having from 3 to 10 atoms in which the point of attachment may be carbon or nitrogen. Examples of "heterocyclyl" include, but are not limited to, azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, tetrahydrofuranyl, 1,4-dioxanyl, morpholinyl, thiomorpholinyl,

tetrahydrothienyl and the like. Heterocycles can also exist in tautomeric forms, e.g., 2- and 4-pyridones. Heterocycles moreover includes such moieties in charged form, e.g., piperidinium.

"Halogen" (Halo) includes fluorine, chlorine, bromine and iodine.

The phrase "in the absence of substantial flushing" refers to the side effect that is often seen when nicotinic acid is administered in therapeutic amounts. The flushing effect of nicotinic acid usually becomes less frequent and less severe as the patient develops tolerance to the drug at therapeutic doses, but the flushing effect still occurs to some extent and can be transient. Thus, "in the absence of substantial flushing" refers to the reduced severity of flushing when it occurs, or fewer flushing events than would otherwise occur. Preferably, the incidence of flushing (relative to niacin) is reduced by at least about a third, more preferably the incidence is reduced by half, and most preferably, the flushing incidence is reduced by about two thirds or more. Likewise, the severity (relative to niacin) is preferably reduced by at least about a third, more preferably by at least half, and most preferably by at least about two thirds. Clearly a one hundred percent reduction in flushing incidence and severity is most preferable, but is not required.

One aspect of the invention relates to a compound represented by formula I:



I

or a pharmaceutically acceptable salt or solvate thereof is disclosed wherein:

X represents CH₂, O, S, S(O), SO₂ or NH, such that when X represents NH, the nitrogen atom may be optionally substituted with R⁶, C(O)R⁶, or SO₂R⁶, wherein:

R⁶ represents C₁₋₃alkyl optionally substituted with 1-3 groups, 0-3 of which are halo, and 0-1 of which are selected from the group consisting of: OC₁₋₃alkyl, OH, NH₂, NHC₁₋₃alkyl, N(C₁₋₃alkyl)₂, CN, Hetcy, Aryl and HAR,

said Aryl and HAR being further optionally substituted with 1-3 groups, 1-3 of which are halo, and 0-1 of which are selected from the group consisting of: OH, NH₂, C₁₋₃alkyl, C₁₋₃alkoxy, haloC₁₋₃alkyl and haloC₁₋₃alkoxy groups;

a and b are each integers 1, 2 or 3, such that the sum of a and b is 2, 3 or 4;

ring A represents a 6-10 membered aryl, a 5-13 membered heteroaryl or a partially aromatic heterocyclic group, said heteroaryl and partially aromatic heterocyclic group containing at least one heteroatom selected from O, S, S(O), S(O)₂ and N, and optionally containing 1 other heteroatom

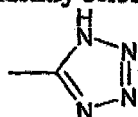
selected from O and S, and optionally containing 1-3 additional N atoms, with up to 5 heteroatoms being present;

each R^2 and R^3 is independently H, C_{1-3} alkyl, halo C_{1-3} alkyl, OC_{1-3} alkyl, halo C_{1-3} alkoxy, OH or F;

n represents an integer of from 1 to 5;

each R^4 is H or is independently selected from halo and R^6 ;

R^5 represents $-CO_2H$,



or $-C(O)NHSO_2R^e$ wherein R^e

represents C_{1-4} alkyl or phenyl, said C_{1-4} alkyl and phenyl each being optionally substituted with 1-3 groups, 1-3 of which are selected from halo and C_{1-3} alkyl, and 1-2 of which are selected from the group consisting of: OC_{1-3} alkyl, halo C_{1-3} alkyl, halo C_{1-3} alkoxy, OH, NH_2 and NHC_{1-3} alkyl;

and each R^1 is H or is independently selected from the group consisting of:

a) halo, OH, CO_2H , CN, NH_2 , $S(O)_{0-2}R^e$, $C(O)R^e$, $OC(O)R^e$ and CO_2R^e , wherein R^e is as

previously defined;

b) C_{1-6} alkyl and OC_{1-6} alkyl, said C_{1-6} alkyl and alkyl portion of OC_{1-6} alkyl being optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, CO_2H , CO_2C_{1-4} alkyl, CO_2C_{1-4} haloalkyl, OCO_2C_{1-4} alkyl, NH_2 , NHC_{1-4} alkyl, $N(C_{1-4}alkyl)_2$, Hetcy and CN;

c) NHC_{1-4} alkyl and $N(C_{1-4}alkyl)_2$, the alkyl portions of which are optionally substituted as set forth in (b) above;

d) $C(O)NH_2$, $C(O)NHC_{1-4}alkyl$, $C(O)N(C_{1-4}alkyl)_2$, $C(O)Hetcy$, $C(O)NHOC_{1-4}alkyl$ and $C(O)N(C_{1-4}alkyl)(OC_{1-4}alkyl)$, the alkyl portions of which are optionally substituted as set forth in (b) above;

e) $NR'C(O)R''$, $NR'SO_2R''$, $NR'CO_2R''$ and $NR'C(O)NR''R'''$ wherein:

R' represents H, C_{1-3} alkyl or halo C_{1-3} alkyl,

R'' represents (a) C_{1-8} alkyl optionally substituted with 1-4 groups, 0-4 of which are halo, and 0-1 of which are selected from the group consisting of: OC_{1-6} alkyl, OH, CO_2H , CO_2C_{1-4} alkyl, CO_2C_{1-4} haloalkyl, NH_2 , $NHC_{1-4}alkyl$, $N(C_{1-4}alkyl)_2$, CN, Hetcy, Aryl and HAR,

said Hetcy, Aryl and HAR being further optionally substituted with 1-3 halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl or halo C_{1-4} alkoxy groups; or

(b) Hetcy, Aryl or HAR, each being optionally substituted with 1-3 members selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl and halo C_{1-4} alkoxy groups;

and R''' representing H or R'' ;

f) phenyl or a 5-6 membered heteroaryl or a Hetcy group attached at any available ring atom and each being optionally substituted with 1-3 groups, 1-3 of which are selected from halo, C₁₋₃alkyl and haloC₁₋₃alkyl groups, and 1-2 of which are selected from OC₁₋₃alkyl and haloOC₁₋₃alkyl groups, and 0-1 of which is selected from the group consisting of:

- 5 i) OH; CO₂H; CN; NH₂ and S(O)₀₋₂R^e wherein R^e is as described above;
- ii) NHC₁₋₄alkyl and N(C₁₋₄alkyl)₂, the alkyl portions of which are optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, CO₂H, CO₂C₁₋₄alkyl, CO₂C₁₋₄haloalkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)₂ and CN;
- 10 iii) C(O)NH₂, C(O)NHC₁₋₄alkyl, C(O)N(C₁₋₄alkyl)₂, C(O)NHOC₁₋₄alkyl and C(O)N(C₁₋₄alkyl)(OC₁₋₄alkyl), the alkyl portions of which are optionally substituted as set forth in b) above; and
- iv) NR'C(O)R'', NR'SO₂R'', NR'CO₂R'' and NR'C(O)NR''R''' wherein R', R'' and R''' are as described above.

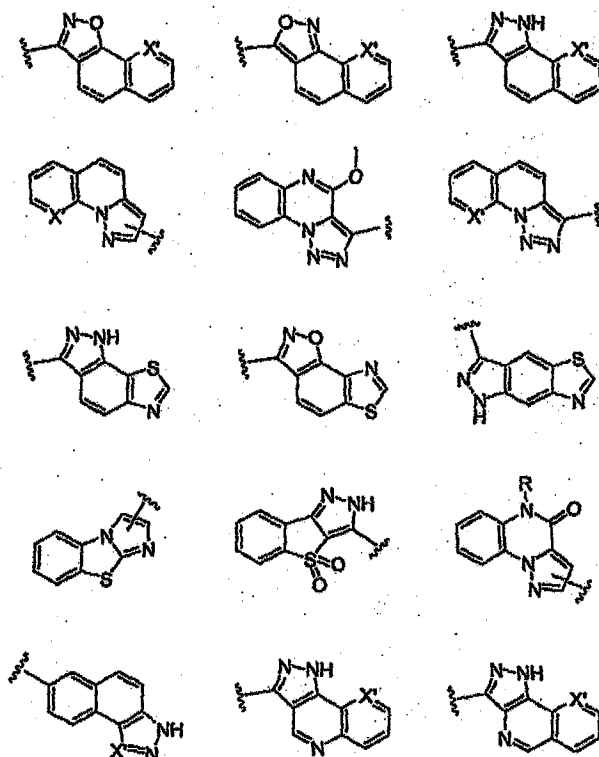
15 One aspect of the invention that is of interest relates to a compound of formula I wherein up to 4 R² and R³ moieties are selected from the group consisting of: C₁₋₃alkyl, haloC₁₋₃alkyl, OC₁₋₃alkyl, haloC₁₋₃alkoxy, OH and F, and any remaining R² and R³ moieties represent H.

Another subset of compounds that is of interest relates to compounds of formula I wherein ring A is a phenyl or naphthyl group, a 5-6 membered monocyclic heteroaryl group or a 9-13 membered bicyclic or tricyclic heteroaryl group. Within this subset of compounds, all other variables are
20 as defined with respect to formula I.

More particularly, a subset of compounds that is of interest relates to compounds of formula I wherein ring A is selected from the group consisting of: phenyl; naphthyl;

HAR which is a member selected from the group consisting of: pyrrolyl, isoxazolyl, isothiazolyl, pyrazolyl, pyridyl, oxazolyl, oxadiazolyl, thiadiazolyl, thiazolyl, imidazolyl, triazolyl,
25 tetrazolyl, furanyl, triazinyl, thienyl, pyrimidyl, pyridazinyl, pyrazinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, benzopyrazolyl, benzotriazolyl, furo(2,3-b)pyridyl, benzoxazinyl, tetrahydroquinolyl, tetrahydroisoquinolyl, quinolyl, isoquinolyl, indolyl, dihydroindolyl, quinoxalyl, quinazolinyl, naphthyridinyl, pteridinyl, 2,3-dihydrofuro(2,3-b)pyridyl, indolinyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, or a member selected
30 from the group consisting of:

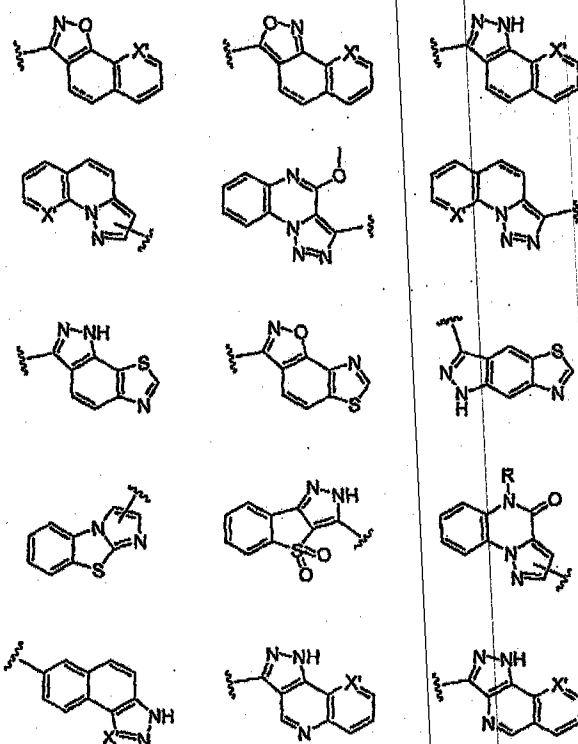
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== is a single or double bond
 X' = CH or N
 R = H or CH₃

Even more particularly, an aspect of the invention that is of interest relates to a compound of formula I wherein ring A is selected from the group consisting of: phenyl; naphthyl;

HAR which is a member selected from the group consisting of: isoxazolyl, pyrazolyl, oxazolyl, oxadiazolyl, thiazolyl, triazolyl, thienyl, benzothiazolyl, or a member selected from the group consisting of:



$\sim$ is a single or double bond
 $X = CH$ or N
 $R = H$ or CH_3

Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein each R^1 is H or is selected from the group consisting of:

- 5 a) halo, OH, CN, NH_2 and $S(O)_{0-2}R^e$ wherein R^e is methyl or phenyl optionally substituted with 1-3 halo groups;
- b) C_{1-3} alkyl and OC_{1-3} alkyl, each being optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, NH_2 , NHC_{1-4} alkyl and CN;
- c) $NR'SO_2R''$ and $NR'C(O)NR''R'''$ wherein:
 - 10 R' represents H, C_{1-3} alkyl or halo C_{1-3} alkyl,
 - R'' represents (a) C_{1-8} alkyl optionally substituted with 1-4 groups, 0-4 of which are halo, and 0-1 of which are selected from the group consisting of: OC_{1-6} alkyl, OH, CO_2H , CO_2C_{1-4} alkyl, CO_2C_{1-4} haloalkyl, OCO_2C_{1-4} alkyl, NH_2 , NHC_{1-4} alkyl, $N(C_{1-4}$ alkyl) $_2$, CN, Hetcy, Aryl and HAR, said Hetcy, Aryl and HAR being further optionally substituted with 1-3 groups
 - 15 selected from: halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl and halo C_{1-4} alkoxy;
 - (b) Hetcy, Aryl or HAR, said Aryl and HAR being optionally substituted with 1-3 groups selected from: halo, C_{1-4} alkyl, C_{1-4} alkoxy, halo C_{1-4} alkyl and halo C_{1-4} alkoxy; and R''' representing H or R'' ; and

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d) phenyl or a 5-6 membered heteroaryl or a heterocyclic group attached at any available point and being optionally substituted with 1-3 groups, 1-3 of which are halo, C₁₋₃alkyl or haloC₁₋₃alkyl groups, 1-2 of which are OC₁₋₃alkyl or haloOC₁₋₃alkyl groups, and 1 of which is selected from the group consisting of:

- 5 i) OH; CO₂H; CN; NH₂ and S(O)₀₋₂R^a wherein R^a is as described above;
 ii) NHC₁₋₄alkyl, the alkyl portion of which is optionally substituted with 1-3 groups, 1-3 of which are halo and 1 of which is selected from: OH, CO₂H, CO₂C₁₋₄alkyl, CO₂C₁₋₄haloalkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)₂ and CN;
 iii) C(O)NH₂, C(O)NHC₁₋₄alkyl and C(O)N(C₁₋₄alkyl)₂, the alkyl portions of
10 which are optionally substituted as set forth in (b) above; and
 iv) NR'C(O)R" and NR'SO₂R" wherein R' and R" are as described above.

Within this subset of compounds, all other variables are as defined with respect to formula I.

In particular, another subset of compounds that is of interest relates to compounds of formula I wherein each R¹ is H or is selected from the group consisting of:

- 15 a) halo, OH, CN and NH₂ ;
 b) C₁₋₃alkyl and OC₁₋₃alkyl, each being optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, NH₂, NHC₁₋₄alkyl and CN;
 c) phenyl or a 5-6 membered heteroaryl or a heterocyclic group attached at any available point and being optionally substituted with 1-3 groups, 1-3 of which are halo, C₁₋₃alkyl or haloC₁₋₃alkyl groups, 1-2 of which are OC₁₋₃alkyl or haloOC₁₋₃alkyl groups, and 1 of which is selected from the group consisting of:

20 i) OH, CN and NH₂. Within this subset of compounds, all other variables are as defined with respect to formula I.

25 Another subset of compounds that is of interest relates to compounds of formula I wherein a and b are 1 or 2 such that the sum of a and b is 2 or 3. Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein X represents O, S, N or CH₂. Within this subset of compounds, all other variables are as defined with respect to formula I.

30 More particularly, another subset of compounds that is of interest relates to compounds of formula I wherein X represents O or CH₂. Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein R² and R³ are independently H, C₁₋₃alkyl, OH or haloC₁₋₃alkyl. Within this subset of
35 compounds, all other variables are as defined with respect to formula I.

More particularly, another subset of compounds that is of interest relates to compounds of formula I wherein R^2 and R^3 are independently H, C_{1-3} alkyl or halo C_{1-3} alkyl. Within this subset of compounds, all other variables are as defined with respect to formula I.

5 More particularly, a subset of compounds that is of interest relates to compounds of formula I wherein R^2 and R^3 are independently H or methyl. Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein n represents an integer of from 2 to 4. Within this subset of compounds, all other variables are as defined with respect to formula I.

10 More particularly, a subset of compounds that is of interest relates to compounds of formula I wherein n is 2. Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein each R^4 is H or is independently selected from the group consisting of: halo, C_{1-3} alkyl optionally substituted with 1-3 halo groups and 0-1 OC_{1-3} alkyl groups. Within this subset of compounds, all other variables are as defined with respect to formula I.

15 Another subset of compounds that is of interest relates to compounds of formula I wherein each R^4 is H or is independently selected from halo or C_{1-3} alkyl optionally substituted with 1-3 halo groups. Within this subset of compounds, all other variables are as defined with respect to formula I.

Another subset of compounds that is of interest relates to compounds of formula I wherein R^5 represents $-CO_2H$. Within this subset of compounds, all other variables are as defined with respect to formula I.

20 A particular subset of compounds that is of interest relates to compounds of formula I or a pharmaceutically acceptable salt or solvate thereof wherein:

ring A is a phenyl or naphthyl group, a 5-6 membered monocyclic heteroaryl group or a 9-13 membered bicyclic or tricyclic heteroaryl group;

each R^1 is H or is selected from the group consisting of:

a) halo, OH, CN, NH_2 and $S(O)_{0-2}R^e$ wherein R^e is methyl or phenyl optionally substituted with 1-3 halo groups;

b) C_{1-3} alkyl and OC_{1-3} alkyl, each being optionally substituted with 1-3 groups, 1-3 of which are halo and 1-2 of which are selected from: OH, NH_2 , NHC_{1-4} alkyl and CN;

c) $NR'SO_2R''$ and $NR'C(O)NR''R'''$ wherein:

R' represents H, C_{1-3} alkyl or halo C_{1-3} alkyl,

35 R'' represents (a) C_{1-3} alkyl optionally substituted with 1-4 groups, 0-4 of which are halo, and 0-1 of which are selected from the group consisting of: OC_{1-6} alkyl, OH, CO_2H , CO_2C_{1-4} alkyl, CO_2C_{1-4} haloalkyl, OCO_2C_{1-4} alkyl, NH_2 , NHC_{1-4} alkyl, $N(C_{1-4}alkyl)_2$, CN, Hetcy, Aryl and HAR,

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said Hetcy, Aryl and HAR being further optionally substituted with 1-3 halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl and haloC₁₋₄alkoxy groups;

(b) Hetcy, Aryl or HAR, said Aryl and HAR being further optionally substituted with 1-3 halo, C₁₋₄alkyl, C₁₋₄alkoxy, haloC₁₋₄alkyl and haloC₁₋₄alkoxy groups;

and R''' representing H or R''; and

d) phenyl or a 5-6 membered heteroaryl or a heterocyclic group attached at any available point and being optionally substituted with 1-3 groups, 1-3 of which are halo, C₁₋₃alkyl or haloC₁₋₃alkyl groups, 1-2 of which are OC₁₋₃alkyl or haloOC₁₋₃alkyl groups, and 1 of which is selected from the group consisting of:

i) OH; CO₂H; CN; NH₂; S(O)₀₋₂R^e wherein R^e is as described above;

ii) NHC₁₋₄alkyl the alkyl portion of which is optionally substituted with 1-3 groups, 1-3 of which are halo and 1 of which is selected from: OH, CO₂H, CO₂C₁₋₄alkyl, CO₂C₁₋₄haloalkyl, NH₂, NHC₁₋₄alkyl, N(C₁₋₄alkyl)₂ and CN;

iii) C(O)NH₂, C(O)NHC₁₋₄alkyl, C(O)N(C₁₋₄alkyl)₂, the alkyl portions of which are optionally substituted as set forth in (b) above; and

iv) NR'^cC(O)R'' and NR'^cSO₂R'' wherein R' and R'' are as described above;

a and b are 1 or 2 such that the sum of a and b is 2 or 3;

X represents O or CH₂;

R² and R³ are independently H, OH, C₁₋₃alkyl or haloC₁₋₃alkyl;

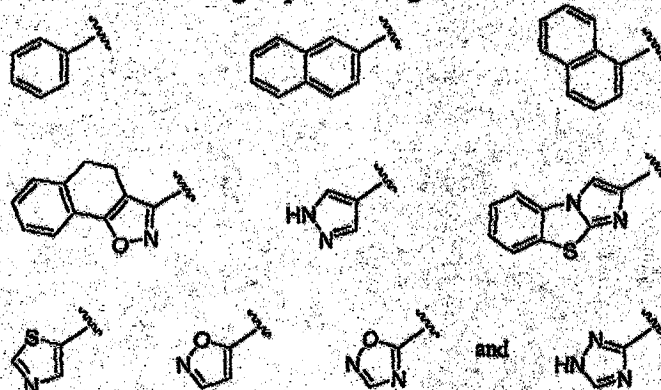
n represents 2;

R⁴ is H or is independently selected from the group consisting of: halo, C₁₋₃alkyl optionally substituted with 1-3 halo groups or 0-1 OC₁₋₃alkyl groups; and

R⁵ represents -CO₂H.

A more particular subset of compounds that is of interest relates to compounds of formula I or a pharmaceutically acceptable salt or solvate thereof wherein:

ring A is selected from the group consisting of:



each R¹ is independently H, CH₃, phenyl, 4-hydroxy-phenyl, OH, 2-hydroxy-phenyl, 3-hydroxy-phenyl, 3-amino-phenyl, 2,3-dihydro-benzofuran-6-yl, 2-chloro-4-hydroxy-phenyl, 1H-pyrazol-4-yl, 5-hydroxy-pyridin-2-yl, 4-hydroxy-pyrazol-1-yl, 1H-[1,2,3]triazol-4-yl, or 5-fluoro-pyridin-2-yl;

a and b are 1 or 2 such that the sum of a and b is 2 or 3;

X represents CH_2 ;

each R^2 and R^3 is independently H, OH or CH_3 ;

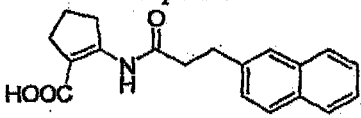
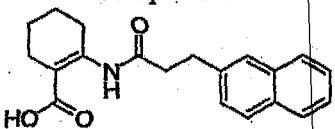
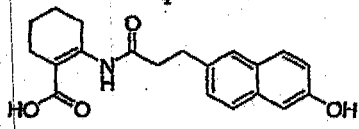
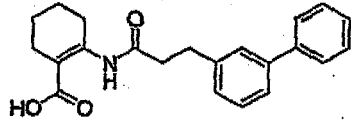
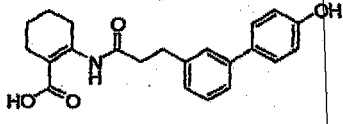
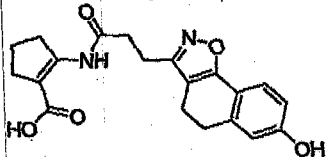
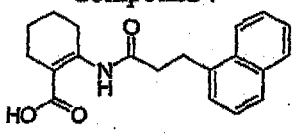
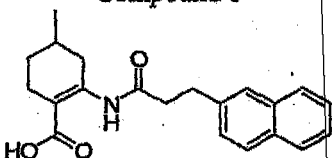
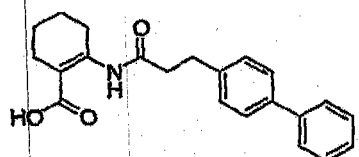
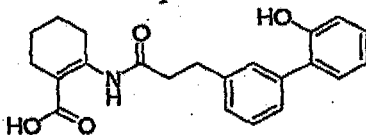
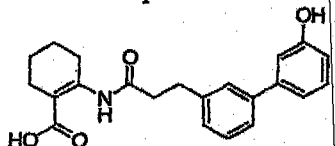
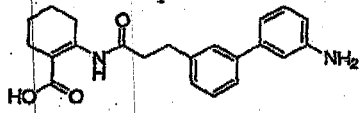
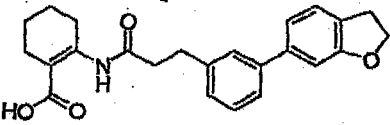
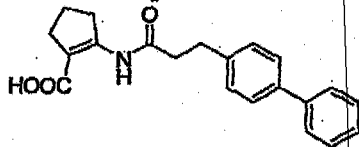
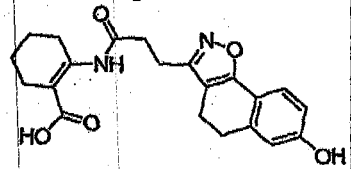
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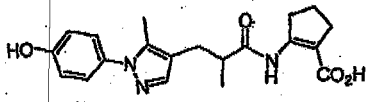
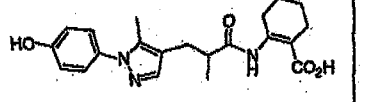
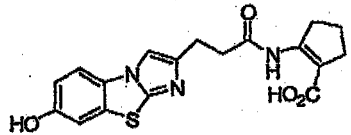
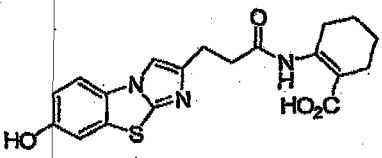
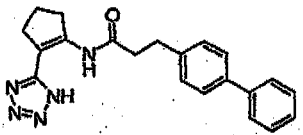
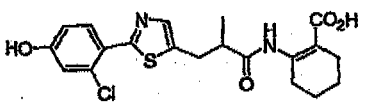
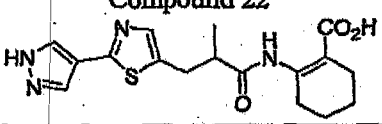
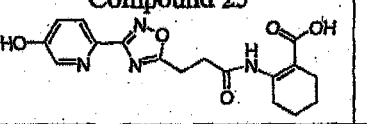
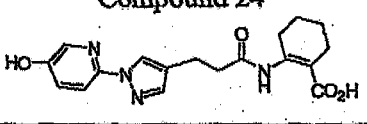
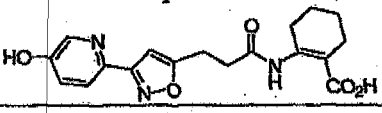
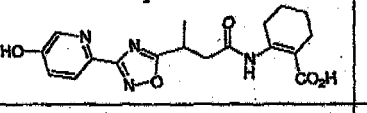
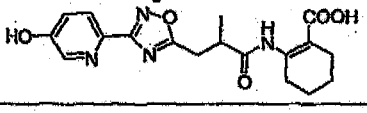
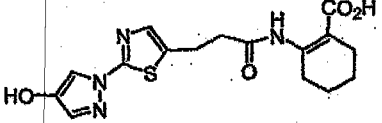
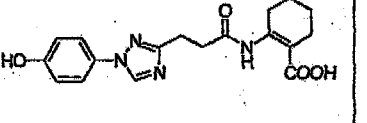
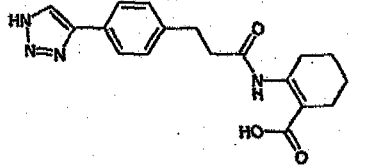
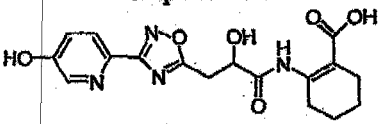
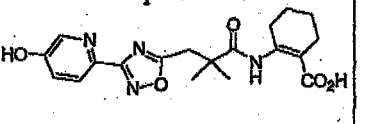
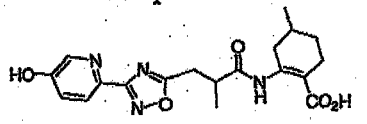
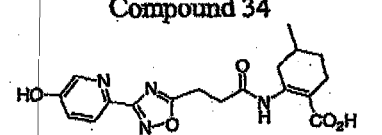
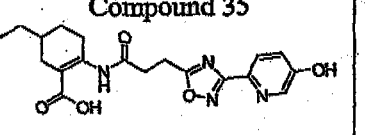
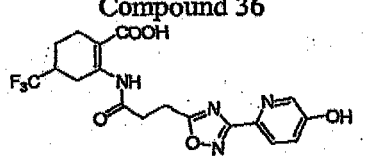
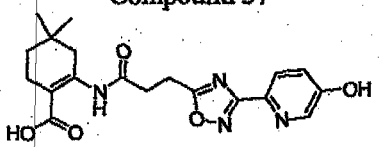
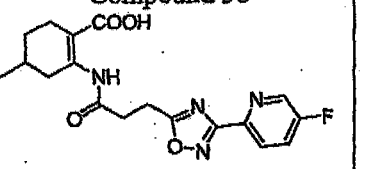
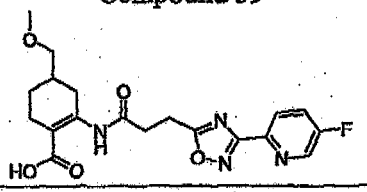
R^4 is H, CH_3 , CH_2CH_3 , CF_3 or CH_2OCH_3 ; and

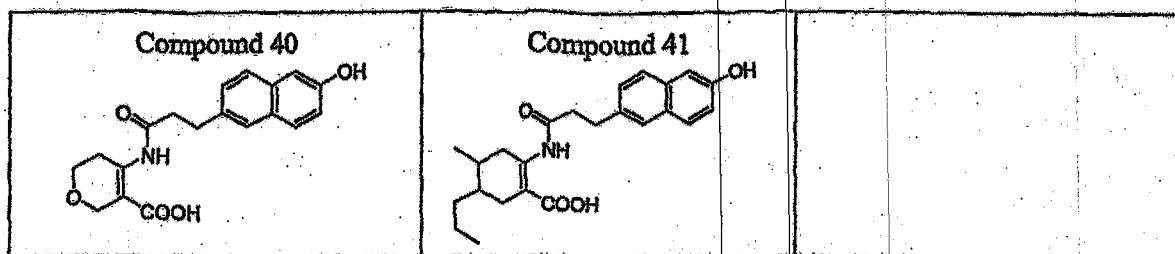
R^5 represents $-\text{CO}_2\text{H}$.

Representative examples of species that are of interest are shown below in Table I.

Within this subset of compounds, all other variables are as originally defined with respect to formula I.

TABLE I		
Compound 1 	Compound 2 	Compound 3 
Compound 4 	Compound 5 	Compound 6 
Compound 7 	Compound 8 	Compound 9 
Compound 10 	Compound 11 	Compound 12 
Compound 13 	Compound 14 	Compound 15 

Compound 16 	Compound 17 	Compound 18 
Compound 19 	Compound 20 	Compound 21 
Compound 22 	Compound 23 	Compound 24 
Compound 25 	Compound 26 	Compound 27 
Compound 28 	Compound 29 	Compound 30 
Compound 31 	Compound 32 	Compound 33 
Compound 34 	Compound 35 	Compound 36 
Compound 37 	Compound 38 	Compound 39 



Pharmaceutically acceptable salts and solvates thereof are included as well.

Many of the compounds of formula I contain asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms are included.

Moreover, chiral compounds possessing one stereocenter of general formula I, may be resolved into their enantiomers in the presence of a chiral environment using methods known to those skilled in the art. Chiral compounds possessing more than one stereocenter may be separated into their diastereomers in an achiral environment on the basis of their physical properties using methods known to those skilled in the art. Single diastereomers that are obtained in racemic form may be resolved into their enantiomers as described above.

If desired, racemic mixtures of compounds may be separated so that individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds of Formula I to an enantiomerically pure compound to form a diastereomeric mixture, which is then separated into individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to substantially pure enantiomers by cleaving the added chiral residue from the diastereomeric compound.

The racemic mixture of the compounds of Formula I can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, enantiomers of compounds of the general Formula I may be obtained by stereoselective synthesis using optically pure starting materials or reagents.

Some of the compounds described herein exist as tautomers, which have different points of attachment for hydrogen accompanied by one or more double bond shifts. For example, a ketone and its enol form are keto-enol tautomers. Or for example, a 2-hydroxyquinoline can reside in the tautomeric 2-quinolone form. The individual tautomers as well as mixtures thereof are included.

Dosing Information

The dosages of compounds of formula I or a pharmaceutically acceptable salt or solvate thereof vary within wide limits. The specific dosage regimen and levels for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the

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patient's condition. Consideration of these factors is well within the purview of the ordinarily skilled clinician for the purpose of determining the therapeutically effective or prophylactically effective dosage amount needed to prevent, counter, or arrest the progress of the condition. Generally, the compounds will be administered in amounts ranging from as low as about 0.01 mg/day to as high as about 2000 mg/day, in single or divided doses. A representative dosage is about 0.1 mg/day to about 1 g/day. Lower dosages can be used initially, and dosages increased to further minimize any untoward effects. It is expected that the compounds described herein will be administered on a daily basis for a length of time appropriate to treat or prevent the medical condition relevant to the patient, including a course of therapy lasting months, years or the life of the patient.

Combination Therapy

One or more additional active agents may be administered with the compounds described herein. The additional active agent or agents can be lipid modifying compounds or agents having other pharmaceutical activities, or agents that have both lipid-modifying effects and other pharmaceutical activities. Examples of additional active agents which may be employed include but are not limited to HMG-CoA reductase inhibitors, which include statins in their lactonized or dihydroxy open acid forms and pharmaceutically acceptable salts and esters thereof, including but not limited to lovastatin (see US Patent No. 4,342,767), simvastatin (see US Patent No. 4,444,784), dihydroxy open-acid simvastatin, particularly the ammonium or calcium salts thereof, pravastatin, particularly the sodium salt thereof (see US Patent No. 4,346,227), fluvastatin particularly the sodium salt thereof (see US Patent No. 5,354,772), atorvastatin, particularly the calcium salt thereof (see US Patent No. 5,273,995), pitavastatin also referred to as NK-104 (see PCT international publication number WO 97/23200) and rosuvastatin, also known as CRESTOR[®]; see US Patent No. 5,260,440); HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT) inhibitors including selective inhibitors of ACAT-1 or ACAT-2 as well as dual inhibitors of ACAT-1 and -2; microsomal triglyceride transfer protein (MTP) inhibitors; endothelial lipase inhibitors; bile acid sequestrants; LDL receptor inducers; platelet aggregation inhibitors, for example glycoprotein IIb/IIIa fibrinogen receptor antagonists and aspirin; human peroxisome proliferator activated receptor gamma (PPAR-gamma) agonists including the compounds commonly referred to as glitazones for example pioglitazone and rosiglitazone and, including those compounds included within the structural class known as thiazolidine diones as well as those PPAR-gamma agonists outside the thiazolidine dione structural class; PPAR-alpha agonists such as clofibrate, fenofibrate including micronized fenofibrate, and gemfibrozil; PPAR dual alpha/gamma agonists; vitamin B6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof such as the HCl salt; vitamin B12 (also known as cyanocobalamin); folic acid or a pharmaceutically acceptable salt or ester thereof such as the sodium salt and the methylglucamine salt; anti-oxidant vitamins such as vitamin C and E and beta carotene; beta-blockers; angiotensin II antagonists such as losartan; angiotensin

converting enzyme inhibitors such as enalapril and captopril; renin inhibitors, calcium channel blockers such as nifedipine and diltiazem; endothelin antagonists; agents that enhance ABCA1 gene expression; cholesteryl ester transfer protein (CETP) inhibiting compounds, 5-lipoxygenase activating protein (FLAP) inhibiting compounds, 5-lipoxygenase (5-LO) inhibiting compounds, farnesoid X receptor (FXR) ligands including both antagonists and agonists; Liver X Receptor (LXR)-alpha ligands, LXR-beta ligands, bisphosphonate compounds such as alendronate sodium; cyclooxygenase-2 inhibitors such as rofecoxib and celecoxib; and compounds that attenuate vascular inflammation.

Cholesterol absorption inhibitors can also be used in the present invention. Such compounds block the movement of cholesterol from the intestinal lumen into enterocytes of the small intestinal wall, thus reducing serum cholesterol levels. Examples of cholesterol absorption inhibitors are described in U.S. Patent Nos. 5,846,966, 5,631,365, 5,767,115, 6,133,001, 5,886,171, 5,856,473, 5,756,470, 5,739,321, 5,919,672, and in PCT application Nos. WO 00/63703, WO 00/60107, WO 00/38725, WO 00/34240, WO 00/20623, WO 97/45406, WO 97/16424, WO 97/16455, and WO 95/08532. The most notable cholesterol absorption inhibitor is ezetimibe, also known as 1-(4-fluorophenyl)-3(R)-[3(S)-(4-fluorophenyl)-3-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, described in U.S. Patent Nos. 5,767,115 and 5,846,966.

Therapeutically effective amounts of cholesterol absorption inhibitors include dosages of from about 0.01 mg/kg to about 30 mg/kg of body weight per day, preferably about 0.1 mg/kg to about 15 mg/kg.

For diabetic patients, the compounds used in the present invention can be administered with conventional diabetic medications. For example, a diabetic patient receiving treatment as described herein may also be taking insulin or an oral antidiabetic medication. One example of an oral antidiabetic medication useful herein is metformin.

In the event that these niacin receptor agonists induce some degree of vasodilation, it is understood that the compounds of formula I may be co-dosed with a vasodilation suppressing agent. Consequently, one aspect of the methods described herein relates to the use of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in combination with a compound that reduces flushing. Conventional compounds such as aspirin, ibuprofen, naproxen, indomethacin, other NSAIDs, COX-2 selective inhibitors and the like are useful in this regard, at conventional doses. Alternatively, DP antagonists are useful as well. Doses of the DP receptor antagonist and selectivity are such that the DP antagonist selectively modulates the DP receptor without substantially modulating the CRTH2 receptor. In particular, the DP receptor antagonist ideally has an affinity at the DP receptor (i.e., K_i) that is at least about 10 times higher (a numerically lower K_i value) than the affinity at the CRTH2 receptor. Any compound that selectively interacts with DP according to these guidelines is deemed "DP selective". This is in accordance with US Published Application No. 2004/0229844A1 published on November 18, 2004, incorporated herein by reference.

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Dosages for DP antagonists as described herein, that are useful for reducing or preventing the flushing effect in mammalian patients, particularly humans, include dosages ranging from as low as about 0.01 mg/day to as high as about 100 mg/day, administered in single or divided daily doses. Preferably the dosages are from about 0.1 mg/day to as high as about 1.0 g/day, in single or divided daily doses.

Examples of compounds that are particularly useful for selectively antagonizing DP receptors and suppressing the flushing effect include the following:

Compound A	Compound B	Compound C
Compound D	Compound E	Compound F
Compound G	Compound H	Compound I
Compound J	Compound K	Compound L
Compound M	Compound N	Compound O
Compound P	Compound Q	Compound R

Compound S	Compound T	Compound U
Compound V	Compound W	Compound X
Compound Y	Compound Z	Compound AA
Compound AB	Compound AC	Compound AD
Compound AE	Compound AF	Compound AG
Compound AH	Compound AI	Compound AJ

as well as the pharmaceutically acceptable salts and solvates thereof.

The compound of formula I or a pharmaceutically acceptable salt or solvate thereof and the DP antagonist can be administered together or sequentially in single or multiple daily doses, e.g., bid,

tid or qid, without departing from the invention. If sustained release is desired, such as a sustained release product showing a release profile that extends beyond 24 hours, dosages may be administered every other day. However, single daily doses are preferred. Likewise, morning or evening dosages can be utilized.

Salts and Solvates

Salts and solvates of the compounds of formula I are also included in the present invention, and numerous pharmaceutically acceptable salts and solvates of nicotinic acid are useful in this regard. Alkali metal salts, in particular, sodium and potassium, form salts that are useful as described herein. Likewise alkaline earth metals, in particular, calcium and magnesium, form salts that are useful as described herein. Various salts of amines, such as ammonium and substituted ammonium compounds also form salts that are useful as described herein. Similarly, solvated forms of the compounds of formula I are useful within the present invention. Examples include the hemihydrate, mono-, di-, tri- and sesquihydrate.

The compounds of the invention also include esters that are pharmaceutically acceptable, as well as those that are metabolically labile. Metabolically labile esters include C₁₋₄ alkyl esters, preferably the ethyl ester. Many prodrug strategies are known to those skilled in the art. One such strategy involves engineered amino acid anhydrides possessing pendant nucleophiles, such as lysine, which can cyclize upon themselves, liberating the free acid. Similarly, acetone-ketal diesters, which can break down to acetone, an acid and the active acid, can be used.

The compounds used in the present invention can be administered via any conventional route of administration. The preferred route of administration is oral.

Pharmaceutical Compositions

The pharmaceutical compositions described herein are generally comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, in combination with a pharmaceutically acceptable carrier.

Examples of suitable oral compositions include tablets, capsules, troches, lozenges, suspensions, dispersible powders or granules, emulsions, syrups and elixirs. Examples of carrier ingredients include diluents, binders, disintegrants, lubricants, sweeteners, flavors, colorants, preservatives, and the like. Examples of diluents include, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate and sodium phosphate. Examples of granulating and disintegrants include corn starch and alginic acid. Examples of binding agents include starch, gelatin and acacia. Examples of lubricants include magnesium stearate, calcium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques. Such coatings may delay disintegration and thus, absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.

One embodiment of the invention that is of interest is a tablet or capsule that is comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount ranging from about 0.1mg to about 1000mg, in combination with a pharmaceutically acceptable carrier.

5 In another embodiment of the invention, a compound of formula I or a pharmaceutically acceptable salt or solvate thereof is combined with another therapeutic agent and the carrier to form a fixed combination product. This fixed combination product may be a tablet or capsule for oral use.

More particularly, in another embodiment of the invention, a compound of formula I or a pharmaceutically acceptable salt or solvate thereof (about 0.1 to about 1000 mg) and the second
10 therapeutic agent (about 0.1 to about 500 mg) are combined with the pharmaceutically acceptable carrier, providing a tablet or capsule for oral use.

Sustained release over a longer period of time may be particularly important in the formulation. A time delay material such as glyceryl monostearate or glyceryl distearate may be employed. The dosage form may also be coated by the techniques described in the U.S. Patent Nos.
15 4,256,108; 4,166,452 and 4,265,874 to form osmotic therapeutic tablets for controlled release.

Other controlled release technologies are also available and are included herein. Typical ingredients that are useful to slow the release of nicotinic acid in sustained release tablets include various cellulosic compounds, such as methylcellulose, ethylcellulose, propylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, starch and the like.
20 Various natural and synthetic materials are also of use in sustained release formulations. Examples include alginic acid and various alginates, polyvinyl pyrrolidone, tragacanth, locust bean gum, guar gum, gelatin, various long chain alcohols, such as cetyl alcohol and beeswax.

Optionally and of even more interest is a tablet as described above, comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, and further containing an
25 HMG Co-A reductase inhibitor, such as simvastatin or atorvastatin. This particular embodiment optionally contains the DP antagonist as well.

Typical release time frames for sustained release tablets in accordance with the present invention range from about 1 to as long as about 48 hours, preferably about 4 to about 24 hours, and more preferably about 8 to about 16 hours.

30 Hard gelatin capsules constitute another solid dosage form for oral use. Such capsules similarly include the active ingredients mixed with carrier materials as described above. Soft gelatin capsules include the active ingredients mixed with water-miscible solvents such as propylene glycol, PEG and ethanol, or an oil such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions are also contemplated as containing the active material in
35 admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, tragacanth and acacia; dispersing

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or wetting agents, e.g., lecithin; preservatives, e.g., ethyl, or n-propyl para-hydroxybenzoate, colorants, flavors, sweeteners and the like.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredients in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above.

Syrups and elixirs may also be formulated.

More particularly, a pharmaceutical composition that is of interest is a sustained release tablet that is comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, and a DP receptor antagonist that is selected from the group consisting of compounds A through AJ in combination with a pharmaceutically acceptable carrier.

Yet another pharmaceutical composition that is of more interest is comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and a DP antagonist compound selected from the group consisting of compounds A, B, D, E, X, AA, AF, AG, AH, AI and AJ, in combination with a pharmaceutically acceptable carrier.

Yet another pharmaceutical composition that is of more particular interest relates to a sustained release tablet that is comprised of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, a DP receptor antagonist selected from the group consisting of compounds A, B, D, E, X, AA, AF, AG, AH, AI and AJ, and simvastatin or atorvastatin in combination with a pharmaceutically acceptable carrier.

The term "composition", in addition to encompassing the pharmaceutical compositions described above, also encompasses any product which results, directly or indirectly, from the combination, complexation or aggregation of any two or more of the ingredients, active or excipient, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical composition of the present invention encompasses any composition made by admixing or otherwise combining the compounds, any additional active ingredient(s), and the pharmaceutically acceptable excipients.

Another aspect of the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and a DP antagonist in the manufacture of a medicament. This medicament has the uses described herein.

More particularly, another aspect of the invention relates to the use of a compound of formula I or a pharmaceutically acceptable salt or solvate thereof, a DP antagonist and an HMG Co-A reductase inhibitor, such as simvastatin, in the manufacture of a medicament. This medicament has the uses described herein.

Compounds of the present invention have anti-hyperlipidemic activity, causing reductions in LDL-C, triglycerides, lipoprotein (a), free fatty acids and total cholesterol, and increases in HDL-C. Consequently, the compounds of the present invention are useful in treating dyslipidemias. The

present invention thus relates to the treatment, prevention or reversal of atherosclerosis and the other diseases and conditions described herein, by administering a compound of formula I or a pharmaceutically acceptable salt or solvate in an amount that is effective for treating, preventing or reversing said condition. This is achieved in humans by administering a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective to treat or prevent said condition, while preventing, reducing or minimizing flushing effects in terms of frequency and/or severity.

One aspect of the invention that is of interest relates to a compound in accordance with formula I or a pharmaceutically acceptable salt or solvate thereof for use in a method of treatment of the human or animal body by therapy.

Another aspect of the invention that is of interest relates to a compound in accordance with formula I or a pharmaceutically acceptable salt or solvate thereof for use in a method for the treatment of atherosclerosis, dyslipidemia, diabetes, metabolic syndrome or a related condition in the human or animal body by therapy.

More particularly, an aspect of the invention that is of interest is a method of treating atherosclerosis in a human patient in need of such treatment comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for treating atherosclerosis in the absence of substantial flushing.

Another aspect of the invention that is of interest relates to a method of raising serum HDL levels in a human patient in need of such treatment, comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for raising serum HDL levels.

Another aspect of the invention that is of interest relates to a method of treating dyslipidemia in a human patient in need of such treatment comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for treating dyslipidemia.

Another aspect of the invention that is of interest relates to a method of reducing serum VLDL or LDL levels in a human patient in need of such treatment, comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for reducing serum VLDL or LDL levels in the patient in the absence of substantial flushing.

Another aspect of the invention that is of interest relates to a method of reducing serum triglyceride levels in a human patient in need of such treatment, comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for reducing serum triglyceride levels.

Another aspect of the invention that is of interest relates to a method of reducing serum Lp(a) levels in a human patient in need of such treatment, comprising administering to the patient a

28

compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for reducing serum Lp(a) levels. As used herein Lp(a) refers to lipoprotein (a).

Another aspect of the invention that is of interest relates to a method of treating diabetes, and in particular, type 2 diabetes, in a human patient in need of such treatment comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for treating diabetes.

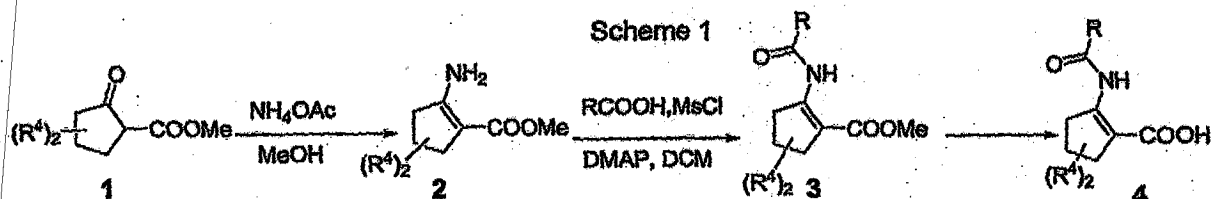
Another aspect of the invention that is of interest relates to a method of treating metabolic syndrome in a human patient in need of such treatment comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof in an amount that is effective for treating metabolic syndrome.

Another aspect of the invention that is of particular interest relates to a method of treating atherosclerosis, dyslipidemias, diabetes, metabolic syndrome or a related condition in a human patient in need of such treatment, comprising administering to the patient a compound of formula I or a pharmaceutically acceptable salt or solvate thereof and a DP receptor antagonist, said combination being administered in an amount that is effective to treat atherosclerosis, dyslipidemia, diabetes or a related condition in the absence of substantial flushing.

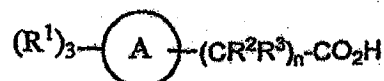
Another aspect of the invention that is of particular interest relates to the methods described above wherein the DP receptor antagonist is selected from the group consisting of compounds A through AJ and the pharmaceutically acceptable salts and solvates thereof.

METHODS OF SYNTHESIS FOR COMPOUNDS OF FORMULA I

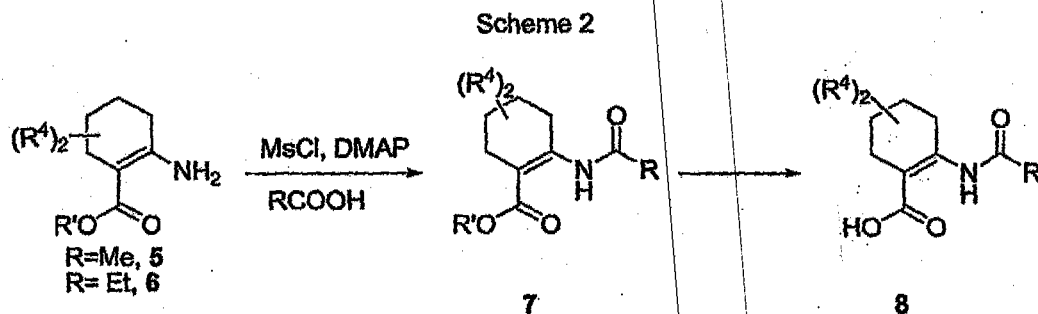
Compounds of Formula I have been prepared by the following representative reaction schemes. It is understood that similar reagents, conditions or other synthetic approaches to these structure classes are conceivable to one skilled in the art of organic synthesis. Therefore these reaction schemes should not be construed as limiting the scope of the invention. All substituents are as defined above unless indicated otherwise.



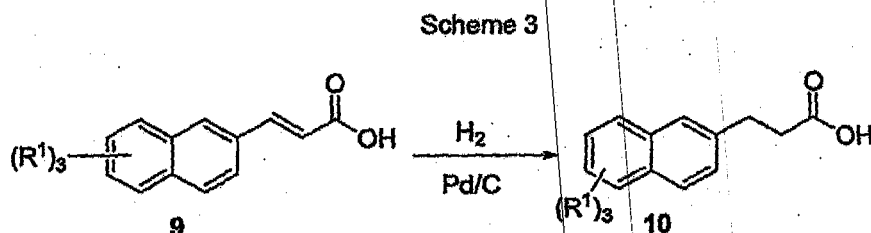
Compounds of Formula I, where X represents CH₂, a and b equal 1 and RCOOH represents:



can be prepared as illustrated in Scheme 1 by treatment of commercially available methyl 2-oxocyclopentane-1-carboxylate 1 with ammonium acetate in a polar solvent such a methanol or ethanol to give the methyl 2-amino cyclopent-1-ene-1-carboxylate 2. The amine 2 can be coupled with the appropriate acid in the presence of methanesulfonyl chloride (MsCl) and DMAP to give the desired amide 3. Finally, the ester can be saponified by one skilled in the art using such methods as NaOH or LiOH -dioxane to give compounds with the structure 4.

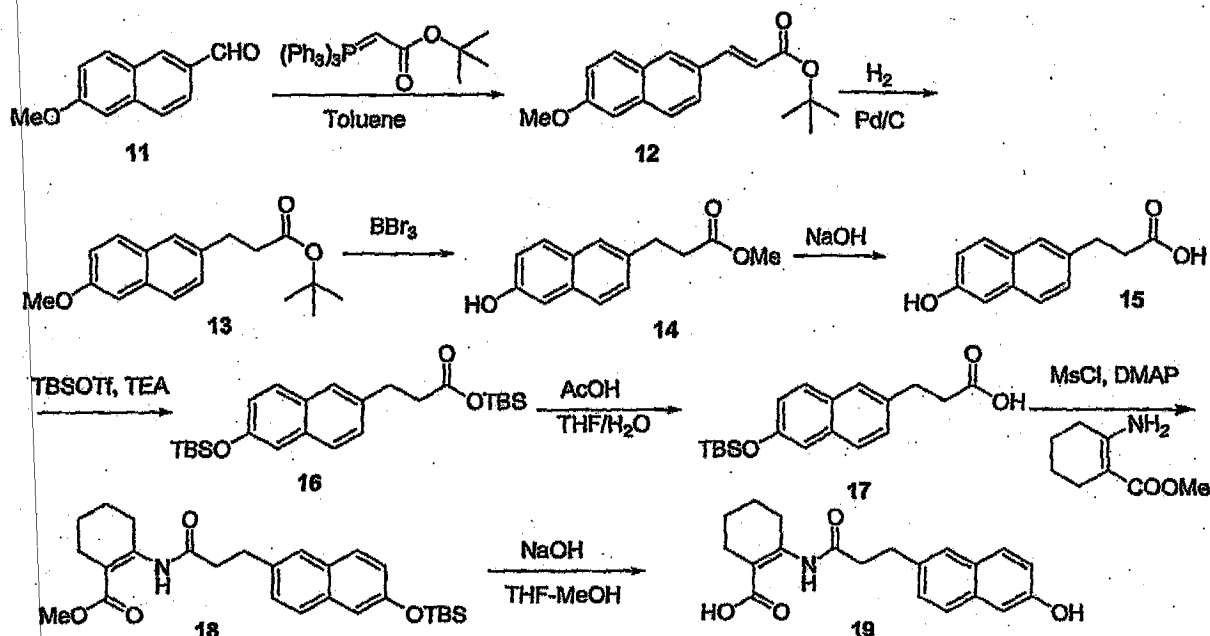


Compounds of Formula I, where X represents CH₂, a represents 2, and b represents 1 such that the sum of a and b is 3, can be prepared as illustrated in Scheme 2 by coupling commercially available methyl or ethyl 2-amino-cyclo-hex-1-ene-1-carboxylate 5 or 6 with the appropriate acid in the presence of methanesulfonyl chloride and DMAP to give the desired amide 7. The ester can be saponified to the desired compound 8 by methods known to those skilled in the art.



Shown in Scheme 3 is the preparation of acid of the structure 10 from commercially available material 9 by methods known to one skilled in the art, such as hydrogenation in a polar solvent, such as methanol or ethanol, using Pd/C as a catalyst.

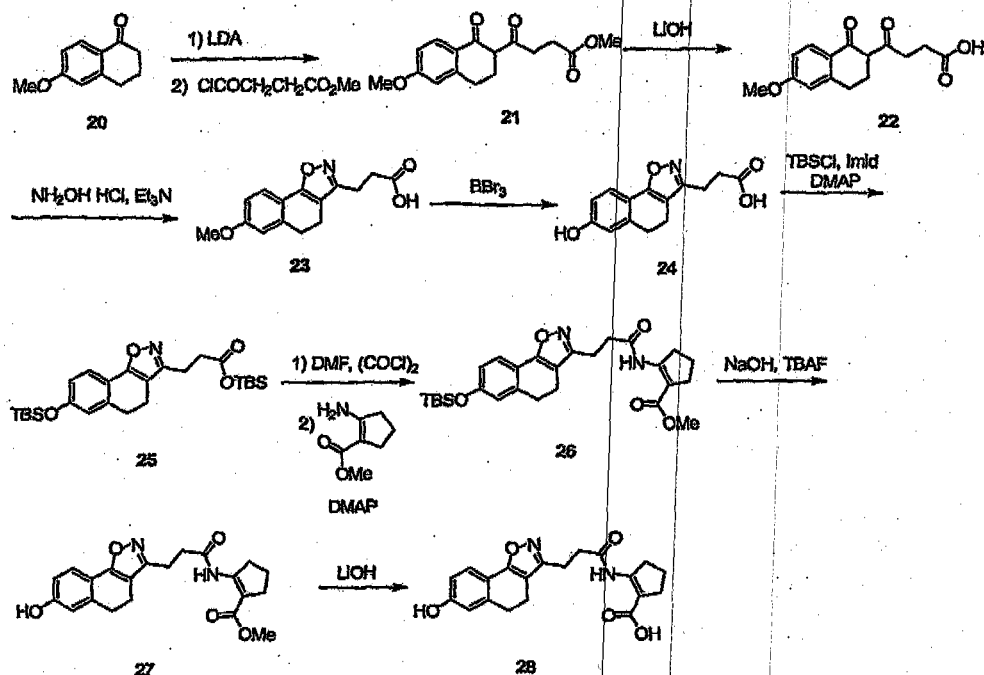
Scheme 4



Compounds with the structure 19 can be prepared by the chemistry outlined in Scheme 4.

Thus, 6-methoxy-2-naphthaldehyde 11 can be treated with a suitable ylide such as (tert-Butoxycarbonyl-methylene)triphenyl-phospharane in a non-polar solvent such as toluene or xylenes under refluxing conditions to give the desired olefin 12. Hydrogenation of the double bond can be accomplished using standard conditions such as $\text{H}_2(\text{g})$, Pd/C in a suitable polar solvent like methanol or ethanol to give 13. Removal of the methyl group in the methoxynaphthyl moiety can be accomplished with boron tribromide at low temperature, followed by a careful quenching of the reaction with methanol to give the trans-esterified product 14. Saponification of the ester was accomplished using conditions described earlier. The naphthol can be protected as the TBS ether using TBSOTf or TBS-Cl in the presence of a suitable base such as triethylamine or imidazole in dichloromethane. The TBS ester can be hydrolyzed with a mild acid such as acetic acid in THF- H_2O to give the desired acid 17. This acid can be coupled to the methyl or ethyl 2-aminocyclo-hex-1-ene-1-carboxylate in the presence of methanesulfonyl chloride and DMAP to give the desired amide 18. Finally, TBS ether removal and methyl ester saponification can be achieved using NaOH/THF- H_2O providing compounds of the structure 19.

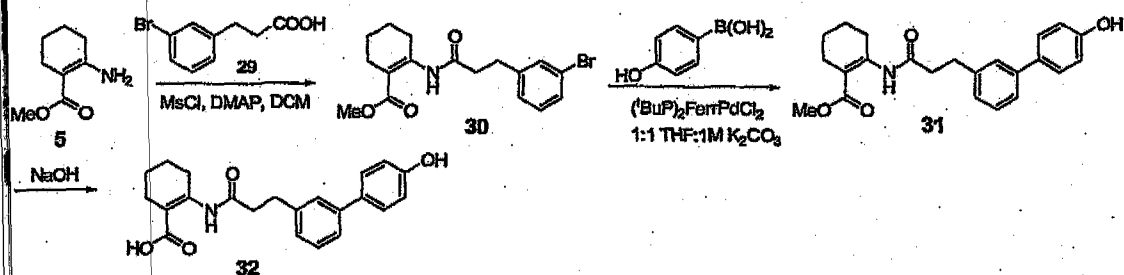
Scheme 5



Compounds with the structure 28 can be prepared by the chemistry outlined in Scheme 5.

Thus, treating a suitable tetralone such as 20 with LDA at low temperature followed by the addition of a suitable acylating agent such as 4-chloro-4-oxobutyrates provides the desired diketo-ester 21. The ester can be saponified using standard conditions known to one skilled in the art to give the acid 22. The diketone 22 can be converted to the fused isoxazole of the structure 23 by refluxing with hydroxylamine hydrochloride in the presence of a base such as triethylamine in an alcoholic solvent such as methanol or ethanol. De-protection of the methyl ether can be done with boron tribromide in a suitable solvent such as dichloromethane to give the desired alcohol 24. Treatment of the intermediate 24 with a silylating agent such as TBS-Cl in the presence of a base such as imidazole or triethylamine in a chlorinated solvent like DCM gives the bis-silyl protected ester 25. The silyl ester 25 can be treated with oxalyl chloride in a solvent such as DCM under anhydrous conditions followed by coupling with methyl 2-aminocyclopent-1-ene-1-carboxylate to give the desired amide 26. The TBS group can be removed using aqueous TBAF. Finally, the methyl ester can be saponified using standard conditions to give compounds of the structure 28.

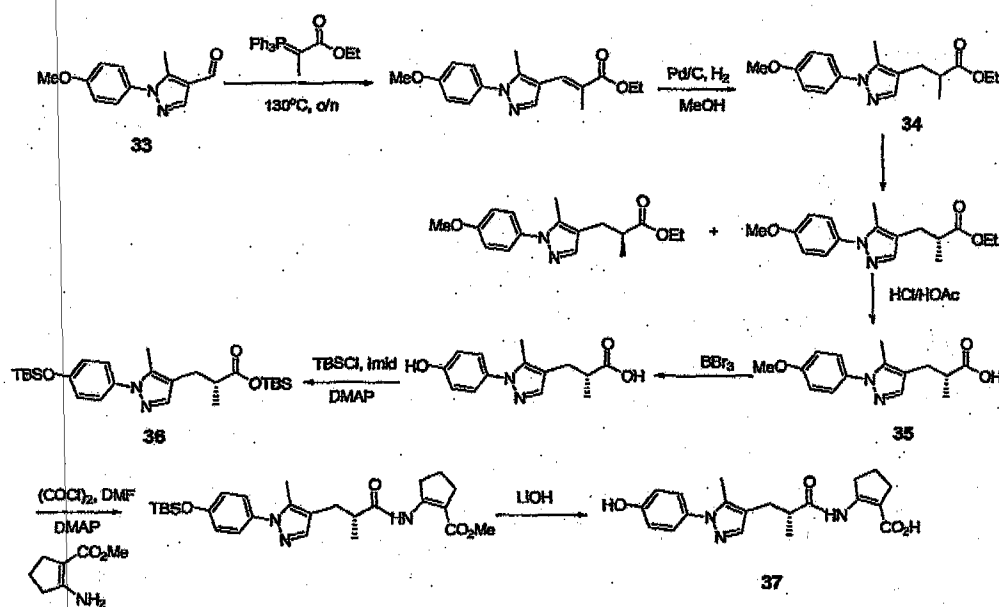
Scheme 6



Scheme 6 outlines the strategy used to synthesize compounds of the structure 32.

Coupling commercially available methyl or ethyl 2-aminocyclo-hex-1-ene-1-carboxylate 5 or 6 with 3-(3-bromophenyl) propionic acid 29 in the presence of methanesulfonyl chloride and DMAP gives the desired amide 30. The bromide 30 can be converted to 31 via a Suzuki reaction with a suitable boronic acid such as 4-hydroxy phenyl boronic acid in the presence of a catalyst such as Bis-tert-butyl-ferrocene palladium dichloride. The ester can be saponified by methods known to those skilled in the art providing compounds of the structure 32.

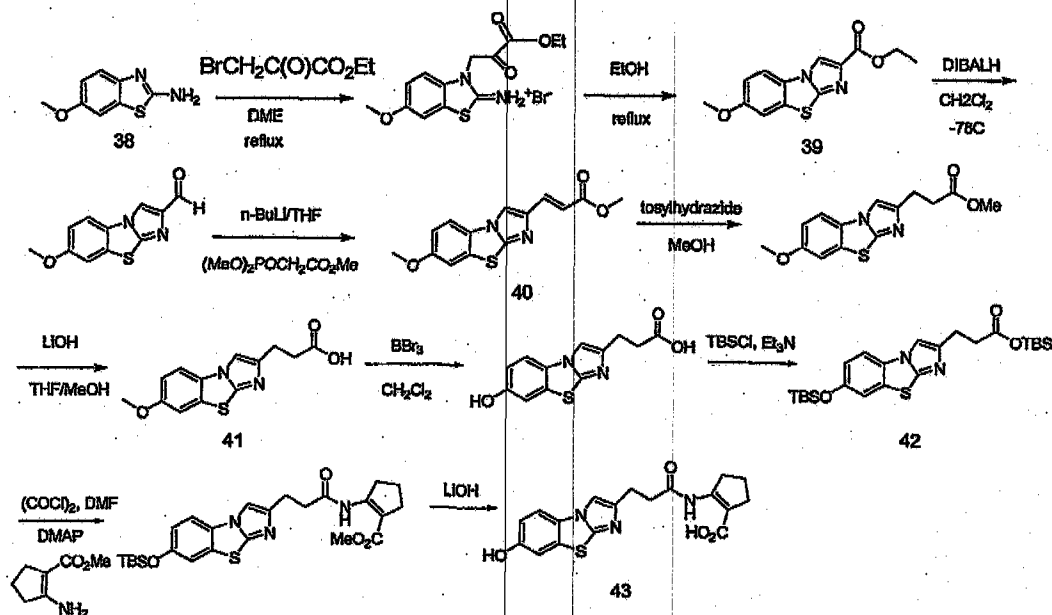
Scheme 7



Scheme 7 outlines the strategy used to synthesize compounds of the structure 37.

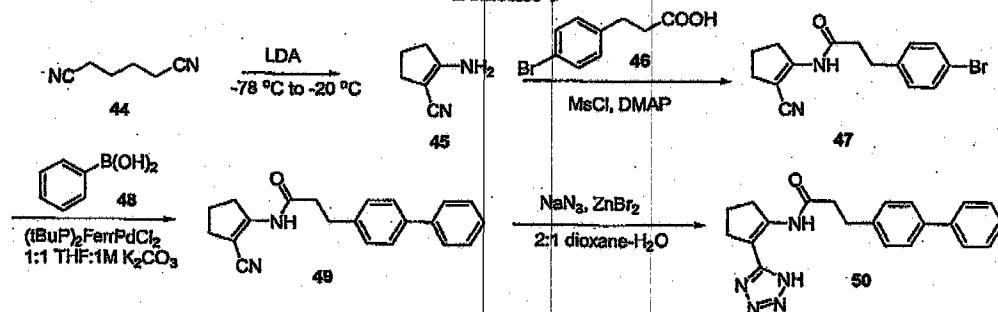
Homologating aldehyde 33, followed by reduction provides 34 which may be resolved into its enantiomers via chiral HPLC. One enantiomer is shown in Scheme 7 for illustrative purposes. Hydrolysis of the ethyl esters provides the acid 35, followed by demethylation and silylation to give 36. This intermediate can be acylated with the cyclopentene fragment, and saponified to provide biaryl products such as 37.

Scheme 8



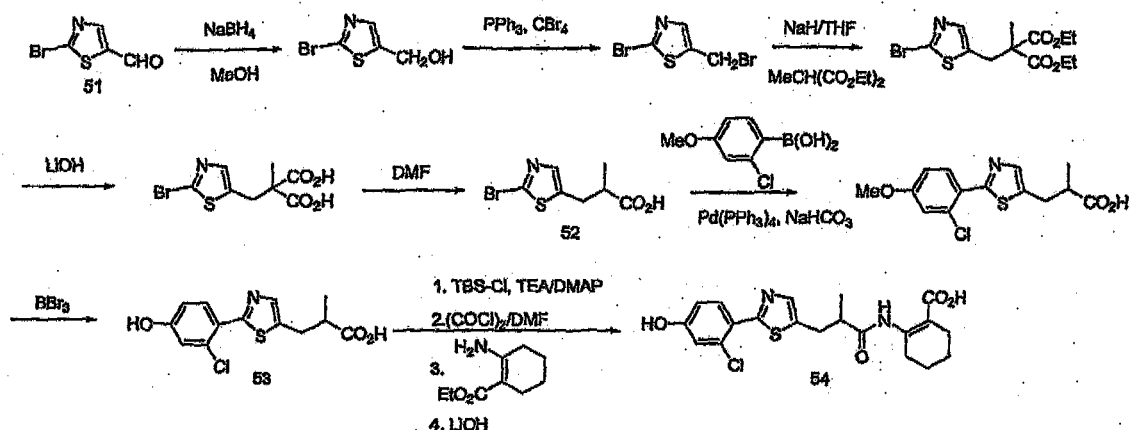
Scheme 8 outlines the strategy used to synthesize compounds of the structure 43. The aminobenzothiazole 38 may be N-alkylated and cyclized to form intermediate 39. The ester can be reduced to the aldehyde, and homologated to the enoate 40. This intermediate can then be reduced and saponified to provide the acid 41. Demethylation and silylation affords intermediate 42, which can be acylated and saponified once again as in Scheme 7 above, to provide products such as 43.

Scheme 9



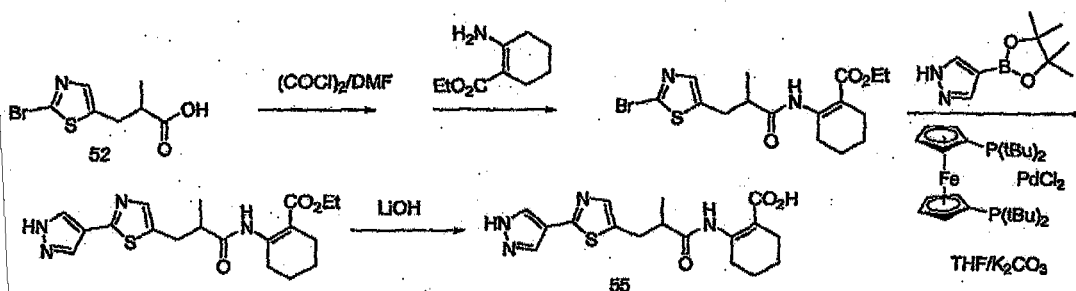
Scheme 9 outlines the strategy used to synthesize compounds of the structure 50. Adiponitrile can be converted to the amino-nitrile 45 via a Thorpe-Ziegler reaction using a suitable base such as LDA in a solvent such as THF. Coupling the amino nitrile 45 to 3-(4-bromophenyl) propionic acid 46 in the presence of methanesulfonyl chloride and DMAP gives the desired amide 47. The bromide 47 can be converted to 49 via a Suzuki reaction with a suitable boronic acid such as phenyl boronic acid in the presence of a catalyst such as 1,1 bis(di-*tert*-butylphosphino)-ferrocene palladium dichloride. Finally, treatment of the nitrile 49 with NaN_3 in the presence of a Lewis acid such as zinc bromide, in a suitable solvent mixture such as dioxane-water gives tetrazoles such as 50.

Scheme 10



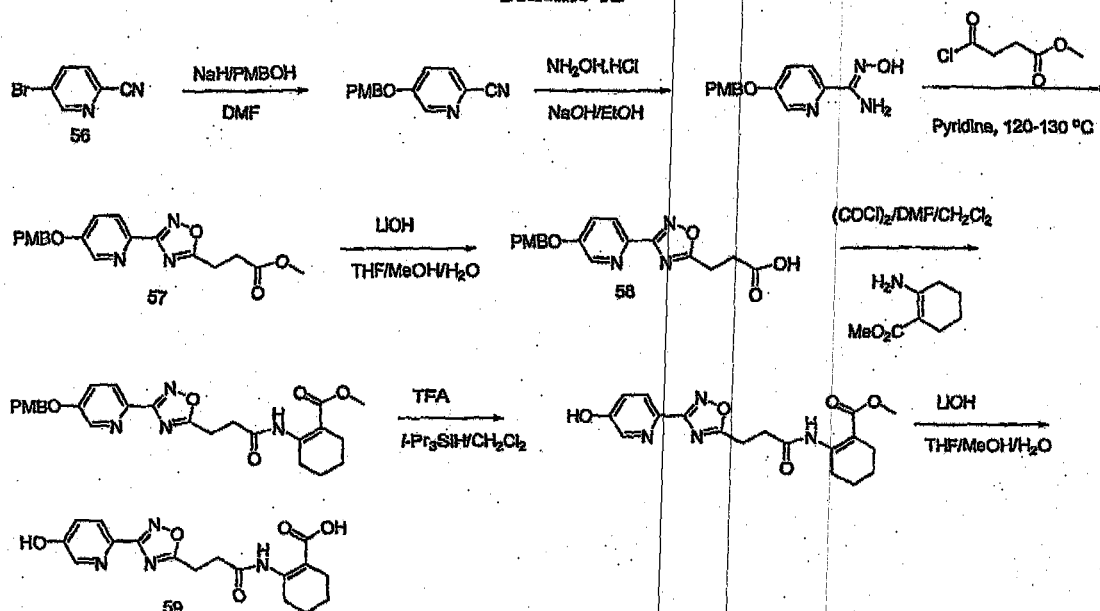
Scheme 10 outlines the strategy used to synthesize compounds of the structure 54. The heterocyclic bromo aldehyde 51 can be homologated to the intermediate 52 via several transformations including the displacement of an activated bromide with a malonate anion. The bromide 52 can be arylated and demethylated to provide acid 53, which in turn may be acylated and deprotected to provide compounds such as 54.

Scheme 11



Scheme 11 displays a method for generating compounds of the structure 55. The acid intermediate 52 from Scheme 10 above may be acylated, the bromide coupled with a heterocyclic boronate ester, and this intermediate deprotected to provide compounds such as 55.

Scheme 12

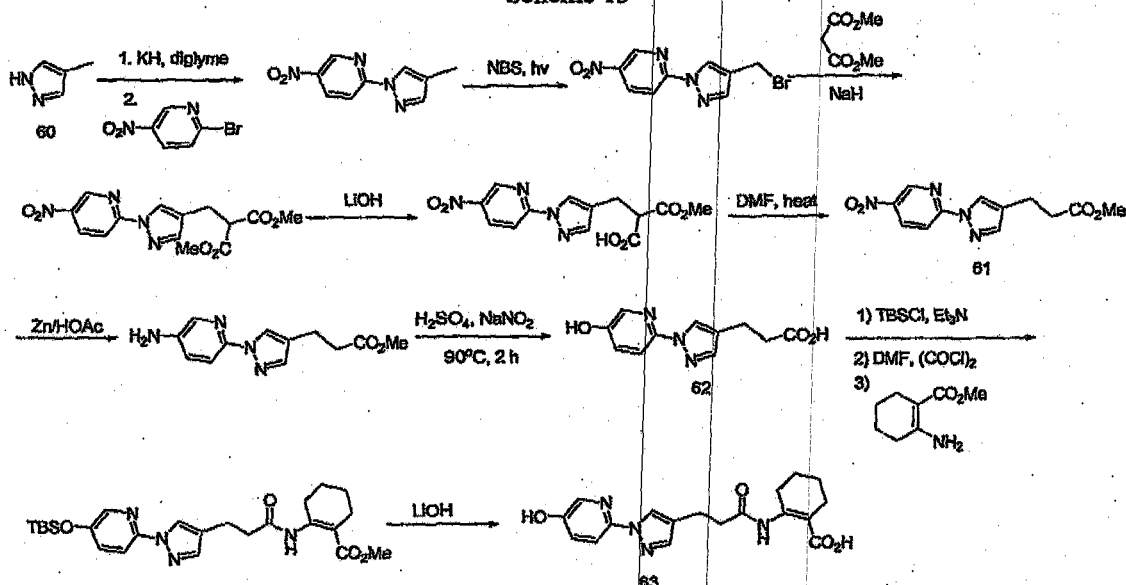


Scheme 12 demonstrates a synthetic strategy to access compounds of the structure 59.

- 5 Starting from a pyridyl bromo nitrile such as 56, the bromide may be displaced, the nitrile transformed to an N-hydroxy amidine, this intermediate acylated and then cyclized to provide the intermediate 57. Saponification of 57 can give acid 58, which may be acylated, and after deprotection provide compounds such as 59.

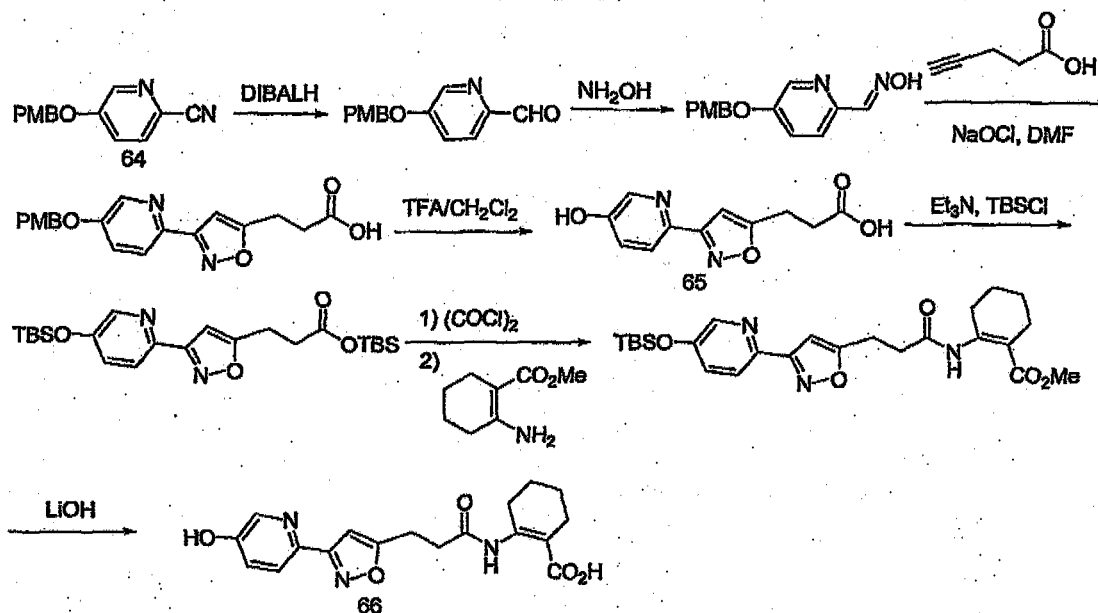
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Scheme 13



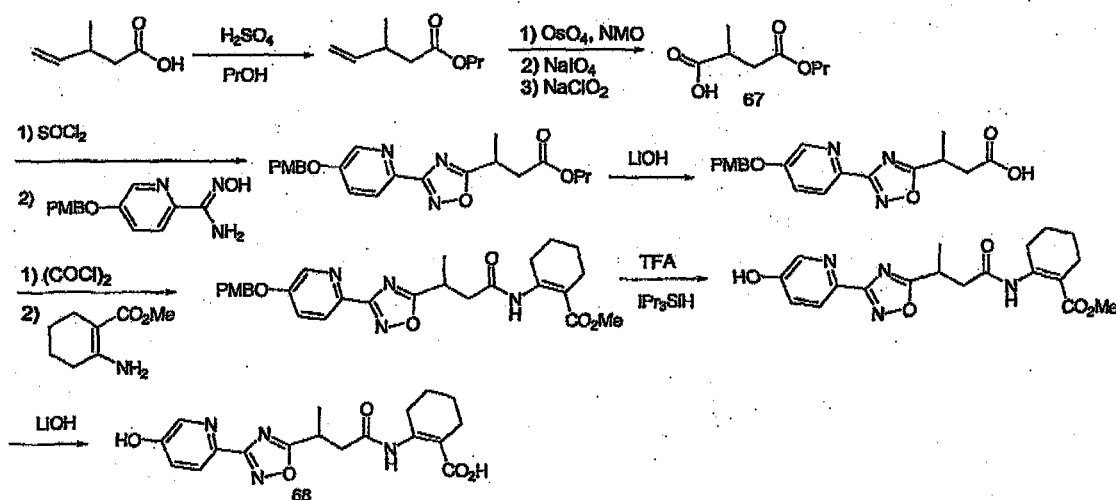
Scheme 13 outlines the strategy used to synthesize compounds of the structure 63. The pyrazole 60 may be N-arylated, this intermediate homologated to nitro 61, which in turn may be transformed to hydroxy acid 62. Upon acylation and deprotection, compounds such as 63 may be obtained.

Scheme 14



Scheme 14 displays a method to access compounds of the structure 66. The intermediate 64 generated in Scheme 12, may be elaborated into 65 via an intermediate oxime cycloaddition with an alkyne. The hydroxy acid 65 can be protected, acylated and deprotected to provide compounds such as 66.

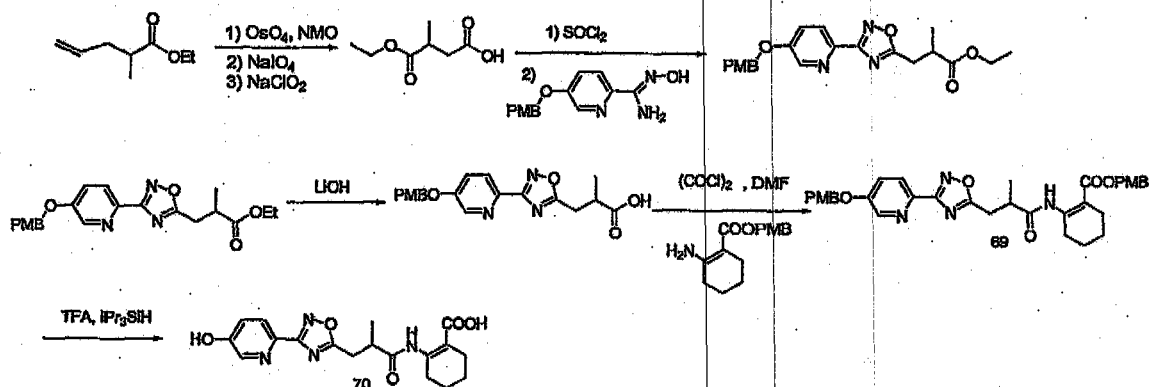
Scheme 15



Scheme 15 shows a synthetic route used to generate compounds of the structure 68. The intermediate 67 may be accessed from an oxidative cleavage of the requisite olefin. This alpha-methyl acid 67 may then be condensed with an N-hydroxy amidine, and this intermediate elaborated into compounds such as 68 using methods illustrated in the Schemes above.

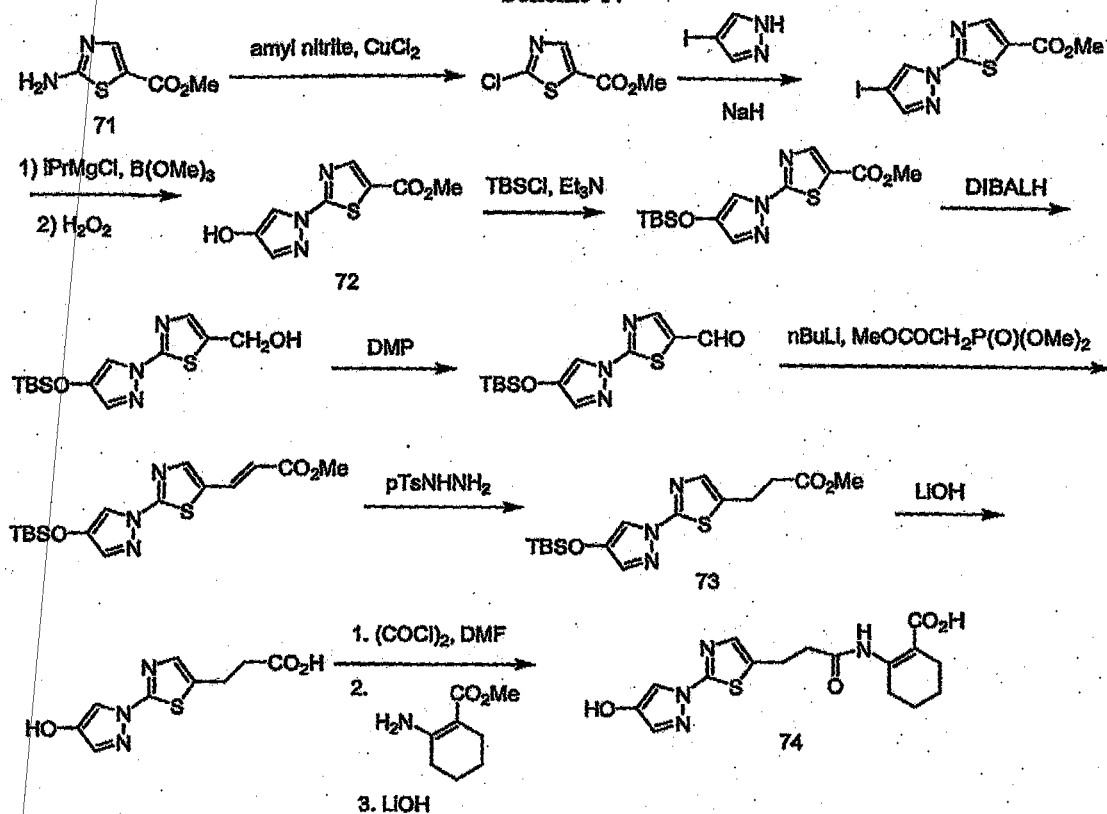
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Scheme 16



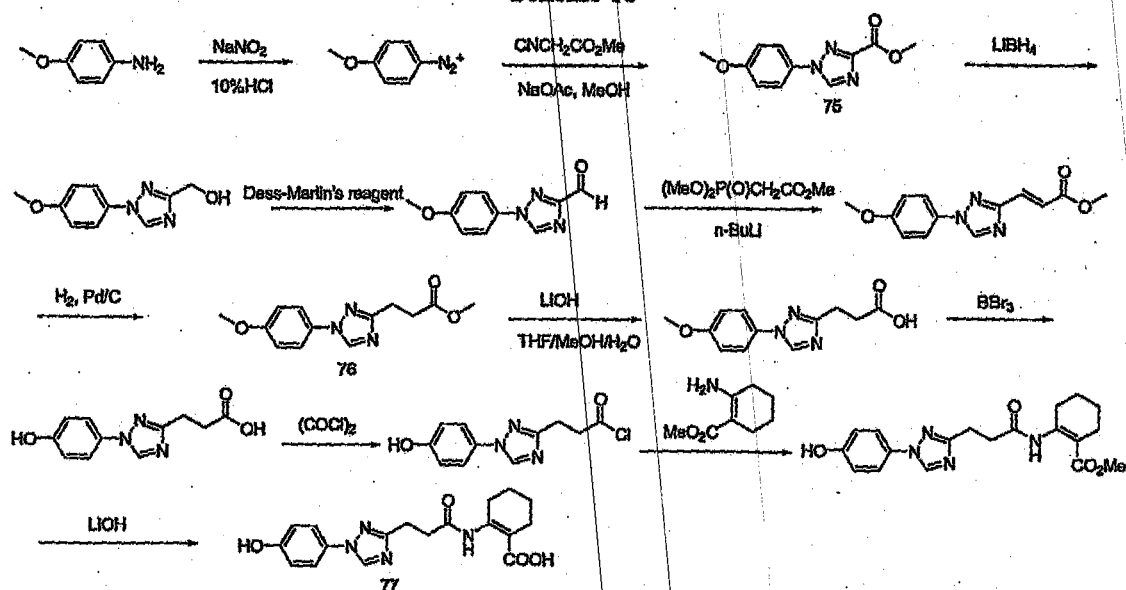
10 Scheme 16 outlines the strategy used to synthesize compounds of the structure 70. This methodology follows closely to that illustrated in Scheme 15 above, where intermediate 69 can now be doubly deprotected in one step to provide compounds such as 70, containing a methyl group alpha to the amide moiety.

Scheme 17



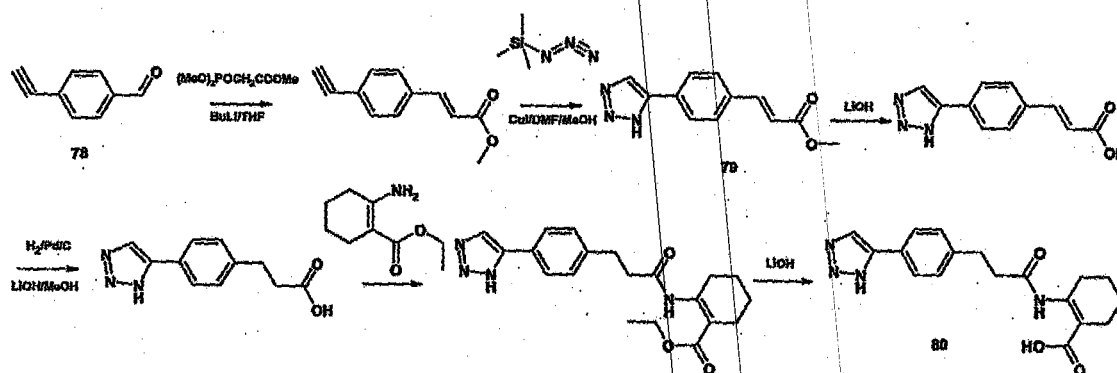
- 5 Scheme 17 displays methodology to synthesize compounds of the structure 74. An amino heterocycle such as 71 can be converted to its halide and displaced with a nitrogen anionic heterocycle, followed by hydroxyl introduction to provide intermediate 72. This ester 72 may be homologated to 73, and upon acylation and protecting group manipulation, converted to compounds such as 74.

Scheme 18

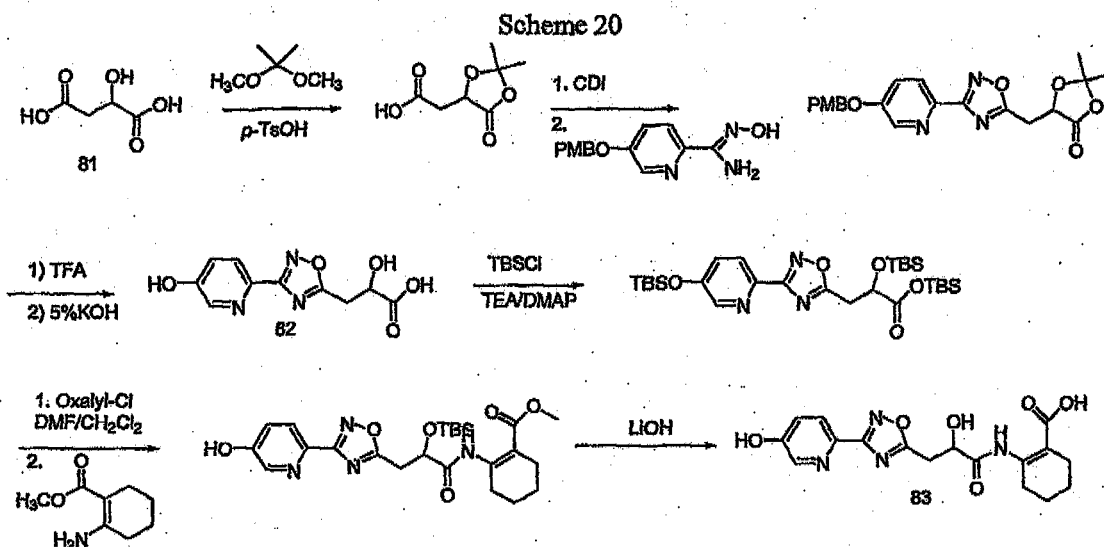


Scheme 18 displays a method for generating compounds of the structure 77. The intermediate 75 can be accessed from 4-methoxyaniline via dipolar cycloaddition, and then homologated into 76. Following some of the methods illustrated in the Schemes above, 76 can be converted into compounds such as 77.

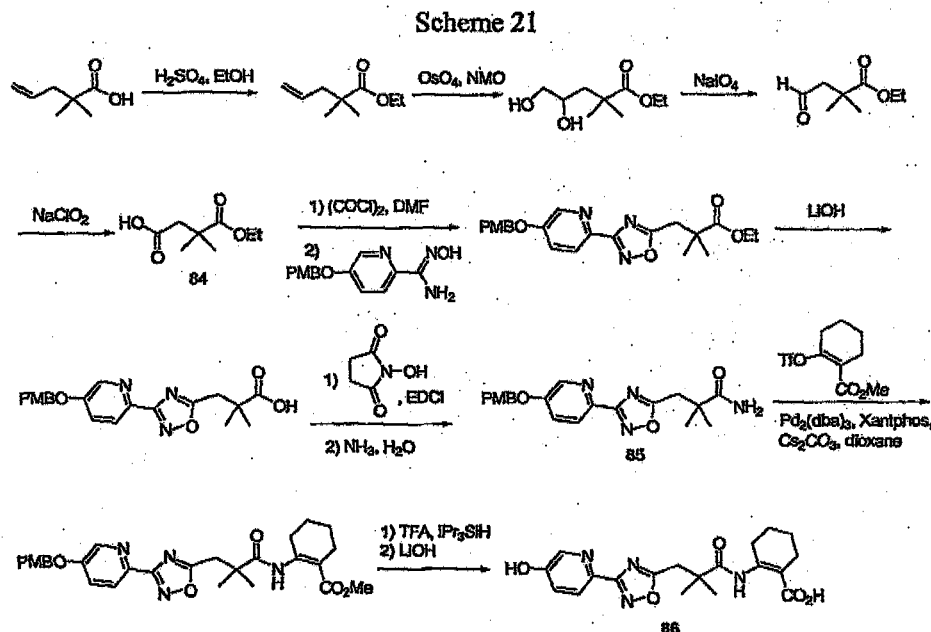
Scheme 19



Scheme 19 displays a method to access compounds of the structure 80. Alkyne 78 may be homologated and undergo a cycloaddition reaction to generate intermediate 79. The enoate 79 may then be converted into compounds such as 80 using methods illustrated in the Schemes above.



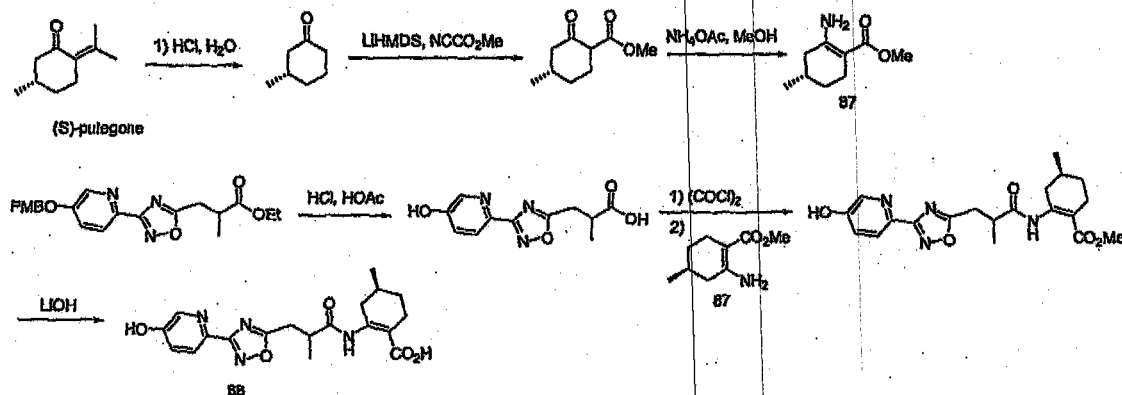
Scheme 20 illustrates a strategy used to synthesize compounds of the structure 83. Malic acid 81 can be orthogonally protected, condensed with an N-hydroxy amidine, and deprotected to generate 82. The bis-hydroxyacid 82 may be globally silylated, and then acylated and deprotected to provide alpha-hydroxy compounds such as 83.



Scheme 21 displays a strategy used to generate compounds of the structure 86. Orthogonally protected acid ester intermediate 84 can be obtained via oxidative degradation of the requisite olefinic starting material. The acid 84 may then be condensed with an N-hydroxy amidine, and manipulated to provide a primary carboxamide 85. A primary carboxamide intermediate such as 85 may

undergo a coupling reaction with an enol triflate, and upon further deprotection reactions, provide geminal dimethyl compounds such as 86.

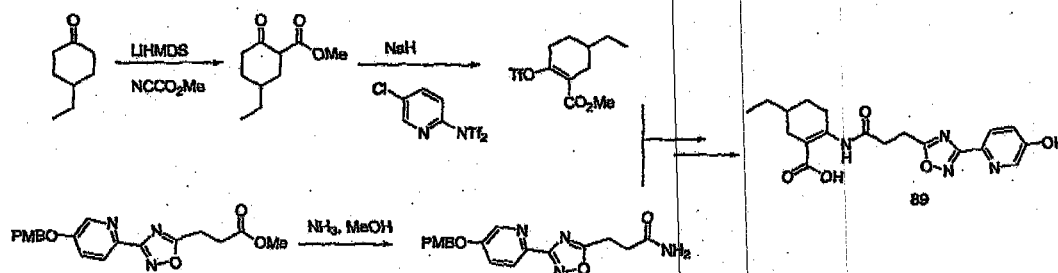
Scheme 22



Scheme 22 outlines a methodology to access compounds of the structure 88.

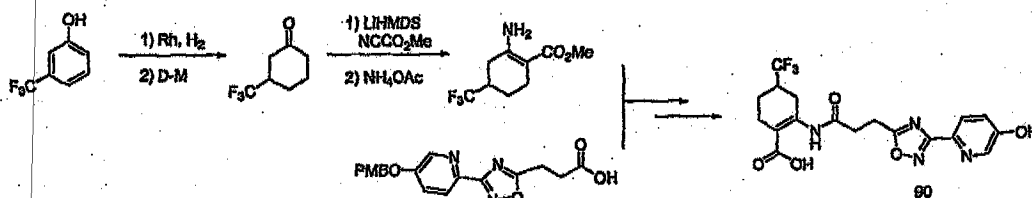
Commercially available (S)-pulegone can be converted into intermediate 87 via reverse aldol, acylation with Mander's reagent, and enamine formation. Using a similar alpha-methyl ester intermediate illustrated in Scheme 16, chiral amine 87 may be elaborated into compounds such as 88.

Scheme 23



Scheme 23 displays a strategy to access compounds of the structure 89. Commercially available symmetrical ketones, such as 4-ethylcyclohexanone, can be acylated with Mander's reagent, followed by enol triflate formation with Comins' reagent. Using similar metal catalyzed coupling methodology illustrated in Scheme 21, different regioisomerically substituted cyclohexene compounds such as 89 may be accessed.

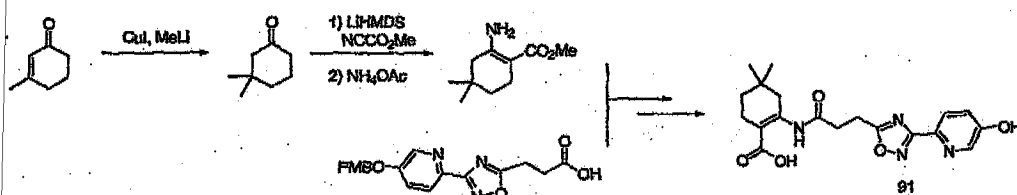
Scheme 24



Scheme 24 illustrates a methodology to access compounds of the structure 90.

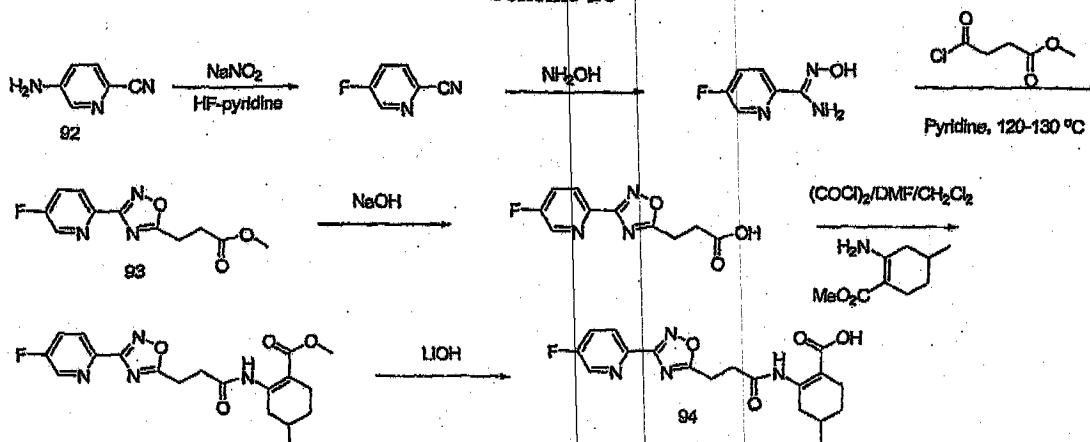
Commercially available 3-(trifluoromethyl)phenol can be reduced to a hydroxy cyclohexane, oxidized with Dess-Martin reagent to the ketone, acylated with Mander's reagent, and followed by enamine formation. Using similar methodologies illustrated above, compounds such as 90 may be obtained that possess a trifluoromethyl substituted cyclohexene.

Scheme 25



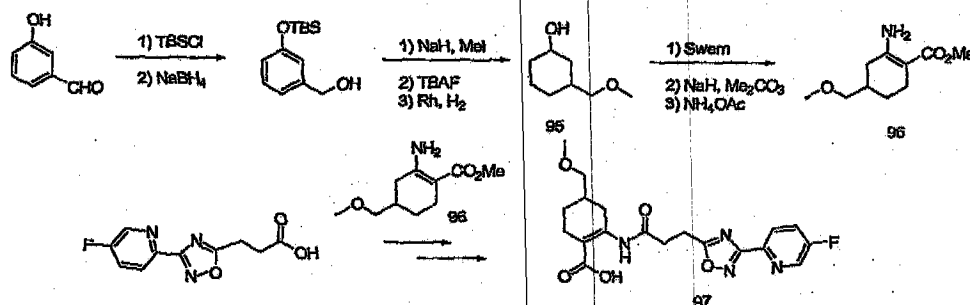
Scheme 25 displays a strategy to access compounds of the structure 91. Commercially available 3-methyl-2-cyclohexen-1-one can be substituted to generate a 3-geminal-dialkyl cyclohexanone. Upon acylation with Mander's reagent, enamine formation, and following similar methodologies illustrated above, compounds such as 91 may be obtained that possess a geminal dialkyl substituted cyclohexene.

Scheme 26



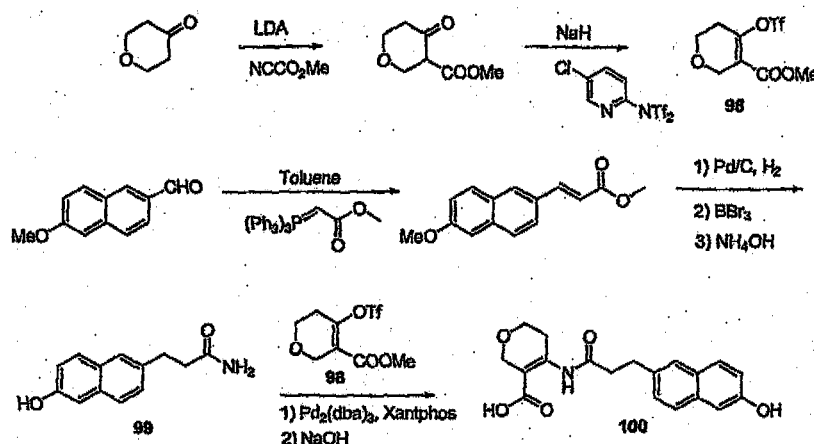
Scheme 26 shows a method to access compounds of the structure 94. Commercially available pyridine 92 can be fluorinated and incorporated into a fluoro biaryl intermediate such as 93. Subsequent hydrolysis, acylation, and saponification following similar methodologies illustrated above, may provide fluoropyridyl compounds such as 94.

Scheme 27



Scheme 27 illustrates a method to generate compounds of the structure 97. Commercially available 3-hydroxybenzaldehyde can be converted into the ether substituted cyclohexane intermediate 95 via the key reduction of the phenyl ring. Upon ketone formation and similar methodologies described above, the ether substituted cyclohexene aminoester 96 can be obtained. This enamine intermediate may be acylated and deprotected as described above, to generate compounds such as 97 that possess an ether substituted cyclohexene.

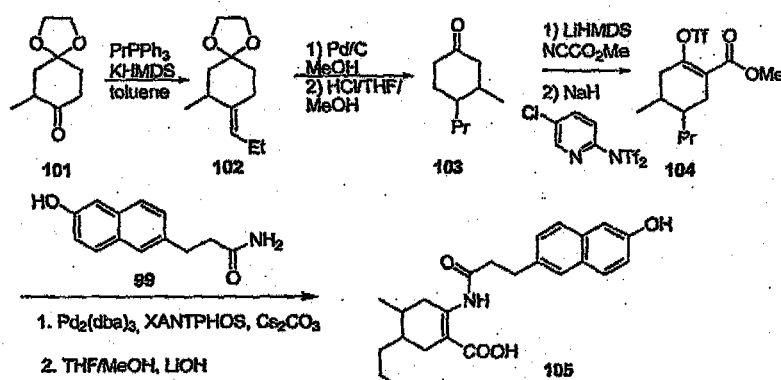
Scheme 28



Scheme 28 displays methodology to access compounds of the structure 100.

Commercially available tetrahydro-4H-pyran-4-one can be converted into the dihydropyran triflate intermediate 98 via similar methodologies described above. In parallel, commercially available 6-methoxy-2-naphthaldehyde can be converted into the primary carboxamide intermediate 99, also via similar methodologies described above. Intermediates 98 and 99 may be coupled under similar metal catalyzed methodology illustrated in Scheme 21, to generate compounds such as 100 that possess a dihydropyran carboxylic acid moiety.

Scheme 29



Scheme 29 illustrates a methodology to access compounds of the structure 105. The ketone 101 (for preparation see Danishefsky, *et al J. Am. Chem. Soc.* 2004, 126, 14358) can be converted to the olefin 102, followed by reduction of the double bond using standard hydrogenation conditions, and acid catalyzed removal of the ketal protecting group to provide the ketone 103. This material can be acylated using Mander's reagent to give the desired ketoester that is converted to the enol triflate 104 with Comins' reagent. Intermediates 104 and 99 may be coupled using similar metal catalyzed methodology

illustrated in Scheme 21. Saponification of the methyl ester using standard conditions can generate vicinal disubstituted cyclohexene compounds such as 105.

The various organic group transformations and protecting groups utilized herein can be performed by a number of procedures other than those described above. References for other synthetic procedures that can be utilized for the preparation of intermediates or compounds disclosed herein can be found in, for example, M.B. Smith, J. March Advanced Organic Chemistry, 5th Edition, Wiley-Interscience (2001); R.C. Larock Comprehensive Organic Transformations, A Guide to Functional Group Preparations, 2nd Edition, VCH Publishers, Inc. (1999); T.L. Gilchrist Heterocyclic Chemistry, 3rd Edition, Addison Wesley Longman Ltd. (1997); J.A. Joule, K. Mills, G.F. Smith Heterocyclic Chemistry, 3rd Edition, Stanley Thornes Ltd. (1998); G.R. Newkome, W.W. Paudler Contemporary Heterocyclic Chemistry, John Wiley and Sons (1982); or Wuts, P. G. M.; Greene, T. W.; Protective Groups in Organic Synthesis, 3rd Edition, John Wiley and Sons, (1999), all six incorporated herein by reference in their entirety.

REPRESENTATIVE EXAMPLES

The following examples are provided to more fully illustrate the present invention, and shall not be construed as limiting the scope in any manner. Unless stated otherwise:

(i) all operations were carried out at room or ambient temperature (RT), that is, at a temperature in the range 18-25°C;

(ii) evaporation of solvent was carried out using a rotary evaporator under reduced pressure (4.5-30 mmHg) with a bath temperature of up to 50°C;

(iii) the course of reactions was followed by thin layer chromatography (TLC) and/or tandem high performance liquid chromatography (HPLC) followed by mass spectroscopy (MS), herein termed LCMS, and any reaction times are given for illustration only;

(iv) yields, if given, are for illustration only;

(v) the structure of all final compounds was assured by at least one of the following techniques: MS or proton nuclear magnetic resonance (¹H NMR) spectrometry, and the purity was assured by at least one of the following techniques: TLC or HPLC;

(vi) ¹H NMR spectra were recorded on either a Varian Unity or a Varian Inova instrument at 500 or 600 MHz using the indicated solvent; when line-listed, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to residual solvent peaks (multiplicity and number of hydrogens); conventional abbreviations used for signal shape are: s. singlet; d. doublet (apparent); t. triplet (apparent); m. multiplet; br. broad; etc.;

(vii) MS data were recorded on a Waters Micromass unit, interfaced with a Hewlett-Packard (Agilent 1100) HPLC instrument, and operating on MassLynx/OpenLynx software; electrospray ionization was used with positive (ES+) or negative ion (ES-) detection; the method for LCMS ES+ was 1-2 mL/min, 10-95% B linear gradient over 5.5 min (B = 0.05% TFA-acetonitrile, A = 0.05% TFA-

water), and the method for LCMS ES- was 1-2 mL/min, 10-95% B linear gradient over 5.5 min (B = 0.1% formic acid - acetonitrile, A = 0.1% formic acid - water), Waters XTerra C18 - 3.5 μ m - 50 x 3.0 mmID and diode array detection;

(viii) automated purification of compounds by preparative reverse phase HPLC was performed on a Gilson system using a YMC-Pack Pro C18 column (150 x 20 mm i.d.) eluting at 20 mL/min with 0 - 50% acetonitrile in water (0.1% TFA);

(ix) the manual purification of compounds by preparative reverse phase HPLC (RPHPLC) was conducted on either a Waters Symmetry Prep C18 - 5 μ m - 30 x 100 mmID, or a Waters Atlantis Prep dC18 - 5 μ m - 20 x 100 mmID; 20 mL/min, 10-100% B linear gradient over 15 min (B = 0.05% TFA-acetonitrile, A = 0.05% TFA-water), and diode array detection;

(x) the purification of compounds by preparative thin layer chromatography (PTLC) was conducted on 20 x 20 cm glass prep plates coated with silica gel, commercially available from Analtech;

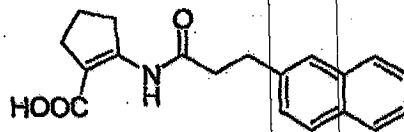
(xi) flash column chromatography was carried out on a glass silica gel column using Kieselgel 60, 0.063-0.200 mm (SiO₂), or a Biotage SiO₂ cartridge system including the Biotage Horizon and Biotage SP-1 systems;

(xii) chemical symbols have their usual meanings, and the following abbreviations have also been used: h (hours), min (minutes), v (volume), w (weight), b.p. (boiling point), m.p. (melting point), L (litre(s)), mL (millilitres), g (gram(s)), mg (milligrams(s)), mol (moles), mmol (millimoles), eq or equiv (equivalent(s)), IC₅₀ (molar concentration which results in 50% of maximum possible inhibition), EC₅₀ (molar concentration which results in 50% of maximum possible efficacy), μ M (micromolar), nM (nanomolar);

(xiii) definitions of acronyms are as follows:

BBr ₃ is boron tribromide	B(OMe) ₃ is trimethyl borate
Comins' reagent is 2-[N,N-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine	CDI is 1,1'-carbonyl diimidazole
DCM is dichloromethane (methylene chloride)	DIBALH is diisobutyl aluminum hydride
DMF is dimethylformamide	DMAP is 4-dimethyl amino pyridine
DMSO is dimethyl sulfoxide	iPrMgCl is isopropyl magnesium chloride
KHMDS is potassium bis(trimethylsilyl) amide	LDA is lithium diisopropyl amide
LiHMDS is lithium bis(trimethylsilyl) amide	Mander's reagent is methyl cyanoformate
NBS is N-bromo-succinimide	
NaOCl is sodium hypochlorite	NMO is 4-methylmorpholine N-oxide
OTf is triflate	Pd(PPh ₃) ₄ is tetrakis triphenylphosphine palladium (0)
Pd ₂ (dba) ₃ is Tris(dibenzylideneacetone) dipalladium (0);	TBAF is tetrabutylammonium fluoride;
TBS Chloride is t-butyl dimethyl silyl chloride	TBSOTf is t-butyl dimethyl silyl trifluoromethane sulfonate
TFA is trifluoroacetic acid	THF is tetrahydrofuran
XANTPHOS is 9,9-Dimethyl-4,5-bis(diphenyl-phosphino)xanthene	

EXAMPLE 1



To a solution of methyl-2-oxocyclopentane-1-carboxylate (1.5g, 10.55 mmol) in methanol was added ammonium acetate (4.07 g, 52.76 mmol). After stirring the reaction at room temperature for 18 h, it was concentrated *in vacuo*. The residue was dissolved in DCM, washed with water, brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. This cyclopentene aminoester intermediate was used without any further purification.

To a solution of 3-(2-naphthyl) acrylic acid (1.5 g, 7.56 mmol) in 1:1 ethanol-ethyl acetate (50 mL) was added Pd/C and the resulting mixture stirred under a H_2 balloon for 18 h. The reaction mixture was filtered through celite, and concentrated *in vacuo* to give the desired saturated naphthyl acid as a white solid.

To a solution of this saturated naphthyl acid intermediate (150 mg, 0.75 mmol) in DCM (6 mL) cooled to 0°C was added DMAP (201 mg, 1.65 mmol) followed by methanesulfonyl chloride (0.059 mL, 0.75 mmol). After 5 min, the cyclopentene aminoester intermediate (95 mg, 0.67 mmol) was added as a solid. The mixture was stirred at RT for 18 h, and quenched with saturated NH_4Cl solution. The resulting mixture was extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by flash chromatography using 10% ethyl acetate-hexanes as the eluant to give the desired amide product as a methyl ester.

To a solution of this ester intermediate (15 mg, 0.046 mmol) in THF (2 mL), was added methanol (1 mL) followed by 1 N NaOH (1 mL). The resulting reaction mixture was stirred at 23°C for 6 h. It was neutralized to pH=7 by the addition of 1N HCl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC (Gilson) to provide Example 1. ^1H NMR (500 MHz, CD_3OD) δ 1.85 (m, 2H), 2.49 (m, 2H), 2.8 (t, 2H), 3.1 (m, 4H), 7.4 (m, 3H), 7.7 (bs, 1H), 7.8 (m, 3H); LCMS m/z 308 (M-1).

PREPARATION OF CYCLOHEXENE AMINOESTER AND ENOL TRIFLATE ESTER INTERMEDIATES

